ROLE OF HEALTH ECONOMIC DATA IN POLICY MAKING AND REIMBURSEMENT OF NEW MEDICAL TECHNOLOGIES

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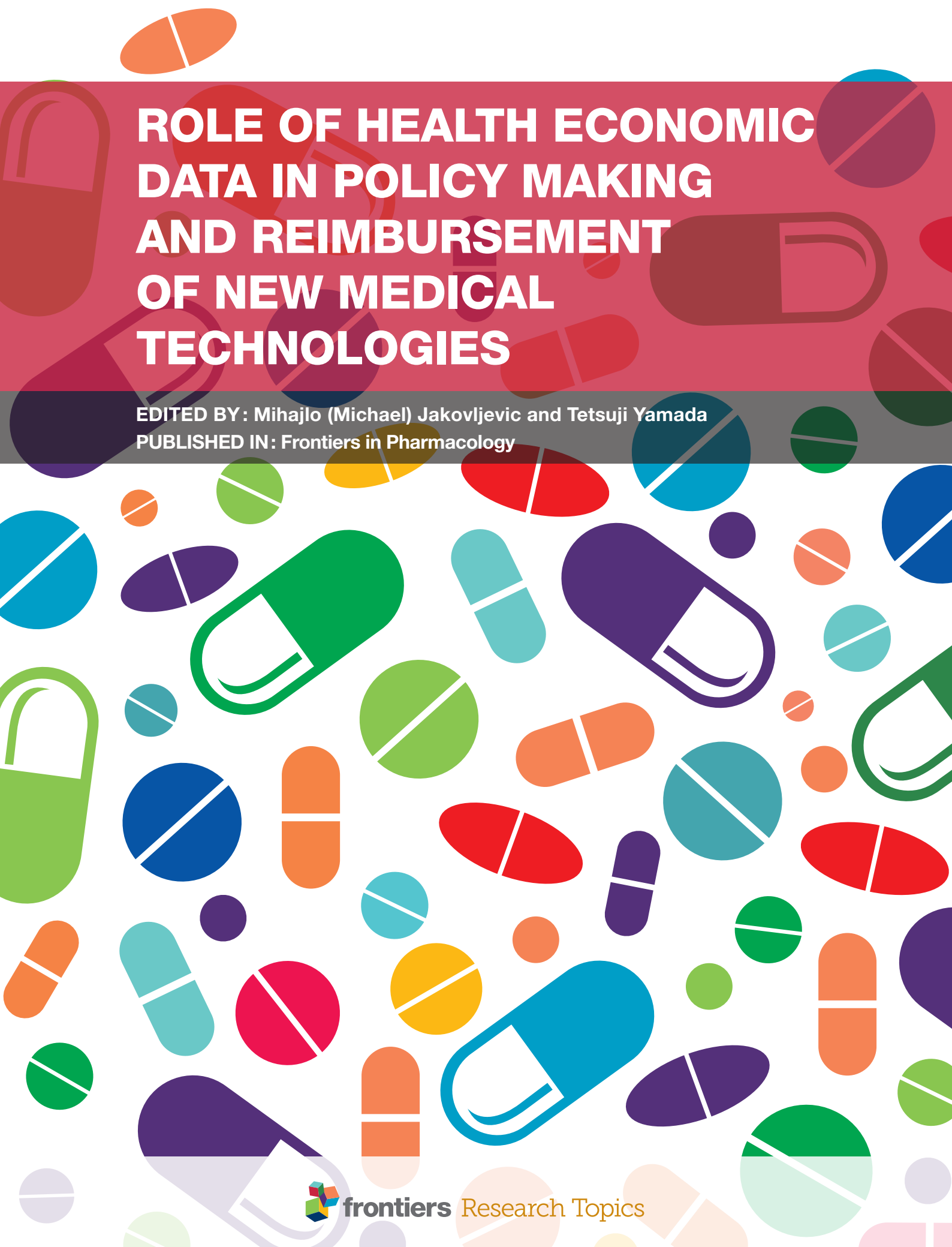

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ROLE OF HEALTH ECONOMIC DATA IN POLICY MAKING AND REIMBURSEMENT OF NEW MEDICAL TECHNOLOGIES

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This Research Topic was focused on provision of novel medical technologies worldwide keeping in mind financial sustainability challenge. An exemplary area certainly are oncology pharmaceuticals where prices have increased 10-fold in recent years leading to concerns on affordability. The objective of this collection of studies was to reveal some of the hidden underlying causes of unequal access to the medicines. Another core issue is the growing proportion of out-of-pocket health spending in many world regions. In line with the joint efforts of the editors and authors we received an exceptionally high response worldwide. This E-Book attracted a total of 37 self-standing research submissions out of which 32 ultimately passed external peer review and got published. Base affiliations of the authors spread across academia, pharmaceutical and medical device industry, governmental authorities and clinical medicine. Their home institutions were situated in fifteen different countries inclusive of Japan, Israel, Russia, USA, Germany, Italy, Netherlands, Austria, Spain, Malta, Serbia, Poland, Bulgaria, Hungary and Malaysia. We frankly believe that authors succeeded to cover important literature gaps referring to these world regions. We solicit global professional audience to put our efforts to the test and read this contribution to the health economics literature.

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EDITORIAL
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Editorial: Role of Health Economic Data in Policy Making and Reimbursement of New Medical Technologies

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Editorial on the Research Topic

Role of Health Economic Data in Policy Making and Reimbursement of New Medical Technologies

This Research Topic was created with a mission to tackle the core challenges for the provision of new medical technologies across the globe considering increasing prices and finite financial resources (Malmström et al., 2013; Permanand and Pedersen, 2015). A key area certainly includes anti-cancer drugs where prices have increased 10-fold in recent years (Kelly and Smith, 2014) leading to concerns with affordability for both health services and patients (Ghinea et al., 2015; Tefferi et al., 2015). The objective was to reveal some of the hidden underlying causes of unequal access to the medicines as well as the growing proportion of out-of-pocket health spending in many world regions (Global Burden of Disease Health Financing Collaborator Network, 2017). In line with the joint efforts of the editors and authors we received an exceptionally high response worldwide. The topic attracted a total of 36 self-standing research submissions out of which 31 ultimately passed external peer review and got published. Base affiliations of the authors spread across academia, pharmaceutical and medical device industry, governmental authorities and clinical medicine. Their home institutions were situated in 15 different countries inclusive of Japan, Israel, Russia, USA, Germany, Italy, Netherlands, Austria, Spain (Basque), Malta, Serbia, Poland, Bulgaria, Hungary and Malaysia.

In published health economics literature, there is straightforward evidence that accelerated growth of health spending began in the 1960s exceeding the historical 4% GDP threshold (Jakovljevic and Ogura, 2016). This phenomenon was noticed early on in mature market economies led by the US, and during the following decades spread to many global regions (Getzen, 2000). Health policy makers became increasingly exposed to new harsh challenges in the uneasy task to provide universal health coverage and decent equity of access to medical services. Among the most prominent demand-side issues are population aging (Murata et al., 2010), rise of non-communicable diseases (Jakovljevic and Milovanovic, 2015), and growing patient expectations. Supply-side causes include improvements in societal welfare (Yamada et al., 1992) and living standards, technological innovation in medicine, and continuing rapid urbanization in developing world regions. Experience with implementation of insurance-based risk sharing agreements which aim to facilitate access to new medicine varies substantially (Adamski et al., 2010; Ferrario and Kanavos, 2013; Ferrario et al., 2017). There are growing measures to enhance the prescribing of low cost generics and biosimilars across Europe and other countries without compromising care as the savings can be considerable and used to fund new technologies

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(Cameron et al., 2012; Simoens, 2012; Vogler, 2012; Godman et al., 2014). Published studies have shown that prices of good quality generics can as low as 2% of prepatent loss prices (Woerkom et al., 2012). Also, the considerable build-up of workforce capacities and strengthening of primary care and hospital networks contributed to the "supplier induced demand" phenomenon (Richardson and Peacock, 2006).

There is straightforward historical evidence of long term growth in pharmaceutical and overall health spending both in absolute and GDP % terms worldwide (Dieleman et al., 2017). The accumulated constraints resulting from rising costs of care were felt in many areas of clinical medicine even among the richest societies (Kotlikoff and Hagist, 2005). Examples of expensive and hardly affordable novel therapeutic areas are orphan drugs indicated to treat rare diseases (Cohen and Felix, 2014; Taruscio et al., 2015) and targeted biologicals used in autoimmune disorders and cancer; new cancer drugs often with limited health gain (Kantarjian et al., 2013; Wild et al., 2016). Frequently denied access to even essential generic pharmaceuticals (Jakovljevic et al., 2014) is still taking place, in rural and suburban areas of certain countries (e.g., Japan). These difficulties are worsened by the lack of evidence-based resource allocation strategies and less sustainable financing strategies (Jakovljevic et al., 2016).

Core goals of the Editors of this collection of articles were to cover a growing gap between the medical technology innovation, its dissemination, and cost containment issues. The European Commission has estimated that there is almost 36% room for efficiency gains and costs reductions in most contemporary European health systems (COST Action, 2016). So-called "emerging costs for healthcare" have an estimated growth of almost €1,400 billion annually EU wide. Similar issues were clearly recognized in other major global health care markets such as USA (Anderson et al., 2005) and Japan (Ogura and Jakovljevic, 2014) among the mature ones, and the BRICs led by People's Republic of China among the emerging ones (Jakovljevic, 2015). In addition, situation in China is hampered by the hospitals' and physicians' need for profits for their survival made from drug procurement which leads to the high use of injections and infusions (Reynolds and McKee, 2011; Yang et al., 2013; Zeng et al., 2014). There is an ongoing public debate about the effective introduction and spreading of value based medicine concepts, and introduction of cost-effectiveness criteria into official policy making in most world regions. Since the pioneering moves by Australia (Parker and Guthrie, 1993) and Canada (Grosse, 2008) back in early 1990s, in many countries these efforts were rather slow and less successful. To a large extent the solution was found in health technology assessment (HTA) procedures and establishment of a strong network of national HTA Agencies in North America, Europe and Asia (Banta and Jonsson, 2009). However, a thorough search through the health economics literature testifies that authorities and experts alike are shifting their focus of interest toward other possible strategies to deliver cost-effective health care (Neumann, 2005). This is a notable challenge in low- and middle-income world regions (Stafinski et al., 2011) and even in some high-income OECD economies where HTA did not grasp its roots inside official policy making on resource allocation in health care (Perry et al., 1997). Particular challenge in low- and middle-income countries include the fact that medicines may account for up to 70% of total health care expenditure, much of which is currently out-of-pocket, although starting to change with Namibia and South Africa striving for universal access (Cameron et al., 2009).

One group of contributions to our topic referred to the Eastern European health systems of Hungary, Poland, Bulgaria, Serbia and Bosnia. The University of Debrecen, Hungary, brought attention to the relationship between statin prescription and socioeconomic deprivation of patients (Boruzs et al.). However, restrictions in countries such as Lithuania where only patented statins are available eased with generic availability enhancing utilization (Garuolienė et al., 2016). On the other hands some authors have questioned whether increasing statin utilization reduces cardiovascular diseases (Vancheri et al., 2016). The Medical University of Silesia in Poland conducted several studies covering the areas: health promotion development in spa treatment (Woźniak-Holecka et al.), perspectives of use of social media in pharmaceutical marketing (Syrkiewicz-Świtała et al.), systemic changes in efficiency of Polish primary health care (Holecki et al.), and clustering policy effects within their national health system (Romaniuk et al.). The Medical University of Plovdiv, Bulgaria, acting as one of the European centers of excellence in rare diseases and orphan medicines, published a piece on importance of the socio-economic burden as a decision-making criterion (Iskrov et al.). University of Belgrade and Institute of Public Health in Serbia jointly presented insight into the socio-economic inequalities, out-of-pocket payments in large national consumers' satisfaction survey samples (Vojvodic et al.). The Military Medical Academy in Belgrade contributed with a study on pharmaceutical expenditure and burden of non-communicable diseases in Serbia (Kovacevic et al.). This was complemented by findings on contribution of health workforce to the structure of health spending (Jakovljevic and Varjacic) coming from the University of Kragujevac, Serbia. Other reported trials from this country refer to hepatitis treatment among former addicts (Jovanovic et al.), socioeconomic factors associated with psychoactive substance abuse among the adolescents (Janicijevic et al.), and tobacco use patterns (Vasiljevic et al.). A variety of clinical entities ranging from dentistry (Djordjevic et al.) to the gynecological conditions and fertility (Djukic et al.), were processed as well due to their relevance for the national health system financing and medical service provision. Nation-wide health surveys in the country were used as a ground for research on citizen satisfaction with health sector (Mihailovic et al.) and self-assessed health and socioeconomic inequalities (Radevic et al.). A prominent piece providing a big picture on former Yugoslavia's health systems referred to length of hospital stay and bed occupancy rates (Cvetkovic et al.). Ultimately Western Balkan/former Yugoslavia—related research was concluded with a critical appraisal of Bosnia's medicines reimbursement list (Mujkic and Marinkovic).

Broader perspectives on Pan-European pharmaceutical spending brought in another contribution reflecting East-West split in expenditure evolution patterns inside EU

(Jakovljevic et al.). There is a diversity of contributions provided by some academic centers based in Western European EU-15 countries. Here we witness a paper on alcohol beverage taxation and government revenues in European WHO Region brought to us by Vienna Medical University, Austria and Federal Research Institute for Public Health Organization and Information (CNIIOIZ) Moscow, Russia (Jakovljevic et al.). Dutch health economists delivered several prominent studies including ones on stratified medicine (Fugel et al.), barriers to market access of biosimilar monoclonal antibodies in European Union (Moorkens et al.), and industrial landscape in pharmaceutical biotechnology (Moorkens et al.). We had as well a valuable commentary coming from Malta reflecting ration between health expenditure growth in leading G7 industrialized nations compared to the BRICs (Buttigieg et al.) referring to the original article published in Journal of Medical Economics back in 2016 (Jakovljevic, 2016). These findings were complemented by a piece on long term health spending in low- and middle-income countries co-authored contribution of Temple University, Philadelphia, USA (Jakovljevic and Getzen). Western European cluster of papers had conclusive remarks on observed and normative functions applied to addiction disorders coming from Almeria University, Spain (Cruz Rambaud et al.) and the review on life cycle of health technologies (Gutiérrez-Ibarluzea et al.) brought to us jointly by the Basque and German Offices for HTA and Italian Society of Clinical Pharmacy and Therapeutics.

Ultimately a number of contributions coming from vast Asian continent referred to the commentary on population aging in Japan (Jakovljevic) as depicted in the original article by Fukushima et al. (2016). A self-standing piece on children medical expenses in current Japanese legislation came to us by Hosei University, Tokyo (Sugahara). Remaining studies published in this series were related to causal connection between physical exercise and pharmacological treatment of mood disorders such as major depression submitted by the Wingate Institute, Israel (Netz). Island state of Malaysia and its University Teknologi Petronas has published a piece on long term modeling of health expenditures. Keeping in mind strong pace of economic development in South-East Asia, these projections might be very valuable and fill an important knowledge gap on emerging markets (Khan et al.).

AUTHOR CONTRIBUTIONS

MJ and TY have jointly designed the research question, prepared the manuscript and revised it for important intellectual content.

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Growth of Global Health Spending Share in Low and Middle Income Countries

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HISTORICAL PATTERNS OF GLOBAL HEALTH SPENDING

Over the past century medical technology has provided bold gains extending human longevity for almost several decades in most welfare economies worldwide. These public health victories came at the cost of huge increase in health spending. The USA, the largest health care market where total health expenditure (THE) grew from 4% of GDP to 15%, may serve as an example of such changes. The secular trend consisting of rising wages and incomes constitutes major factor in the rising resources dedicated to the medical care. Business cycle booms and recessions affected health care spending slowly and with a significant lag. In this sense health expenditures should not be compared to short term, quarterly or yearly fluctuations in Gross Domestic Product (GDP) but correlates well to "smoothed" income over the previous 3–6 years (Getzen, 1990).

Growth of health expenditure is driven by several underlying issues: population birth rates, per-capita income, inflation and so called "excess growth" that is mostly explained by medical technology advances or increased patient demand for services. This "excess growth" is responsible for raising the share of health care in national GDP, and thus challenging fiscal sustainability. Evidence of excess growth is seen in health insurance premiums that persistently rise faster than tax revenues or wages. Isolated excess cost growth was the key underlying reason for the surmountable surge in health care costs visible in the United States since the late 1950s. Unlike the contemporary post WWII era, previous historical records testify of stable medical costs of about 4% of GDP from 1929 to the late 1950s. U.S. Census records of employment in clinical medicine and published consumer expenditure evidence from 1850–1950 show that these costs were mostly keeping pace with wages. If they were slightly exceeding wages it was only about 0.5% annually thus it took more than a century for them to double, much slower than the quadrupling from 1960 to 2000 (Getzen, 2000). Major causes of such a sudden rise in health expenditures were huge economic development, distinctively extended longevity, control of contagious diseases, rising availability of income used to fund research in medicine, effective financing instruments, and ultimately significant discoveries in medical technologies that supported public willingness for further investment into potential novel biological drugs, implants, robotic surgery, radiation therapy, organ transplants, and other wonder technologies (Getzen, 2014).

With several decades delay, due to dissemination of knowledge and improved societal welfare across the globe, similar developments began at the far smaller scale in a large number of low and middle income world economies. Among 160 such nations in the beginning of 1990s long term trends have revealed 16 countries which made greater investments in health care and its core outcomes than most comparable nations. These countries were described by Goldman-Sachs as the world's leading emerging markets. They are listed under the acronyms BRICS (Brazil, Russia, India, China, South Africa) and Next Eleven (N-11: Bangladesh, Egypt, Indonesia, Iran, South Korea, Mexico, Nigeria, Pakistan, the Philippines, Turkey, and Vietnam). This ongoing evolution will most

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likely shape the appearance of global demand and supply of medical services in XXI century and we believe that therefore it deserves closer examination.

GROWTH OF HEALTH CARE SPENDING IN LOW AND MIDDLE INCOME COUNTRIES SINCE 1995

The last two decades have been particularly dynamic due to ending the Cold War and accelerated pace of globalization. Contemporary evolution was promising for most nations with average world THE rising from 5.7 to 6.8% GDP [a 19.3% gain or approximately 1% yearly increase over 19 years (**Table 1**)]. Since 1995 World Health Organization (WHO) has established and disseminated National Health Accounts (NHA) system worldwide. These efforts allowed reliable international comparison of financial flows among national health systems with diverse historical legacies. The World Bank (WB) introduced the measure of gross national income (GNI) classification of countries in 1987 with their Atlas method and GNI per capita indexed in US$ currency (World Bank Income Groups, 2015). Availability of national income per capita strongly influences health expenditure. The correlation is straightforward with a secular trend visible in long time horizons in most world regions. We applied historical lists of WB income classification to reveal patterns in global health spending. Participation of 160 low and middle income countries (as defined by WB in 1995) in global health spending (in million const. 2005 $US) was 10.7%. Nineteen years later the world was a much different place. Global welfare of nations recorded bold increases while 23 countries crossed the WB threshold for high income economies. The remaining 137 low and middle income countries (as defined by WB in 2013) were now spending 14.6% of global THE expressed in millions of constant 2005 $US. The landscape of national medical spending has evolved in favor of developing regions. The 160 countries classified as low and middle by WB in 1995 grew from 26.1% of global THE in 1995 to 39.7% in 2013. While high income economies still dominate the global landscape of medical spending, the growth of emerging economies has reduced their share of the total.

CAUSES OF CHANGES AND LEADERSHIP OF BRICS + NEXT-11 EMERGING NATIONS

Jim O'Neil's grouping of BRICs was driven primarily designating those whose nominal and purchase power parity (PPP) adjusted GDP growth rates significantly outpaced those of most OECD nations before and during the worldwide economic recession. Similar ongoing development characterizes another group, identified by Goldman-Sachs' as the "Next Eleven." Profound changes with deep and lasting impact to the global demand for and provision of healthcare services and associated expenditure have occurred. Rapid expansion of civil middle class in most of these societies has been a major underlying factor (Jakovljevic, 2015). Substantial gains in overall welfare are reflected in the expansion of health insurance coverage and diversity of medical services provided. Growth of purchasing power effectively improved affordability of advanced medical care that remains out-of-pocket expense. We witness continuing movement of global growth in health care markets from the established mature economies toward the emerging ones. Slower economic growth in most saturated high-income markets is a contributing factor. Consumer demand for medical services remains larger in traditional wealthy countries, but their share has been decreasing steadily for at least two decades.

Total amount of health care spending among BRICS and Next-11 nations became approximately six fold stronger since 1995. Share of Global Health Spending (million current US$) of these emerging nations grew almost two and a half times. This pace of development is far faster compared to that of vast majority of remaining low and middle income countries across the globe. If we observe per capita health spending it appears that general government expenditure on health and private expenditure is consistently stronger among BRICS compared to N-11. Such a historical trend was actually present prior to 1990s and spending differentials continued to exist as paths diverted even further in recent years. Out-of-pocket (OOP) expenditure on health is a significant outlier in this regard. Although both country group averages were similar at the start, N-11 OOP spending soon exceeded BRICs. These facts indicate better success rates among the BRICs in terms of reimbursement policies and insurance coverage over the past 20 years (Jakovljevic, 2014).

PROSPECTS FOR THE FUTURE

Observation of health spending trends over 20 years is still insufficient to understand a "medical transformation" taking place in major national health systems worldwide. Limitations to our judgment might be imposed by reliability and comparability of large international datasets as well (Rayne, 2013). Nevertheless contemporary transformation of global health spending lays grounds for some forecasts on likely scenarios for the future. Low and middle income countries are likely to become more relevant contributor to the global health care market in the long run. Minor proportion of these countries will likely become high income economies over the next decade. Vast majority of them will continue to experience serious obstacles to the fiscal feasibility of their national health systems. Crucial challenges will remain population aging, prosperity disease and rapid urbanization leaving vulnerable rural areas. Universal health insurance coverage will still be a distant policy target for most of these governments with the notable exception of Russian Federation (Jakovljevic et al., in press). Large out of pocket expenses and informal payments will leave ordinary citizens, living close to the poverty line, vulnerable to the illness-induced catastrophic household expenditure (McIntyre et al., 2006). In some world regions with still young populations, communicable diseases control and satisfactory maternal and neonatal medical care provision shall still be a long way ahead (Barik and Thorat, 2015). Regardless of all the aforementioned weaknesses of developing world regions, it appears that most successful among these nations will become even more important players in global health arena. Heavily domination of People's Republic

TABLE 1 | Transformation of Global Total Health Expenditure (THE) 1995–2013.

		Top tier emerging markets (BRICS + Next-11)	Low and middle income countries as of 1995	Low and middle income countries as of 2013	WORLD (total amount of all national THE)
Total number of countries observed in 1995 and 2013*, **		16	160	137	192
Share of global health spending % (million constant 2005 $US)	1995	N/A****	10.7	7.0	≈100
	2013	N/A****	19.5	14.6	≈100
Share of global health spending % (million current US$)	1995	7.1	11.8	8.5	≈100
	2013	17.9	24.5	19.3	≈100
Share of global health spending % (million current PPP international $US)	1995	16.2	26.1	20.3	≈100
	2013	26.2	39.7	32.7	≈100
THE (% of GDP) M ± SD (Min-Max)	1995	4.2 ± 1.4 (2.0–7.4)	5.5 ± 2.4 (2.0–15.8)	5.4 ± 2.4 (2.0–5.8)	5.7 ± 2.4 (2.0–15.8)
	2013	5.6 ± 2.0 (2.8–9.7)	6.4 ± 2.6 (1.3–19.7)	6.4 ± 2.7(1.3–19.7)	6.8 ± 2.9 (1.3–19.7)
THE (% of GDP) percentage point increase 1995–2013		33.3%	16.4%	18.5%	19.3%

Table based on WHO National Health Accounts data 1995–2013; Classification based on World Bank Historical Lists of Income level country groups 1995/2013 based on GNI per capita in US$ (Atlas methodology); Top tier Emerging Markets definition adopted based on Goldman-Sachs acronyms BRICs and Next-11.

**WB Note: Income classifications are set each year on July 1 for all World Bank member economies, and all other economies with populations of more than 30,000. These official analytical classifications are fixed during the World Bank's fiscal year (ending on June 30), thus economies remain in the categories in which they are classified irrespective of any revisions to their per capita income data. The historical classifications used are as published on July 1 of each fiscal year.*

***Total of 13 countries/legal entities were not classified according to WB Income groups while three countries ceased to exist in 1995. In 2013 there were two of such non-classified entities listed together with five countries that ceased to exist.*

****For a total of 18 countries inclusive of Japan 2013 data are still not released officially therefore closest year available (2012 data in most cases) was used. Joint total health expenditure of these countries excluding Japan remains significantly below 1% of global THE.*

*****Among the BRICS and Next–11 emerging markets THE data expressed in terms of constant 2005 $US are lacking for Russian Federation and Pakistan for the entire 19 years long observation period and therefore inclusion of this indicator among the emerging markets was omitted entirely due to absence of data for two large nations.*

of China (He and Meng, 2016) followed by India in medical spending worldwide will exceed that of all other emerging markets combined. As we approach 2050 it is highly likely that financing of health care in top tier emerging nations will converge toward OECD average in terms of its effectiveness and affordability of medical care to the ordinary citizen (Jakovljevic, 2016). Major imperatives for national policy makers shall remain how to achieve universal health coverage, what services would be covered by basic insurance package and at what cost. Future research in the field should primarily be focused on key causes of out-of-pocket medical spending growth, deepening social gap among the rich and poor communities leading to health inequalities and effectiveness of contemporary policies in low and middle income countries.

DATA REPORT METHODOLOGY

Public data sources used were WHO issued Global Health Expenditure Database relying on NHA records: http://apps.who.int/nha/database/Select/Indicators/en and World Bank (WB) Income Groups; Historical country classifications based on Atlas method: http://data.worldbank.org/about/country-and-lending-groups. Filters applied to these extensive data sources were indicators referring to the national level and Global Total Health Expenditure (THE) expressed in following units: million constant 2005 $US, million current US$, million current PPP international $US and THE percentage share of national Gross Domestic Product available (GDP). Data were acquired based on reported values to the WHO and WB by the national authorities as well as independent assessments and calculations provided by WHO and WB and officially released in respective years. Readers are free to access and reuse these publicly available data at the links provided above.

AUTHOR CONTRIBUTIONS

MJ and TG have jointly developed the research questions, study design, did all the calculations and prepared manuscript for this Data report. Therefore, they share the first authorship in this paper.

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PERSPECTIVE
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Economic Evaluation in Stratified Medicine: Methodological Issues and Challenges

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Background: Stratified Medicine (SM) is becoming a practical reality with the targeting of medicines by using a biomarker or genetic-based diagnostic to identify the eligible patient sub-population. Like any healthcare intervention, SM interventions have costs and consequences that must be considered by reimbursement authorities with limited resources. Methodological standards and guidelines exist for economic evaluations in clinical pharmacology and are an important component for health technology assessments (HTAs) in many countries. However, these guidelines have initially been developed for traditional pharmaceuticals and not for complex interventions with multiple components. This raises the issue as to whether these guidelines are adequate to SM interventions or whether new specific guidance and methodology is needed to avoid inconsistencies and contradictory findings when assessing economic value in SM.

Objective: This article describes specific methodological challenges when conducting health economic (HE) evaluations for SM interventions and outlines potential modifications necessary to existing evaluation guidelines /principles that would promote consistent economic evaluations for SM.

Results/Conclusions: Specific methodological aspects for SM comprise considerations on the choice of comparator, measuring effectiveness and outcomes, appropriate modeling structure and the scope of sensitivity analyses. Although current HE methodology can be applied for SM, greater complexity requires further methodology development and modifications in the guidelines.

Keywords: stratified medicine, health technology assessments, guidelines, reimbursement mechanisms, reimbursement, biomarkers

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INTRODUCTION

The concept of "Stratified Medicine"(SM) is becoming a practical reality with the targeting of medicines by using a biomarker or genetic-based diagnostic to identify the eligible patient sub-population (Payne and Annemans, 2013). The quantity of biomarkers, prognostic, and diagnostic tests available for patients has increased significantly over the last decade and SM interventions are increasingly being developed and used in clinical care. In the SM concept, subgroups of responders are selected or identified based on risk of disease or response to therapy, with the notion to improve treatment outcomes in these subgroups by increasing efficacy and/or reducing toxicity.

This stratification of the population by using diagnostic tests or techniques is intended to reduce the use of ineffective or unsafe drugs, which should translate into improved health outcomes for patients and more efficient use of health care resources. However, there is much debate and uncertainty on which SM tests provide economic value and how to balance the need for innovative new technologies with affordability. Decision makers and stakeholders need information on which tests provide added value in order to make appropriate decisions about where to invest efforts in development and adoption (Phillips et al., 2014). A number of analysts have observed that the promise of SM is yet to be realized, partly due to the lack of sufficiently robust clinical and economic evidence based to support the widespread use in clinical practice (Faulkner et al., 2012; Berger and Olson, 2013; The Academy of Medical Sciences, 2013; Phillips et al., 2014; Rogowski et al., 2014). Several published systematic reviews had suggested there are limitations in the quantity and quality of economic evaluations of examples of targeted therapies, imposed by weak clinical and economic evidence base (Vegter et al., 2010; Wong et al., 2010; Hatz et al., 2014). Annemans et al. as well as Buchanan et al explored methodological challenges of conducting economic evaluations of targeted interventions, and outlined new measurement issues for traditional cost-effectiveness analysis (CEA) when adding a test or sequence of tests into the clinical car pathway (Annemans et al., 2013; Buchanan et al., 2013). Furthermore, there is uncertainty in methods to be used with testing of multiple biomarkers or clinical applications based on whole exome or genome sequencings. In addition, challenges arise if the economic evaluation of SM interventions is understood as an evaluation of the benefits, harms and cost-effectiveness at the individual patient preference level; (Basu, 2011; Rogowski et al., 2014) it should rather be conceived as applying to subpopulations as a whole.

Methodological standards and guidelines exist for economic evaluations in clinical pharmacology and are an important component of programs for health technology assessment (HTAs) in many countries. However, these guidelines have initially been developed for traditional pharmaceuticals and not for complex interventions with multiple components. This raises the issue as to whether these standards and guidelines are adequate to address more targeted approaches to therapy or whether new specific guidance and methodology is needed to avoid inconsistencies and contradictory findings when assessing economic value in SM.

This article addresses key methodological issues and challenges when conducting health economic evaluations for SM interventions and outlines potential modifications necessary to existing evaluation guidelines and principles that would promote consistent economic evaluations for decision making in SM. Utilizing a set of criteria represented by the guidelines for cost-effectiveness (such as, ISPOR, NICE)[1,2] we identified various aspects of the criteria/guidelines which require specific attention/modification for SM interventions.

SPECIFIC METHODOLOGICAL ASPECTS IN SM

While the basic framework for economic evaluations of SM interventions is similar to traditional clinical pharmacology some specific issues and challenges can be identified and assessed based on economic evaluation checklists[2] (Huseruau et al., 2013; see **Table 1**).

PERSPECTIVE AND TARGET AUDIENCE

Health Economic evaluations can be performed from the perspective of the society and the national third party payer according to country-specific economic guidelines in health technology assessments. From a methodological point of view, the societal perspective should be preferred over the national third party payer perspective, especially for SM, which requires a more system wide (holistic) approach to perceive the full health- and economic- value taking into considerations costs and long-term benefits having less adverse therapies target toward those who benefit most. However, in practice most economic analyses of SM interventions are performed from a third party perspective, since there is no longitudinal accounting in many healthcare systems in EU and the US which would enable payers to capture long-term cost savings from near-term testing. In addition, pharmaceuticals and diagnostics are considered under separate appraisal and payment processes in many healthcare systems. Only NICE (UK) has so far established a Diagnostic Assessment program (DAP) which carries out cost-effectiveness assessments of selected diagnostics (Bücheler et al., 2014). Funding silos may lead to different payer perspectives, e.g., those who pay for drugs vs. those pay for diagnostic requiring different questions. Hence, the defined perspective which determines the relevant cost and benefits relates much to the discussion on the target audience. For instance, in hospital setting, diagnostic testing is covered by the fee-based DRG system in several EU countries (e.g., Germany, France) or on budget-based systems (e.g., UK, Spain) where a global budget is allocated to local budget holders for payment processes. Further specification of what defines a third party payer, a clear understanding of target audience and broadening to societal perspectives will increase relevance of policy decision making and is useful to identify their evidence needs and incentives to adopt a new technology when proven valuable.

TARGET POPULATION AND COMPARATORS

SM interventions may accelerate the evolution and development of clinical treatment pathways which makes the specification of target populations groups a challenge. Technological advances in genetic sequencing and identification of biomarkers have made it feasible to test multiple biomarkers to inform treatment

[1]Pharmacoeconomic Guidelines Around The World, www.Ispor.org/PEguidelines/index.asp

[2]National Institute for Health and Clinical Excellence. The guideline manual—assessing cost effectiveness, https://www.nice.org.uk/guidelinemanual/7-assessing-cost-effective

TABLE 1 | Summary of methodological issues in economic evaluations of SM interventions.

Statements	Guidelines	Issues /challenges	Possible solutions/new guidance
Perspectives and Target Audience	Societal or third party	Societal perspective is preferred (ideally), although third-party is most used. Funding silos may lead to different payer perspectives, i.e., those paying for drugs vs. those paying for diagnostics.	Clear understanding of target audience and further specification of what defines a third-party-payer will increase relevance for decision-making.
Target Population	Clear description of target population and subgroups analyzed.	Testing reveals heterogeneity and creates multiple subgroups & treatment pathways which may challenge specification of target population groups. Identifying the exact place of a test within care pathway is critical.	Specification of target populations groups according testing rules will guide the selection of relevant comparator and may reduce variability of evaluation findings.
Comparators	Standard care being most widely used.	Multiple potential test designs may exist and makes defining testing interventions a challenge. The sequence of testing and the inclusion of a "no test" comparator is often variable and can lead to different coverage recommendations.	An additional comparison should be considered by splitting the SM treatment. A comparison of the "test first with the new compound/drug" vs. "treat all with new compound/drug" vs. "standard care" is crucial for payers.
Measuring Effectiveness	Systematic review; incorporate real-world factors that modify effectiveness which also may include indirect comparisons.	Estimates of effectiveness relies on various data sources and is more sensitive to adherence and compliance effects.	Strict recommendations that compliance and adherence must be accounted for in sensitivity analysis.
Valuing outcomes	Use appropriate preference-based measures to value differences between the intervention and alternatives (e.g., OALY).	Standard measures (e.g., QALY) have limited applicability and are focused on average population rather than individual/sub-population outcomes. Yet alternative metrics (e.g., personal utility) are underdeveloped and alternative approaches (e.g., cost-benefit analysis) are underused.	Recommendation to incorporate local utilization patterns to improve behavioral assumptions. Further research is needed for quantifying non-health outcomes in evaluations.
Costs and resource use	Measure and value resources that are relevant to study perspective.	Establishing and projecting the additional costs due to testing is challenging.	National price lists of diagnostic test (unit) costs would help avoid reporting variations in costs.
Modeling		Inclusion of sensitivity/specificity and especially false- negative and false- positive considerations will increase structural complexity to establish the relationship between test results and treatment changes and outcomes.	An iterative approach to evaluation is recommended (via early modeling) to identify the need for further evidence generation in alignment with HTA requirements.
Uncertainty	Sensitivity analyses	Extra sensitivity analyses are required for sensitivity/specificity and cost of the test.	Scenario analyses may be more important in SM; especially when considering test characteristics and potential evidence gaps.

choices, or use algorithms to target screening interval strategies. Also next generation sequencing and whole genome or exome sequencing may allow identifying mutations in multiple genes for multiple conditions in parallel. As a consequence, the number of pathways to include into a model-based economic evaluation may grow exponentially with the number of biomarkers used for stratification (Rogowski et al., 2014). A recent evaluation of a gene recurrence score assay enumerated 1000 potential clinical strategies from 24 clinical testing pathways and 12 unique risk categories based on two tests with two chemotherapeutic regimes (Paulden et al., 2011).In this context it is important to consider that targeted subgroup-specific treatment strategies are clinically plausible and implementable. Identifying the exact place of a SM test within care pathways is crucial and may change the cost-effectiveness outcomes of the intervention (e.g., different results of HER2 testing of trastuzumab in breast cancer patients with adjuvant vs. metastatic settings). This will guide the selection of a relevant comparator - which is usually current standard care in economic evaluations conducted for HTA's -, and determines the appropriate clinical testing strategies to be modeled. Unlike traditional interventions, SM interventions should have at least two comparators: comparisons of the "test first with the new compound/drug" vs. "treat all with new compound/drug" and vs. "standard of care" are recommended although various published cost-effectiveness studies to date have used only the "treat all" strategy as a comparator and ignored the "standard of care" (treat-none with new drug) option. From payers' perspectives, comparisons of the SM approach with "standard care" is often crucial (Merlin et al., 2013). For example, a cost-effectiveness analysis of KRAS testing with cetuximab in colorectal cancer performed by Shiroiwas et al in Japan considered three treatment strategies and outlined that the test-first strategy with cetuximab was dominant vs treat-all-with cetuximab but perhaps not cost-effective vs. the treat-none-with cetuximab strategy (Shiroiwa et al., 2010).

MEASURING EFFECTIVENESS AND OUTCOMES

There is general acknowledgement that the quality of effectiveness data for SM interventions is often weak and

challenging to incorporate into standard health economic analyses (Goddard et al., 2012). Effectiveness of SM intervention is a function of both the efficacy of drug and the accuracy of the test and includes considerations on false-positive and false-negative outcomes of testing. One reason why there are relatively few assessments of economic value is that many diagnostic tests do not have widely accepted evidence of clinical utility, i.e., linking test use to patient outcomes. The issues surrounding the definition and measurement of clinical utility are major areas of debate for all kinds of diagnostic testing technologies. Currently, regulators do not require proof of clinical efficacy for a test or even sensitivity/specificity specification which could be used to estimate model effectiveness. Furthermore, data on the effectiveness of laboratory-developed tests is often even more limited due to the ad hoc nature of their development (Faulkner et al., 2012).

There are differences in the evidence generation for the SM-development scenarios. For a test developed in association with a drug (co-development), the economic analysis might be based on randomized controlled trials (RCTs), where the diagnostic test was included in the clinical studies of the drug's efficacy; i.e., sensitivity/specificity data of the test as well as efficacy data of the drug/diagnostic combination are included in the overall outcomes of the trial, which can produce direct evidence of the clinical utility of the test. For a stand-alone test, this is much harder to achieve as RCT's are often not feasible because of ethical reasons, shift to multi-therapeutic regimes, and lack of resources or small patient populations. Real-life data generation is increasingly needed in this case perhaps via prospective cohort studies, observational studies or chart review, as payers might seek additional post-market evidence for clinical utility. It is becoming increasingly apparent that new methods will have to evolve to ensure efficient evidence generation reflecting realistic expectations around evidence standards (thresholds) aligned between stakeholders given the pace of genomic discovery and the associated costs. This implies that health economists and decision makers must be prepared to accept data that have come from different settings (case-control and observational) outside RCT's. Potential alternative solutions may involve the use of novel trial designs, such as adaptive clinical trials.

Furthermore it is to consider, that the overall effectiveness of the SM intervention doesn't only rely on the development of new treatment modalities, but also on providers and patients behavior when using diagnostic-based therapies. How patients are managed in practice is important and will influence the adoption of new technologies (e.g., examples warfarin PGx testing and TMPT testing for patient taking 6-mercaptopurine or allopurinol). SM underscores the need for additional information on patients and physicians response to diagnosis and will require post-approval data collection. Accounting for compliance and adherence (e.g., by use of local utilization pattern to improve behavioral assumptions) will reduce variability of findings and should be incorporated into sensitivity analyses. The recently drafted guidelines for preparing assessment reports for the Medical Services Advisory Committee- Service Type: Investigative (version 1.3) in Australia specifically request a supplementary analysis of the non-health related impacts of diagnostic testing [3].

The impact of an intervention on health status (e.g., cost per QALY's or life year saved) is the preferred outcome measure for several EU governmental advisory bodies (e.g., NICE, SMC, TLV, or CRM) as recommended in the health economic guidelines. However, for third party payers such standard measures may have limited applicability in assessing SM interventions rather requesting cost-offsets and budget impact information to address affordability issues in various health care systems. Methodological issues regarding the valuation of health outcomes for SM, particular the quality-adjustment of utility component in QALYs, are similar to those faced by other health care intervention. There is an ongoing discussion in academia how standard value assessment metrics can be expanded by personal utility data, as current metrics is focussed on average population based preferences rather than individual patient preference valuation. Capturing information on personal utility may be important, because additional benefits may arise from a patient's increased certainty about the likelihood of successful treatment—the "value of knowing" (although ultimately always to be aggregated to population levels). This might affect adherence and thereby patient outcomes. Yet, alternative metrics (e.g., personal utility) are underdeveloped or alternative approaches underused (e.g., state of choice, willingness to pay) in policy decision making (Buchanan et al., 2013). Further, research in this area is required to provide guidance for quantifying and incorporating non-health outcomes in economic evaluations.

ESTIMATE RESOURCE USE AND COST

The costing methodology is straightforward and there may not be methodological differences with the costing methodology in health economic evaluations for traditional pharmaceuticals. Cost calculations in economic evaluation require total average costs (including capital and allocated overhead costs) derived from resources consumed and unit cost measures based on economic (opportunity costs; Conti et al., 2010) Yet, establishing and projecting the additional costs due to testing may provide challenges for analysts. A broad range of direct testing costs may include additional clinic visits, sample collection and testing, the cost of subsequent treatment and genetic counseling as well as re-testing considerations. However, the complete estimation of costs relates to the type of cost items and primarily not a methods issue, beyond the perspective chosen.

Often, there are challenges to identify the unit cost of tests which may depend on number of tests performed or be part of platform diagnostics with multiple applications. Unlike pharmaceutical, there is no national list of available genomic or other tests, as often each laboratory is free to set their own price (or charge) to clinicians requesting the test and negotiations

[3]www.health.gov.au/internet/hta/publishing.nsf - technical guidelines for preparing assessments reports for the Medical Services Advisory Committee - Service Type: Investigative (version 1.3). Draft for public consultation 2015; www.pbs.gov.au/pbac-guidelines/product type 4- hybrid technologies and co-dependent technologies, Version 5.0, March 2016

between suppliers and users often occur at local levels. Large variation in the unit cost of these tests can affect the findings of an economic evaluation and increase uncertainty in the estimated relative cost-effectiveness of a test. Sensitivity analysis should address robust cost estimates relevant to diagnostic testing, yet national price lists of diagnostic test costs would help avoid the currently reported variation in costs (NHS-UK Genetic Testing Network, 2011). One costing question is related to the perspective. If we assume that a test is performed in an inpatient setting, then from a payer perspective, only the diagnosed related group (DRG), including all inpatient resource utilization, needs to be applied and the hospital must take care of being able to finance the test within the DRG. However, from a societal perspective, the cost of the test should be added to the DRG assuming that the current DRG reflects an opportunity cost to the hospitalization. Therefore, micro-costing approach would be most appropriate in order to capture the real/true costs.

MODELING AND DEALING WITH UNCERTAINTY

The existing modeling techniques are appropriate and can be applied for cost-effectiveness models in SM, given that special issues are taken into consideration. The inclusion of sensitivity/specificity and especially false negatives and false positives, requires additional structural complexity in order to make the link between the test and the medication and the subsequent clinical and economic outcomes. Another issue is dealing with gaps in the evidence base, especially for stand-alone tests. Information on treatment patterns, its costs and outcomes, are often lacking, especially for false positive and false negative patients. There is a need to identify best practices for economic modeling including approaches which address these evidence gaps in a manner that is both acceptable to payers and feasible for test manufactures. Thus, extrapolation methods are required in order to extrapolate the short-term sensitivity/specificity data to long-term economic outcomes, as shown in a recent paper by Fugel and Nuijten (2014) Given that health economists will increasingly be faced with poor quality effectiveness and cost data early modeling approaches will become more common in early development stages to better understand the HE value of new technologies. An iterative approach could then be employed that systematically and explicitly considers the need for further evidence to reduce decision uncertainty, and is consistent with an approach to HTAs known as constructive technology assessment (Sculpher et al., 1997; Shabaruddin et al., 2015).

Sensitivity analyses aim at providing information on the degree of uncertainty in economic evaluations and it is currently the most widely applied method of dealing with uncertainty in economic evaluations (Critchfield et al., 1986). Because of the more complex structure, lack of data, and extrapolation, the uncertainty level in the SM model is higher than in a comparable model for traditional pharmaceuticals. In addition, the efficacy of the stand-alone test is often based on a small sample size leading to extra uncertainty, thus, extra sensitivity analyses are required for sensitivity/specificity and cost of the test. In SM, there are more gaps in information and the number of possible assumptions increases with the number of parameters added which may cause interpretation problems. A practical way to overcome this problem is the use of scenarios, in which several factors are set to reflect a specific situation, such as the best-case and worst-case scenarios (Vegter et al., 2008). Hence, for the SM approach, scenario analyses may be more important than sensitivity analyses, especially when considering test characteristics and potential evidence gaps, because there are rather issues on the quality of the data than the distribution of the variable. The structural uncertainty of the assumptions due to gaps in data is larger than the uncertainty due to statistical distribution. Specific scenario analyses in SM, which are not relevant in traditional pharmaceuticals, may be required for a range of estimates in turn, but it may also be possible to perform a "multi-scenario" analysis, where the effect of simultaneous changes in different assumptions is examined on the outcomes of the study.

A probabilistic sensitivity analysis (PSA) permits the analyst to assign a range and distribution to input variables (Doubilet et al., 1985). The results of a PSA are presented in a cost-effectiveness acceptability curve, which displays the probability that a new treatment is the most cost-effective treatment considered in the analysis at a range of different threshold ICER values representing what society might be willing to pay to gain one e.g., QALY. However, the results of a PSA for SM may need to be considered with more prudence than with traditional pharmaceuticals. Gaps in information and subsequent assumptions cannot be captured by a statistical distribution and therefore this type of uncertainty cannot be included fully in a PSA.

CONCLUSION AND FUTURE RESEARCH

In general, we can conclude that current health economics methodology can be applied for SM, although various aspects of the guidelines require specific attention for stratified medicine approaches. These aspects comprise considerations on the choice of comparator, measuring effectiveness and outcomes, appropriate modeling structure and the scope of sensitivity analyses. Many of these aspects refer to a lack of evidence on testing heterogeneity and the quality of effectiveness data. Notably, the level of economic evidence for SM interventions may differ from what is generally experienced with traditional pharmaceuticals, thus stressing the need to identify best practice for economic modeling including approaches which address evidence gaps in a manner that is both acceptable for payers and feasible for test manufactures. This may involve the use of novel trial designs, such as adaptive clinical trials, evidence from observational studies, and the use of coverage-with-evidence development and real-world evidence collection for both drugs and diagnostics. However, the evaluations of both test-treatment interventions (companion diagnostic) and stand-alone diagnostics is occurring in a complex legal, regulatory and reimbursement environment which does not currently fit with SM approaches. New incentive structures are needed to increase the efficiency of evidence generation. Previous suggestions for

economic incentives for evidence generation include value-based price flexibility, intellectual property protection from evidence generated and public investment to complement the effort of payers and manufactures (Towse and Garrison, 2013).

SM underscores the need for additional information on patients and physicians response to diagnosis which is not readily available from clinical trials or administrative data sets. Accounting for compliance and adherence (e.g., by the use of local utilization pattern to improve behavioral assumptions) will provide insight into variability of findings and should be incorporated into sensitivity analyses. Health economist may need to take new accountabilities when using observational research methods to perform additional value from utilization data to payers.

Incorporating complex genetic or genomic data into cost-effectiveness analyses is a challenge that will grow as next generation sequencing technologies enter clinical practice. While there is no need to develop completely new tools, there are requirements for some refinement by including sensitivity and specificity consideration of the test as well as to address consequences of false-negative and false- positive test results on the value proposition. This may require further methodology development to address the increased complexity and the need for additional analyses associated with the testing component. Further research should also consider examining other approaches to measuring values for SM interventions. The specific aspects outlined in this article suggest there may be opportunities to improve current guidelines for economic evaluation of SM interventions.

AUTHOR CONTRIBUTIONS

HF initiated this methodology review, addressed issues through literature review, informal interviews and discussions with international experts and prepared final manuscript. MN participated in interviewing international experts, supported the results generation and provided critical comments to the final manuscript. MP and KR provided substantial commentary for the optimization of this methodology review and critically revised it for important intellectual content.

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ORIGINAL RESEARCH
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Analysis of Regional Variation in the Scope of Eligibility Defined by Ages in Children's Medical Expense Subsidy Program in Japan

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Children's medical expense subsidy programs are programs run by local governments that use public monies to reduce or eliminate the copayments for children's medical treatment including pharmaceutical cost (typically 20% for preschoolers and 30% thereafter). Currently, all prefectures and municipalities in Japan provide subsidies for infants' and children's medical expenses, but scope on ages of eligibility, income limits, and copayment requirements vary. The fact that these programs are run by local governments has given rise to differences in the costs borne by households with children, depending on the jurisdiction in which they live. Therefore, although it would be desirable to gain society's understanding of such variation, the factors have not been fully studied. This analysis investigates what factors could impact such variation. In it, we looked at 219 municipalities in the prefectures in the Kanto region, focusing on the gap from the average age eligibility of municipalities, which reflects the scope of eligibility. Neither a regression analysis using the instrumental variable method to account for simultaneous decision bias nor an ordered logit analysis with rank of coverage as an order variable revealed that differences in copayments by locale had any impact on the scope of age eligibility. Residents' income and the number of children tended to narrow scope of eligibility for subsidies, but the strength of local government finances were not a significant factor of influence. In designing these programs, local government bodies take into account the local population's ability to pay and the number of eligible people, but their awareness of the local government's financial condition seems to be scant. Local governments are currently moving to expand their children's medical expense subsidy programs, but in the future they will need to pay more attention to balancing an expanded scope of eligibility by ages with the maintenance of local government fiscal discipline. In addition, copayments have not been adequately linked to the expansion of eligibility, so it would be advisable to clearly demonstrate the reason for this limit in order to eliminate perceptions of unfairness.

Keywords: medical expense subsidy, regional variation, socio-economic factors, instrumental variables, ordered logit, co-payments, income limits

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INTRODUCTION

Background and Objectives

Under Japan's public health insurance system, copayments that the insured persons pay to the medical institutions and pharmacies for doctor visits and drugs are basically 30 and 20% for children before the age of compulsory schooling. Children's medical subsidy programs are those run by independent local governments which reduce or eliminate the copayments paid when children visiting medical institutions (20% for pre-compulsory education children, 30% thereafter) and are funded by the public funds of each municipality. With regard to this subsidy system in Japan, each prefecture sets their own scope by ages for coverage in children's medical expense subsidy at first. And second, based on the prefectural standard, each municipality within the prefecture sets the scope of the coverage by ages in addition to the prefectural scheme to extend the coverage for the residents. And within this scope of coverage, Children can basically enjoy their medical service at free of charge, even if it was rather tiny copayment. As a result, there exists variation of scope of coverage by ages depending on the municipalities.

Currently such programs are in place in all prefectures and municipalities, according to the FY2015 "Survey of Aid for Medical Expenses for Infants and Children" issued by the Equal Employment, Children and Families Bureau of the Ministry of Health, Labour and Welfare (MHLW). The survey shows that in the largest number of municipalities, aid is available "up to junior high school students" for both "inpatients" and "outpatients"; however, differences exist among the municipalities with respect to "age coverage," "existence or non-existence of income limits," and the "existence or non-existence of copayment."

Advantages cited in the past for the implementation of medical assistance programs include "elimination of unfairness in medical benefits due to economic disparities," "economic support for the child-rearing generation," and "reduction of aggravated cases due to refraining from visiting the doctors." In line with this context, in the United States, some researcher clearly shows that positive correlation between health status of children and socio-economic status (Case et al., 2002; Currie and Stabile, 2003; Condliffe and Link, 2008). Buchmueller et al. (2005) suggest that health coverage surely has effect to increase the number of outpatient visits, and Currie et al. (2008) shows to have this type of health subsidy system contribute to improve the health status.

On the other hand, disadvantages cited for this system include "encouraging competition among the municipalities for the child-rearing generation," "concerns about the possible increase of unnecessary hospital visits" (Bessho, 2011), and "concerns that families will think less about their children's health."

Out of a concern of the potential that the independent assistances by municipalities may encourage easygoing medical consultations, the national government has historically followed "measures to reduce the national health insurance" with respect to medical expenses increases in stemming from the assistance programs (Iwamoto, 2010).

Since the children's medical subsidy programs are basically locally-run programs, they also have given rise to variation in the costs borne by the child-rearing families depending on the local jurisdictions they live in. The factors driving these variation have not yet been fully examined, notwithstanding the desirability of gaining some degree of public understanding.

With that in mind, in this study, we focused on the variation of scope of coverage defined by ages and tried to address the factors that have (or do not have) significant effect to the coverage. This study examined the impact of various program designs and socio-economic factors of 219 municipalities in five prefectures of Kanto Area (Kanagawa, Saitama, Chiba, Tochigi, and Ibaraki), focusing in particular on the "the gap from the average age eligibility of the municipalities for subsidy" that reflects the scope of the children's medical subsidy programs. We look at medical subsidy for "outpatient" visits, where there is a greater variation among locales than for "inpatient treatment."

MATERIALS AND METHODS

Data Sources

We obtained information about, the "scope of coverage for subsidy defined by ages," "existence or non-existence of tiny copayments at the time of medical use," and the "existence or non-existence of income limits at the time of registration," that define the nature of eligibility and the scope for subsidy from the "Operational Status of Publicly Funded Programs for Medical Expenses for Infants and Children" issued by the Ministry of Health, Labour and Welfare: Maternal and Child Health Division of the Equal Employment/Children and Families Bureau (2015). This report is annually published and opened on the websites by Children and Families Bureau of the MHLW. This report gathers information about the current status of Children's Medical Expense Subsidy Program, that completely covers all municipalities in Japan and enough trustworthy. We also consulted the websites of each local municipality in addition to confirm the nature of their subsidy programs to be sure (in weeks 3 and 4 of July, 2016). But there was very few information difference between these two data resources besides the gap of investigation timing.

As for the socio-economic factors on each municipalities that might impact to the scope of coverage defined by ages, we gathered information from "Population by Age Groups" (Ministry of Internal Affairs and Communications, 2015a); "Population Ratios by Age Groups" (Ministry of Internal Affairs and Communications, 2015a); "Per-capita Medical Expenses" (Ministry of Health, Labour and Welfare, 2015); "Average Incomes" (prepared by author from Ministry of Internal Affairs and Communications, 2015b); and "Fiscal Capability Index" (Ministry of Internal Affairs and Communications, 2015b).

Background of Hypothesis

In this study, we assumed that the scope of coverage defined by ages for children's medical subsidy is decided by each local government based on the prefectural-level operations of the program. And that is the reason why the scope of coverage defined by ages has variation among municipalities. It is also natural to assume that "the gap from the average age eligibility of the municipalities for subsidy" has variation

among municipalities and this is largely affected by not only programmatic factors but socio-economic factors.

Based on these ideas, we established the following working hypotheses. As for setting tiny copayments required for subsidy, leaving tiny copayments in place to a certain degree, rather than eliminating them altogether, holds back excessive doctor visits and reduces fiscal burden, freeing up additional fiscal resources which could enable expansion of age eligibility requirements. On the other hand, if a tiny copayment is the proxy expressing a strict stance on the part of local government leaders toward medical subsidy, requiring copayments at the time of medical use has a negative effect on age eligibility. So the expected *a priori* direction of impact on "the gap from the average age eligibility of the municipalities for subsidy" is not so clear in advance.

As for setting income limits for registration of subsidy, restricting the subsidy only to those with incomes under certain limit narrows eligibility with the effect of lightening the cost to the local government, thereby freeing up additional fiscal resources and potentially enabling expansion of scope of age eligibility requirements. On the other hand, if setting the income limit is the proxy expressing a strict stance on the part of local government leaders toward medical subsidy, income limits have a negative effect on age eligibility. Therefore, the expected *a priori* direction of impact is not also clear.

With regard to socio-economic factors, we considered following four factors [i.e., Average income of local residents, Local government fiscal strength, Per capita resident medical expense, and Child (ages 0–14) population and its ratio] that might have some effect to the gap from the average age eligibility of the municipalities for subsidy.

As for the case with average income of local residents, local governments with residents of higher average incomes, meaning the residents have greater ability to pay for medical services themselves, will establish narrower scope for medical subsidy programs for children than the other municipalities. To the contrary, local governments in strong fiscal health can take on additional costs, allowing them to provide expanded government services to their residents, and will thus establish broader scope for medical subsidy programs for children than the other areas. And local governments with higher per capita medical expenses will be concerned about fiscal impact and as such establish narrower scope for medical subsidy programs for children than the others. Of course the greater the absolute number of local children eligible for the program, and the greater the ratio of children in the total population, the greater the concern about the cost to the local government, which will lead to narrower scopes for children's medical subsidy programs than the other municipalities.

Method of Data Analysis

Based on hypotheses, we took as mainly explained variable the "the gap from the average age eligibility of the municipalities for subsidy" and performed a regression analysis with programmatic factors and socio-economic factors as explanatory variables. We first did an ordinary least-square (OLS) estimation with all programmatic factors and socio-economic factors as explanatory variables.

Looking at the distribution of "age limits for coverage" in medical subsidy programs for children, we note that the frequencies are concentrated at ages 12, 15, and 18. We therefore created an order variable with a value of 1 for the upper age of 12 as the narrow scope of coverage, a value of 2 for upper age of 15 as middle scope of coverage, and a value of 3 for upper age of 16 and older as wide scope of coverage and also conducted the ordered logit model estimation with this order variable.

When determining the applicable scope of ages to which subsidy is to be extended in comparison with the status of the other areas, other programmatic factors such as the "establishment of partial copayments" and "income limits" might be considered simultaneously. To deal with this problem, we use the instrumental variable method. In our case, it is required that the instrumental variables be related to the explanatory variables of "copayments" and "income limits," but not to factors impacting the "the gap from the average age eligibility of the municipalities for subsidy." After careful investigation of instrumental variable including endogenous test (Durbin-Wu Hausman Test) and weak correlation test (2Stage Least Square size of nominal 5% test), I found and adopted "Ibaraki(Prefecture) Dummy" as satisfying instrumental variable. It has significant correlation to both "Copayment" and "Income Limit" but does not have any relation to "the gap from the average age eligibility of all the municipalities" that is finally decided by each municipalities. Considering the heteroskedastic problem among cluster on prefecture, we adopted cluster robust regression. We also check the correlation among the variables in advance and investigate VIF (the Variance Inflation Factor) to avoid multicollinearity problem in our estimation.

RESULTS

The basic statistics for the dataset and variable names in the estimation are shown in **Table 1**. Although the dataset we built for this analysis was limited to the five prefectures in Kanto Area, in comparisons with nationwide data, the ratios of "existence or non-existence of partial copayment for subsidy" and "existence or non-existence of income limit for subsidy" were both nearly identical with those of the national data [Children and Families Bureau of the Ministry of Health, Labour and Welfare (2015)].This table shows that the rate of municipalities that is setting any copayment occupy just 40% and Income limit setting is 21% in Kanto Areas respectively. Population ratio of under14 years is now 12% in Kanto areas nearby Tokyo. The correlation among the variables used in the estimation model is summarized in **Table 2.** We can see the existence of strong correlation between financial status of local government and average household income of residents.

Table 3 shows the estimates from the regression model using "the gap from the average age eligibility of all the municipalities" and "order category on rank of coverage" as the explained variable and the programmatic factors and socio-economic factors of each local government as explanatory variables. In

TABLE 1 | Basic statistics of data set.

Variable	Obs	Mean	Std. dev.	Min	Max
DEPENDENT VARIABLES					
Gap from the Average Age eligibility: **GAPAVE**[a]	219	0.00	1.80	−6.05	4.94
Order Category on Rank of Coverage: **ODRCATG** (1,2,3)	219	2.04	0.52	1.00	3.00
INDEPENDENT VARIABLES					
Copayment setting for Subsidy: **COPAY** (No = 0/Yes = 1)	219	0.40	0.49	0.00	1.00
Income Limit setting for Subsidy: **INCMLIM** (No = 0/Yes = 1)	219	0.21	0.41	0.00	1.00
The Number of Population Under14Years :**POP014**	219	16273.67	39282.99	244	481532
Population Ratio Under14 Years: **RATIO014**	219	0.12	0.02	0.07	0.17
Financial Status of Local Government: **FINANIDX**	219	0.76	0.22	0.20	1.50
Medical Expenditure per Capita/year: **MEDEXP**[b]	219	293391.70	20618.55	237495.40	356550.90
Average Household Income: **AVEINCM**[c]	219	298.42	35.15	233.22	434.48
Saitama Prefecture Dummy: **SAITDUM** (No=0/Yes=1)	219	0.29	0.45	0.00	1.00
Chiba Prefecture Dummy: **CHIBADUM** (No=0/Yes=1)	219	0.25	0.43	0.00	1.00
Kanagawa Prefecture Dummy: **KANADUM** (No=0/Yes=1)	219	0.15	0.36	0.00	1.00
Tochighi Prefecture Dummy: **TOCHDUM** (No=0/Yes=1)	219	0.11	0.32	0.00	1.00
Ibaraki Prefecture Dummy: **IBARDUM** (No=0/Yes=1)	219	0.20	0.40	0.00	1.00

[a] *Average Age Eligibility of Municipalities = 15.05.*
[b] *1 Japanese Yen.*
[c] *10,000 Japanese Yen;*
1 dollar = 117.5 Yen in 2016 (in Average).

TABLE 2 | Correlation among variables.

(obs = 219)	GAPAV	COPAY	INCMLIM	POP014	RATIO014	FINANIDX	AVEINCM	MEDEXP
Gap from the Average Age eligibility: **GAPAV**	1							
Copayment setting for Subsidy: **COPAY**	0.1909	1						
Income Limit setting for Subsidy: **INCMLIM**	−0.5239	0.1666	1					
The Number of Population Under14Years : **POP014**	−0.3264	−0.065	0.1877	1				
Population Ratio Under14 Years: **RATIO014**	−0.1652	−0.0405	0.0459	0.2119	1			
Financial Status of Local Government: **FINANIDX**	−0.2407	−0.1695	0.0411	0.2813	0.6633	1		
Average Income: **AVEINCM**	−0.3858	−0.14	0.1907	0.4297	0.6337	0.7214	1	
Medical Expenditure per Capita/year: **MEDEXP**	−0.1921	−0.3486	0.0116	−0.0366	−0.4001	−0.1669	−0.0835	1

Table 3, model (1) and (2) are the results of simple OLS estimations performed without regard to simultaneity of system determination. Models (3) and (4) give the estimates from the ordered logit model we ran with the explained ordered variable. In these estimation, average household income (AVEINCM) and medical expenditure per capita (MEDEXP) was continuously statistically significant as negative effect to expanding scope of coverage. In simple OLS model, the number of population under 14 years old (POP014) was also significant, suggesting that the number of child in the municipalities might have effect to narrow the scope of coverage of subsidy for children.

Model (5) and (6) give the estimates employing the "Ibaraki prefecture Dummy" as instrumental variable. As previously described, we tried endogenous test and weak correlation test (Stock and Yogo, 2005) to check appropriateness of instrumental variable. In these estimations, not only AVEINCM and MEDEXP but also POP014 were significant with negative sign.

DISCUSSION AND CONCLUSION

Japan's overall population is already on the downward trend, with the number of aged increasing rapidly and the number of births dropping. Pushing forward with measures to deal with the declining birthrate is not only one of the pillars of government policy, but for local governments also an urgent challenge on which their continued existence depends. In this context, the topic of medical subsidy programs for children, as one element of child-rearing support, is a matter of high interest, but being managed by local governments, such programs differ in their eligibility details.

Our results indicate that for medical subsidy programs for children leaving in place some kind of copayments within the program was not a clear effect factor on the scope of age eligibility of subsidy. While such program designs might well have the effect of reducing doctor visits, not to mention easing the financial

TABLE 3 | Regression results on simple OLS model, Ordered logit and instrumental variable method.

(Number of Obs = 219)	Simple OLS regression		(Number of Obs = 219)	Ordered logit regression		(Number of Obs = 219)	Instrumental variable method	
	Dependent variable	Gap from the Average Age eligibility GAPAV		Dependent variable	Order Category on Rank of Coverage ODRCATG		Dependent variable	Gap from the Average Age eligibility GAPAV
	(1)	(2)		(3)	(4)		(5)	(6)
Copayment setting for subsidy	0.245		Copayment setting for Subsidy	0.389		Copayment setting for Subsidy	0.080	
COPAY	(1.06)		**COPAY**	(1.17)		**COPAY**	(0.30)	
Income Limit setting for subsidy		−1.9816***	Income limit setting for subsidy		−4.0310***	Income limit setting for subsidy		0.145
INCMLIM		(−6.43)	**INCMLIM**		(−5.44)	**INCMLIM**		(0.28)
The number of population under 14 Years	−0.00001***	−0.00000661***	The number of population under 14 years	−0.00000587	−0.00000309	The number of population under 14 years	−0.00000897***	−0.00000917***
POP014	(−3.85)	(−4.01)	**POP014**	(−1.26)	(−0.82)	**POP014**	(−8.58)	(−5.54)
Population ratio undue 14 Years	−2.6702	−6.0157	Population ratio undue 14 Years	−5.311	−10.4960	Population ratio under 14 Years		
RATIO014	(−0.34)	(−0.88)	**RATIO014**	(−0.40)	(−0.72)	**RATIO014**		
Financial status of Local Government	0.3467	−0.4004	Financial status of local government	0.3497	−0.5761	Financial status of local government	0.181	0.192
FINANIDX	(0.54)	(−0.70)	**FINANIDX**	(0.36)	(−0.54)	**FINANIDX**	(0.18)	(0.19)
Average household income:	−0.016***	−0.0093***	Average household income:	−0.0270***	−0.0219***	Average household income:	−0.017***	−0.017***
AVEINCM	(−3.90)	(−2.65)	**AVEINCM**	(−3.96)	(−2.84)	**AVEINCM**	(−3.52)	(−2.67)
Medical expenditure per Capita/year	−0.00002***	−0.0000209***	Medical expenditure per Capita/year	−0.0000248**	−0.0000326***	Medical expenditure per capita/year	−0.000019***	−0.000020***
MEDEXP	(−2.58)	(−3.77)	**MEDEXP**	(−2.50)	(−3.03)	**MEDEXP**	(−3.07)	(-2.44)
_cons	10.295***	10.483***				_cons	10.548***	10.908***
	(4.52)	(5.54)					(4.71)	(3.15)
F(6, 212)	11.34	22.85	Wald chi2(6)	47.94	59.78	Wald chi2(5)	316.98	387.37
Prob > F	0.00	0.00	Prob > chi2	0.00	0.00	Prob > chi2	0.00	0.00
R-squared	0.24	0.42	Pseudo R2	0.15	0.34	Pseudo R2	0.23	0.20
Root MSE	1.59	1.38	Log likelihood	−141.89	−111.32	Log likelihood	1.568	1.600
Mean VIF	1.93	1.88						

*In model (1) and (2): t value in parentheses: ***t < 0.01, **t < 0.05. HCSE, Heteroscedasticisty-consistent standard errors are used.*

*In model (3) and (4): z value in parentheses: ***z < 0.01, **z < 0.05.*

*In model (5) and (6): z value in parentheses: ***z < 0.01, **z < 0.05. Instrumental variable: Ibaraki Prefecture Dummy Cluster Robust Standard errors are used.*

burden on the local government, they appear to have little impact on expanding the scope of eligibility of the subsidy programs. If, as our estimates suggest, the establishment of copayments do not lead to any expansion of eligibility which would benefit residents even when keeping constant the income level of residents and local government fiscal status, local governments establishing such limits need to explain more clearly to residents the reasons and basis for establishing them. In general, income limits has the effect to narrow scope of age eligibility, which means that the introduction of income limits may be proxy of strict financial stance of policy maker.

With regard to local socio-economic factors, we showed that "AVEINCM" is likely to have the effect of narrowing the scope for age eligibility. This suggests that local governments consider the household income status of local residents in designing the programs. From the perspective of economic bearing ability, local governments with more residents with relatively high incomes have relatively less need to provide unconditional subsidy for medical consultations for children, and in that context, this can be considered a reasonable result. Having said that, income disparities in Japan have become more prominent in recent years, meaning that it is not necessarily appropriate to gauge the economic circumstances of residents by average income alone. Whether or not the magnitude of income disparities within a local government entity affects the scope of eligibility for assistance is an important issue, especially given the overall intent of medical assistance programs for children, which is to provide necessary medical care to children in the area regardless of income level, but due to our data limitations we were unable to incorporate that into the current analysis; we hope to be able to address that issue sometime in the future.

We also showed that both "medical expenses per capita (MEDEXP)" and "The number of population under14 years (POP014)" in the locale had a negative effect on scope for subsidy, in line with our hypothesis. It is understandable that jurisdictions with high per capital medical expenses would be greatly concerned about ballooning medical expenses and show a tendency to narrow the eligibility scope. The number of children in a jurisdiction is a factor determining the number of recipients of subsidy. It is also understandable from the perspective of financial burdens on the government entity, that to the extent the eligible population is greater, the government would tend to want to narrow the eligibility scope for subsidy.

Contrary to our *a priori* expectations, the financial status of local government (FINANIDX) did not have a statistically significant effect on the scope of eligibility of medical subsidy programs for children. One research preceding ours and made at the prefectural level did not demonstrate a clear relationship between the fiscal soundness of the municipality and the income limits, but it has been found that copayments tend to be reduced in prefectures with higher indices of fiscal soundness (Nishikawa, 2010). Conceivable reasons that indices of fiscal soundness had no effect on the scope of eligibility include (1) an increasing perception on the part of local governments that medical subsidy programs for children should be put in place regardless of budgetary considerations, given the fact that child-rearing support is currently a top-priority being pushed by the central government; (2) local residents demand implicitly that their government provide support at least equivalent to that of neighboring entities when the latter expand the scope of their subsidy programs; and (3) medical subsidy programs for children are a mainstay of regional child-rearing support policies, serving as featured policies to attract the child-bearing generation, and should be put in place independent of present financial circumstances. Previous study suggests that there exists some relationship between the timing of the election and the reform of subsidy system (Nishikawa, 2011). Although child-rearing support is unquestionably a critical policy for Japan, discussions must be deepened going forward about to what extent, given the strong demands on local governments for fiscal discipline, should public funds be allocated to medical subsidy programs for children, and to what extent should such public funding be provided by central vs. local governments.

In the current children's medical expense subsidy programs, municipalities consider the expected expenditure size and ability to pay of residents when setting up the system. On the other hand, sufficient consideration has not been given to the financial situation of the municipalities themselves, and there must be a serious problem from the viewpoint of fiscal discipline. In addition, setting of some copayment and income limits have not influenced the scope of coverage even when other factors are fixed (ceteris paribus), and from the view of fairness of the burden of medical expenses among residents of different regions, it is necessary to reconsider its relevance.

This analysis addresses just five prefectures in Kanto Area. In the future it will be necessary to confirm the reliability of our results by expanding our analysis to other areas of Japan.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and approved it for publication.

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Is the Comparison between Exercise and Pharmacologic Treatment of Depression in the Clinical Practice Guideline of the American College of Physicians Evidence-Based?

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Major depression disorder is most commonly treated with antidepressants. However, due to their side effects clinicians seek non-pharmacologic options, and one of these is exercise. The literature on the benefits of exercise for depression is extensive. Nevertheless, two recent reviews focusing on antidepressants vs. other therapies as a basis for clinical practice guidelines recommended mainly antidepressants, excluding exercise as a viable choice for treatment of depression. The aim of this perspective is to analyze the literature exploring the reasons for this discrepancy. Two categories of publications were examined: randomized controlled trials (RCTs) and meta-analyses or systematic reviews. Based on this reassessment, RCTs comparing exercise to antidepressants reported that exercise and antidepressants were equally effective. RCTs comparing exercise combined with antidepressants to antidepressants only reported a significant improvement in depression following exercise as an adjunctive treatment. Almost all the reviews examining exercise vs. other treatments of depression, including antidepressants, support the use of exercise in the treatment of depression, at least as an adjunctive therapy. The two reviews examining pharmacologic vs. non-pharmacologic therapies as a basis for clinical practice guidelines examined limited evidence on exercise vs. antidepressants. In addition, it is possible that academics and health care practitioners are skeptical of viewing exercise as medicine. Maybe, there is a reluctance to accept that changes in lifestyle as opposed to pharmacological treatment can alter biological mechanisms. Longitudinal studies are needed for assessing the effectiveness of exercise in real clinical settings, as well as studies exploring dose-response relationship between exercise and depression.

Keywords: antidepressants, exercise therapy, monotherapy, combination therapy, adjunctive therapy

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INTRODUCTION

The perception of exercise as medicine has been discussed in relation to health conditions such as cognitive decline (e.g., Nagamatsu et al., 2014), cancer (e.g., Lin et al., 2016), cardiac rehabilitation (e.g., Almodhy et al., 2016), schizophrenia (e.g., Firth et al., 2015), alcohol use disorders (e.g., Hallgren et al., 2017), and all-cause mortality (e.g., Eklund et al., 2016). One meta-epidemiological

study on mortality outcomes concluded that in a number of health conditions, such as heart failure, stroke, and diabetes, exercise and various pharmacological treatments are similar in their potential to extend longevity (Naci and Ioannidis, 2013). Thus, exercise interventions should be considered as a viable alternative to, or combination with, drug therapy (Naci and Ioannidis, 2013). It is therefore not surprising that comparative assessments of exercise and drug treatments were performed for some conditions, such as sleep disorders (Buman and King, 2010), chronic pain (Ambrose and Golightly, 2015), and mental health (Firth et al., 2016).

Probably more than for other health conditions, comparative benefits of exercise and pharmacologic treatments have been examined and discussed in relation to depression (e.g., Stubbs et al., 2015; Gartlehner et al., 2016). According to the WHO (World Health Organization), depression is the leading cause of disability worldwide (WHO, 2016 http://www.who.int/mediacentre/factsheets/fs369/en/).

Major depression disorder (MDD) is most commonly treated with antidepressant medication, where second-generation antidepressants are the most commonly prescribed drugs (Agency for Healthcare Research and Quality [AHRQ], 2016). However, many patients do not respond to antidepressant medications, or experience side effects (Gartlehner et al., 2016). In addition, increasing evidence indicated a large placebo response, making it more challenging for novel medications to demonstrate their effectiveness (Rutherford et al., 2012). Therefore, clinicians and patients seek non-pharmacologic options for treating depression – and one of them is physical exercise (e.g., Martiny et al., 2012).

The literature on the benefits of exercise for both minor and major depressive symptoms is extensive, with exceptionally numerous reviews perhaps outnumbering randomized controlled trials (RCTs) (e.g., Mead et al., 2009; Rethorst et al., 2009; Krogh et al., 2011; Rimer et al., 2012; Robertson et al., 2012; Cooney et al., 2013; Danielsson et al., 2013; Silveira et al., 2013; Josefsson et al., 2014; Mura et al., 2014; Knapen et al., 2015; Nyström et al., 2015; Stubbs et al., 2015; Kvam et al., 2016; Schuch et al., 2016b). In addition to exercise, additional studies (Adamson et al., 2016) and reviews (Zhai et al., 2015; Hallgren et al., 2016; Liu et al., 2016; Schuch et al., 2017) in recent years examined the relationship between sedentary behavior, physical activity, and depression. Interestingly, a recent study has shown that a 1-week of forced sedentary behavior may cause bad mood or depression in active individuals (Edwards and Loprinzi, 2016). Furthermore, it has been found that people with depression are at increased risk of sedentary behavior (Dugan et al., 2015; Schuch et al., 2017), which may cause cardiovascular diseases and metabolic syndromes (Gardner-Sood et al., 2015).

Along with RCTs and reviews examining exercise as a treatment for depression, there have been attempts to explore the mediating biological mechanisms explaining the reduction in depression in MDD as a result of exercise (Kandola et al., 2016; Schuch et al., 2016a). One explanation is hippocampus plasticity (Kandola et al., 2016). It has been shown that the hippocampus in depressed individuals may be affected by neuron atrophy (Mendez-David et al., 2013). Aerobic exercise has the potential to promote neuroplasticity and thus facilitate the function of the hippocampus (Erickson et al., 2011). Through increasing neuroplasticity in the hippocampus, it may be possible to generate structural changes that affect the region's functioning and contribute to the alleviation of cognitive malfunction in MDD (Kandola et al., 2016). It has also been hypothesized that there is a relationship between the decline in neurogenesis and depressed mood (Duman et al., 1997). Based on the above, it was concluded that the anti-depressive effects of exercise are due to physiological changes that result in hippocampal neurogenesis (Ernst et al., 2006).

One mechanisms by which exercise could potentially facilitate this neurogenesis is the brain-derived neurotrophic factor (BDNF). A growing number of studies, performed both on animal models of depression and on depressed humans, have focused on the neurotrophic hypothesis of depression (Neto et al., 2011). According to this hypothesis, several alterations in the levels of neurotrophins, particularly of the BDNF, might produce the structural and neurochemical changes that underlie depression (Neto et al., 2011). Both pharmacological and non-pharmacological interventions for depression have been shown to produce changes in the levels of neurotrophins. BDNF increases have been reported to follow the administration of antidepressant drugs (Czubak et al., 2009), which suggests that BDNF expression may mediate the action of antidepressants. Furthermore, when exercise is combined with antidepressants, BDNF levels were found to increase in as little as two days, compared with two weeks with antidepressants alone (Russo-Neustadt et al., 2001).

Another mechanism for enhancing neurogenesis is serotonin. Adaptations in the serotonergic system may serve as potential facilitators of the antidepressant effects of exercise (Schuch et al., 2016a). As a result, antidepressant medications available today target the release and reuptake of serotonin. Exercise increases tryptophan hydroxylase (Chaouloff et al., 1989), which is necessary for serotonin synthesis. Results of animal studies point to a relationship between serotonin elevation and neurogenesis (Brezun and Daszuta, 2000).

According to Schuch et al. (2016a), it is possible that the antidepressant effect of exercise is caused by the interaction of several neurobiological mechanisms rather than by one mechanism exclusively. It is certain that exercise generates both acute and chronic responses, mainly in hormones, neurotrophines, and inflammation biomarkers (Schuch et al., 2016a).

It is, therefore, not surprising that quite a few attempts have been made to compare the effects of exercise to other treatments, including drug treatments, in various depressive disorders, specifically MDD. Four reviews on this topic were published in 2016. Two meta-analyses examining the efficacy of exercise as a treatment for major depression concluded that exercise as a treatment for depression can be recommended as a stand-alone treatment or as an adjunct to antidepressant medication (Kvam et al., 2016), and that exercise can be considered an evidence-based treatment for the management of depression (Schuch et al., 2016b). On the other hand, two systematic reviews comparing antidepressants to other therapies – *including exercise* – as a basis for clinical practice guidelines for depression, disregarded

exercise in their recommendations. One concluded that "The American College of Physicians recommends that clinicians select between either cognitive behavioral therapy or second-generation antidepressants to treat patients with major depressive disorder…" (Qaseem et al., 2016, p. 355), and the other that "given comparable efficacy, cognitive behavioral therapy and antidepressants are both viable choices for initial MDD treatment" (Gartlehner et al., 2016, p. 338). The aim of this perspective is to analyze the available literature on the efficacy of exercise vs. antidepressants in the treatment of depression and to suggest a few explanations for this discrepancy.

Publications Examined

Two categories of publications were examined: RCTs (**Table 1**) and meta-analyses or systematic reviews (**Table 2**).

All RCTs published in 1999–2016 that are included in systematic and/or meta-analyses reviews published from 2009 to 2016 were examined, as well as two recent RCTs found in PubMed search. RCTs were excluded if they assessed participants with additional co-morbid diagnoses, such as cardiovascular diseases (e.g., Blumenthal et al., 2012), or if they assessed two kinds of interventions as add-on therapy – for example chronotherapy vs. exercise (Martiny et al., 2012). One group of RCTs compared exercise to antidepressants – monotherapy comparisons, and the other compared exercise combined with antidepressants to antidepressants only – combination comparisons (**Table 1**).

As a collection of RCTs does not reflect a general effect size, meta-analyses, Cochrane reviews and systematic reviews providing an effect size of exercise vs. antidepressants in the treatment of depression were examined. As a large number of meta-analyses and other reviews were conducted in the last decade, it was decided to screen only reviews from the last seven years (2009–2016). Interestingly, in spite of the large number of reviews, none of them focused solely on exercise vs. antidepressants. One group compared exercise to other treatments of depression, including antidepressants, and the other compared antidepressants to other therapies, including exercise. More specifically, the present review investigated: (1) whether comparisons were conducted specifically between exercise and antidepressants (as opposed to exercise vs. all other treatments together, or antidepressants vs. all other treatments together), (2) which RCTs comparing exercise to antidepressants were included in these reviews, (3) which conclusions were drawn from these comparisons, and (4) whether all published RCTs conducting such comparisons were included in the reviews.

Summary and Conclusions of the Findings

Randomized Controlled Trials

Exercise vs. antidepressants – monotherapy comparisons (Table 1)

Three RCTs compared 4 months of exercise to antidepressants–two for MDD (Blumenthal et al., 1999, 2007) and one for minor depression (Brenes et al., 2007). Two were conducted on older adults (Blumenthal et al., 1999; Brenes et al., 2007). One study (Hoffman et al., 2011) was a follow-up to a previous study (Blumenthal et al., 2007). The Blumenthal et al. (1999, 2007) studies included aerobic exercise, and the Brenes study a combination of aerobic and resistance exercises.

Conclusion: **All these studies reported that exercise and standard antidepressant treatments were equally effective.**

Exercise combined with antidepressants vs. antidepressants only – combination comparisons (Table 1)

Eleven RCTs compared exercise as an adjunctive treatment to antidepressants (combination comparisons) – 10 for MDD and one for minor depression (**Table 1**). The duration of the exercise period varied from 10 days (Knubben et al., 2007; Legrand and Neff, 2016), to 6 weeks (Kerling et al., 2015), 10 weeks (Mather et al., 2002), 3 months (Mota-Pereira et al., 2011), 4 months (Carneiro et al., 2015), 6 months (Murri et al. (2015), 8 months (Pilu et al., 2007), 12 months (Chalder et al., 2012), to throughout a hospitalization period (undefined time period) (Schuch et al., 2011, 2015). Control groups included antidepressants only (Mather et al., 2002; Pilu et al., 2007; Mota-Pereira et al., 2011; Schuch et al., 2011, 2015; Chalder et al., 2012; Carneiro et al., 2015; Kerling et al., 2015), light exercise with both exercise groups receiving antidepressants (Knubben et al., 2007; Legrand and Neff, 2016), and antidepressants only (Murri et al., 2015). The exercise mode included mostly aerobics (Knubben et al., 2007; Mota-Pereira et al., 2011; Schuch et al., 2011, 2015; Kerling et al., 2015; Murri et al., 2015; Legrand and Neff, 2016) or aerobic and strength (Pilu et al., 2007); aerobic, strength, and stretching exercises (Mather et al., 2002); aerobics and strength exercises, games and dancing (Carneiro et al., 2015), and facilitated physical activity chosen and performed individually by participants (Chalder et al., 2012). The studies using exercise in a control group used light stretching (Knubben et al., 2007; Legrand and Neff, 2016) and low-intensity aerobics (Murri et al., 2015). Most studies assessed adults in general; only two studies investigated older adults (Mather et al., 2002; Murri et al., 2015).

Of special interest are the studies using exercise placebo groups as a control group, in which improvements were observed in the aerobic exercise as compared to stretching (Knubben et al., 2007; Legrand and Neff, 2016), and the Murri et al. (2015) study that showed the greatest improvement in high-intensity aerobics, followed by low intensity aerobics, followed by antidepressants only. The Chalder et al. (2012) study only gave guidance about exercise but did not provide an exercise program.

Conclusion: All studies but one (Chalder et al., 2012) informed that patients using exercise as an adjunctive treatment for depression showed a significant depressive improvement after the exercise period, and/or that the proportion of patients with a clinical response was larger for the exercise group than the control.

Meta-Analyses or Systematic Reviews

Table 2 presents a map of RCTs comparing exercise to antidepressants in the meta-analyses or systematic reviews.

Almost all reviews examining exercise vs. other treatments of depression, including antidepressants, support the use

TABLE 1 | Randomized controlled trials (RCTs) comparing exercise to antidepressants in the treatment of depression.

Study	Participants	Treatment groups	Exercise	Duration	Conclusion
Exercise vs. antidepressants (monotherapy comparisons)					
Blumenthal et al., 1999	MDD Older adults,	1.Group exercise 2 Antidepressants 3.Combined	Three times/week Walking or jogging	4 months	Exercise and antidepressants equally effective
Blumenthal et al., 2007	MDD Adults,	1. Group exercise 2. Home-based exercise 3. Antidepressants 4. Placebo pills	Three times/week Walking or jogging	4 months	Participants in either exercise or antidepressants groups tended to show greater improvement in comparison with placebo participants
Hoffman et al., 2011 (follow-up of Blumenthal et al., 2007)	MDD Adults			1 year follow-up	No differences between treatment groups. Those who reported regular exercise following the intervention - the least likely to be depressed at follow-up
Brenes et al., 2007	Minor depression Older adults	1.Group exercise 2. Antidepressants 3.Usual care (discussions on health status)	Three times/week Aerobic and resistance	4 months	Both antidepressants and exercise led to improvements as compared to the usual care. Individuals in the exercise condition also improved in physical functioning
Exercise combined with antidepressants vs. antidepressants only (combination comparisons)					
Knubben et al., 2007	MDD Adults, inpatients	1. Aerobic exercise + antidepressants 2. Low-intensity + antidepressants	1. Individually treadmill walking 2. Individually stretching and relaxation	10 days Every day	Aerobic exercise as add-on therapy significantly improved depression. The proportion of patients with a clinical response was larger for the aerobic exercise group
Pilu et al., 2007	MDD Treatment-resistant women	1. Physiological strengthening + antidepressants 2. Antidepressants	Group cardio-fitness machines – aerobics and strengthening Two times/week	8 months	Exercise group showed a significant depression improvement
Mota-Pereira et al., 2011	MDD Treatment-resistant adults	1. Aerobic exercise + antidepressants. 2. Antidepressants only	Home-based, five times/week (1 day/week supervised	12 weeks	In exercise group, 21% showed response and 26% remission. None in control showed response or remission
Schuch et al., 2011	MDD Adults inpatients	1. Aerobic exercise + antidepressants. 2. Antidepressants only	Stationary bike, or treadmill or an elliptic, on individual basis, Three times/week	Through-out hospitalization	At 2 weeks, – both groups achieved improvements in depressive symptoms and quality of life, but difference favorable to exercise group at discharge.
Chalder et al., 2012	MDD Adults	1. Facilitated physical activity + usual care (58% antidepressants) 2. Usual care (56% antidepressants)	Three face to face sessions and 10 telephone calls with a trained physical activity facilitator	8 months.	Facilitated physical activity did not improve depression or reduce use of antidepressants compared with usual care alone, after 4, 8, and 12 months
Schuch et al., 2015	MDD Adults inpatients	1. Aerobic exercise + antidepressants. 2. Antidepressants only	Treadmill or bike or transport machine, on individual basis, Three times/week	Through-out hospitalization	Exercise group improved significantly more than control group on depressive symptoms and quality of life, as noticed at the second week of hospitalization and at discharge
Carneiro et al., 2015	MDD Adult women	1. Aerobic exercise + antidepressants 2. Antidepressants only	Traditional games, natural circuit workouts with resistance bands, jump ropes, fitness balls, brisk walking, and dancing, Three times/week	4 months	Exercise group decreased in depression, in anxiety and in stress and improved in physical functioning as compared to the control group

(Continued)

TABLE 1 | Continued

Study	Participants	Treatment groups	Exercise	Duration	Conclusion
Kerling et al., 2015	MDD Adults inpatients	1. Aerobic exercise + CBT + antidepressants (only 77% antidepressants) 2. Usual care – CBT + antidepressants (only 75% antidepressants)	Bicycle ergometer followed by personal preference for cross trainer, stepper, arm ergometry, treadmill, recumbent, or a rowing ergometry Three times/week	6 weeks	Decline in depressive symptoms in both groups. Significantly more in exercise group classified as responders - at least 50% reduction in depression. Exercise group improved in physiological measures
Murri et al., 2015	MDD Older adults	1. High-intensity aerobic exercise + antidepressants 2. Low-intensity aerobic exercise+ antidepressants 3. Antidepressants only	1. High-intensity, progressive, mainly bicycles 2. Low-intensity, non-progressive mainly bicycles. Three times/week	24 weeks	Remission occurred in 81% of high-intensity 73% of low-intensity 45% of antidepressants only
Legrand and Neff, 2016	MDD Adult inpatients	1. Aerobic exercise + antidepressants 2. Placebo exercise + antidepressants 3. Antidepressants only	1. Walking or running mostly on individual basis 2. Stretching	10 days upon hospitalization, Every day	Both aerobic and stretching improved. A larger effect size in aerobic exercise. No change in depressive symptoms in control group
Mather et al., 2002	Minor depression, Older adults poorly responsive to depressive symptoms	1. Exercise + antidepressants 2. Health education + antidepressants	Endurance, strength and stretching Two times/week	10 weeks	Significant higher proportion - 55% – of exercise group than control – 33% experienced a greater than 30% decline in depression

of exercise in the treatment of depression, at least as an add-on therapy. Earlier reviews, which included only a few RCTs, were more careful in actually recommending exercise. For example, one review stated that "it is reasonable to recommend exercise. . ." (Mead et al., 2009, p. 14). Another review pointed out that ". . . exercise may be as effective as psychological or pharmacological treatments. . ." (Cooney et al., 2013, p. 35). Later reviews were more conclusive, claiming "a strong effectiveness of exercise combined with antidepressants" (Mura et al., 2014, p. 503); "Overall, our results provide robust evidence that exercise can be considered an evidence-based treatment for the management of depression." (Schuch et al., 2016b, p. 47); and "Physical exercise is an effective intervention for depression. It also could be a viable adjunct treatment in combination with antidepressants" (Kvam et al., 2016, p. 67).

On the other hand, the two recent reviews from 2016 assessing antidepressants vs. other treatments of depression, including exercise, did not recommend exercise for the treatment of depression (Gartlehner et al., 2016; Qaseem et al., 2016). However, when comparing exercise to antidepressants, these reviews examined mainly the Blumenthal et al. (1999, 2007) studies, excluding other RCTs comparing exercise to antidepressants that were included in other recent reviews.

DISCUSSION

Exercise vs. pharmacologic treatment of depression in the clinical practice guideline of the American College of Physicians – is it evidence-based?

It appears that the reviews examining pharmacologic vs. non-pharmacologic treatments of depression as a basis for clinical practice guidelines examined limited evidence on exercise vs. antidepressants, and thus disregarded exercise as a viable choice for treating depression as a stand-alone treatment or as an add-on therapy. This position is contrary to the reviews examining exercise vs. other treatments for depression, including antidepressants, which generally recommend exercise as a stand-alone and/or as adjunctive treatment for depression. The evidence is even greater when considering two additional recent well-designed RCTs not included in any of the reviews (possibly because they were published later than the RCTs mentioned in the reviews) which pointed out the effect of exercise as a complement to antidepressant medication (Carneiro et al., 2015; Legrand and Neff, 2016) (**Table 1**). Furthermore, while the underlying biological mechanisms mediating between exercise and reduced depressive symptoms are not entirely clear, it is apparent that exercise induces both acute and chronic responses, particularly in hormones, neurotrophines, and inflammation biomarkers, and that there is an association between hippocampus neurogenesis as a result of exercise and depressive symptoms' improvement (Schuch et al., 2016a).

Is exercise medicine for the treatment of depression?

Based on the present review, which examined most or all RCTs published in 1999–2016, and most or all meta-analyses/systematic reviews published in 2009–2016, it can be stated that exercise is an evidenced-based medicine for depression – at least as an add-on to antidepressants. Furthermore, people with depression are at increased risk of sedentary behavior (Dugan et al., 2015; Schuch et al.,

TABLE 2 | A map of RCTs in reviews comparing exercise to antidepressants in the treatment of depression, and the conclusions regarding the effect size of exercise.

Reviews	Reviews comparing the effect size of exercise vs. antidepressants in a specific sub-analysis			Reviews assessing a general effect size of exercise	Conclusion
	RCTs included in monotherapy comparison	RCTs included in combination comparison	RCTs together in mono and combination	All RCTs comparing exercise to other treatments including antidepressants	
Rethorst et al., 2009 Meta-analysis of exercise vs. other treatments	2 unpublished papers, 1 irrelevant				A significant overall effect size of exercise. ***No difference between effect sizes of exercise vs. antidepressants,*** but insufficient suitable studies. Supports the use of exercise in the treatment of major depression.
Mead et al., 2009 Cochrane review of exercise vs. other treatments			Blumenthal et al., 1999, 2007		Generally, exercise reduced depression. ***No difference between effect sizes of exercise vs. antidepressants.*** It is reasonable to recommend exercise to people with depressive symptoms but no accurate information
Krogh et al., 2011 Meta-analysis and systematic review of exercise vs. other treatments				Mather et al., 2002; Blumenthal et al., 2007	The ***general effect of exercise on depression is short-term***, little evidence of a long term beneficial effect. High quality trials, with long term follow-up, are required
Robertson et al., 2012 Meta-analysis and systematic review of exercise vs. other treatments				Knubben et al., 2007; Mota-Pereira et al., 2011	***A large (general) effect size of exercise*** (walking) on depression
Cooney et al., 2013 Cochrane review of exercise vs. other treatments			Blumenthal et al., 1999, 2007; Brenes et al., 2007		***No difference between exercise and antidepressants***. Exercise may be as effective as antidepressants, but small number of trials and participants
Silveira et al., 2013 Meta-analysis and systematic review of exercise vs. other treatments (some non-RCTs included)				Blumenthal et al., 2007; Knubben et al., 2007	Exercise is an efficient alternative treatment for depression (***general effect size)***, specifically in old age and for mild depression. Based on Blumenthal et al. (1999, 2007) studies, aerobic training is as effective as antidepressants
Knapen et al., 2015 (review of reviews of exercise vs. other treatments				Cooney et al., 2013; Silveira et al., 2013	***General effect size***: For mild to moderate depression – exercise comparable to antidepressants, for severe depression – exercise valuable as complementary therapy
Mura et al., 2014 Meta-analysis and systematic review (some non-RCTs included)		Blumenthal et al., 1999; Mather et al., 2002; Knubben et al., 2007; Pilu et al., 2007; Mota-Pereira et al., 2011; Schuch et al., 2011			***A strong effectiveness of exercise combined with antidepressants***, but the majority of studies suffered from methodological weaknesses.
Schuch et al., 2016b Meta-analysis of exercise vs. other treatments				Blumenthal et al., 2007; Brenes et al., 2007; Pilu et al., 2007; Mota-Pereira et al., 2011; Kerling et al., 2015; Schuch et al., 2015	***A large and significant effect size of exercise, larger for MDD, for aerobic exercise, and for supervised formats.*** Criticized previous meta-analyses for underestimating benefits of exercise due to publication bias. Not right to calculate exercise-drugs as exercise may potentially overlap with potential mechanisms of drugs.

(Continued)

TABLE 2 | Continued

Reviews	Reviews comparing the effect size of exercise vs. antidepressants in a specific sub-analysis			Reviews assessing a general effect size of exercise	Conclusion
	RCTs included in monotherapy comparison	RCTs included in combination comparison	RCTs together in mono and combination	All RCTs comparing exercise to other treatments including antidepressants	
Kvam et al., 2016 Meta-analysis of exercise vs. other treatments	Blumenthal et al., 1999, 2007	Pilu et al., 2007; Mota-Pereira et al., 2011; Schuch et al., 2011			***Monotherapy: Exercise efficient as drugs. Combination: Moderate effect size trending toward significance. Exercise can be recommended as a stand-alone treatment and as an adjunct to antidepressant medication***
Qaseem et al., 2016 Systematic review of all treatments	Blumenthal et al., 2007; Hoffman et al., 2008 (irrelevant as not assessing depression)	Blumenthal et al., 1999			***Exercise vs. antidepressants: no difference in remission in both mono and combination therapy. However, exercise not recommended as a treatment of depression.*** Low quality evidence
Gartlehner et al., 2016 Systematic review of all treatments	Blumenthal et al., 2007	Blumenthal et al., 1999; Murri et al., 2015			***Exercise vs. antidepressants: no difference in monotherapy, improvement in combination therapy. However, exercise not recommended as a treatment of depression***. Low to moderate quality evidence

2017), which may cause cardiovascular diseases and metabolic syndrome (Gardner-Sood et al., 2015). Thus, exercise contributes to the physical health in addition to mental health. It is also worth mentioning the adverse effects commonly associated with drugs, including constipation, diarrhea, dizziness, headache, insomnia, nausea, adverse sexual events, and somnolence (Qaseem et al., 2016), which may further support the use of exercise as a viable alternative or adjunctive pharmacotherapy.

It is unclear why exercise was disregarded as a viable choice for treating depression in the clinical practice guidelines recommended in the two recent reviews (Gartlehner et al., 2016; Qaseem et al., 2016). Is there a reluctance among academics and health care practitioners to view exercise as medicine? Do they caution that there is no strong evidence to suggest that modifiable lifestyle factors as opposed to pharmacological treatment can alter biological mechanisms in similar pathways or similar dynamics to biochemical interventions?

Interestingly, this argument was raised by Nagamatsu et al. (2014) regarding the effect of exercise on the brain and cognition in old age. These authors made the case that despite the large and consistent pool of evidence generated over the past five decades linking exercise to improved cognitive functions in older adults, skepticism remains and health practitioners continue to hinder the adoption of exercise as a legitimate medical strategy for the prevention of cognitive decline.

Future directions of research should include dose-response interventions to determine the precise dose of exercise required to maximize the benefits for depression. In addition, more studies are needed to inquire the underlying molecular and cellular mechanisms mediating between exercise and depression. Furthermore, another important issue for assessing the benefits of exercise for depression is its effectiveness as opposed to efficacy (Beedie et al., 2016). While efficacy refers to the ability of exercise to achieve the desired effect under well controlled circumstances, effectiveness refers to the ability of exercise to affect depression in real life situations. Therefore, longitudinal observational studies exploring the benefits of exercise in depression are needed, which assess adherence issues as well as economic and professional matters.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and approved it for publication.

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Alcohol Beverage Household Expenditure, Taxation and Government Revenues in Broader European WHO Region

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GLOBAL INDUSTRY OF ALCOHOLIC BEVERAGES AND ITS OUTREACH

The alcohol beverage industry became a significant source of income for several branches in the economy (Kasim, 2006). This has become highly visible in Third World countries during recent years (Caetano and Laranjeira, 2006). Although the alcohol beverage producing industry played an important role in the development of Western economies, its long term balance of gains and harms remains highly disputable (Room and Jernigan, 2000). Sales trends seem to be heavily affected by accelerated globalization. A good example for this is the fact that one of the major manufacturers, Diageo®, which owned 83% of the sales to traditional North American and Western European consumers. However, in 2016 this share has fallen dramatically to only 42% (Institute of Alcohol Studies, 2016). The same scenario has been applied to all top producers such as SABMiller®, Heineken®, Karlsberg®, and others. All of those redirecting their long term investment and expansion strategies toward rapidly developing emerging market economies led by the BRICS (Jakovljevic et al., 2016b). Probably a crucial part for the success rate of the global alcohol beverage industry lies in its devotion to specific focused advertising strategies (Wallack and Montgomery, 1992). It is a well-known fact that major competitors spend some 15% on marketing while approximately only 10% or slightly more on employee payroll expenses. Although, in many of these major companies net profit margin may be up to 25%. The mirror like reflection of this economic activity are revenues gained by the national governments worldwide which come from two sources: taxation on beverage manufacturers and value added tax or excise duties paid by the final consumers (Li and Si, 2016). An exceptionally important feature of global alcohol market is the fact that only the 38%-point share counts for branded beverages. The so called informal manufacturing, such as the rural beer brewing by Sudanese African women or traditional Eastern European distillation of a variety of local brandies, counts for a lion part of consumption worldwide (Jernigan, 2009). These traditional agricultural crafts are quite difficult to target by policy measures unlike major multinational businesses. Companies' irresponsible behavior aimed at increasing profits was documented in a number of publications (Casswell et al., 2016). Nonetheless, companies are accessible by evolving legal framework, imposing trade barriers, taxation measures and advertising bans which are frequently cited among the most cost-effective policy measures (Anderson et al., 2009).

There are visible signs of industrial attempt to adapt to growing public awareness on harmful effects of alcohol beverage advertising and expanding volume of sales. These businesses responded in several different ways. One of them was their investment into basic, clinical and social research on the general topic of alcohol (Babor, 2009), which raised strong concerns about the integrity of such science and conflict of interest issues due to the fact that producers are acting as major sponsors of grant holders (Stenius and Babor, 2010). Another approach was to establish The International Alliance for Responsible Drinking (IARD) while most major producers act as institutional affiliated members (International Alliance for Responsible Drinking n.d.). Its goal and core agenda was declared to tackle the global burden of harmful drinking by the citizens as final consumers. This issue is clearly reflected in the Sustainable Development Goals (GBD 2015 SDG Collaborators, 2016) and WHO's Global Strategy to Reduce the Harmful Use of Alcohol (World Health Organization, 2010). After a prolonged debate among the stakeholders dominant opinion among the experts is that alcohol beverage industry should not be involved in alcohol policy development. Exploration of both the regulatory and educational approaches in controlling alcohol consumption and sales has shown that the first one is by far more effective.

SOCIAL COST OF ALCOHOL CONSUMPTION

The Global Burden of Disease Project provided an in-depth and comparable morbidity and mortality assessments (Global Burden of Disease Cancer Collaboration et al., 2017) for all major world regions. It has clearly pointed out the contribution of alcohol to disability (GBD 2015 Disease Injury Incidence Prevalence Collaborators, 2016) and longevity. In 2015 alcohol use with 85 million global disability adjusted life years (DALYs) was still among the 10 largest contributors to global DALYs, although a decrease of 1.2% was noted since 2005 (Forouzanfar et al., 2016). In European countries a huge variation of years of life lost attributable to alcohol use exists, with almost ten-fold difference between highest and lowest rated country (Rehm et al., 2007). The connection between alcohol consumption and shorter life expectancy was probably the most exemplary in Russian mortality crisis of the 1990s (Andreev et al., 2003; Jakovljevic et al., 2016a).

Harmful use of alcohol imposes significant social and economic costs on society. Alcohol-attributable cost per head may range from I$358 to I$837 in high-income countries and from I$122 to I$524 in middle-income countries (Rehm et al., 2009). Indirect costs due to loss of productivity are the dominant category of costs which accounts about 49–95% of total costs, whereas direct costs encompass multiple types of health-care services representing about 9–24% of all alcohol-attributable social costs and significant costs in the justice sector as well (Rehm et al., 2009; World Health Organization, 2014).

Health authorities in a variety of countries became increasingly aware of the necessity to create strategies aimed to contain alcohol consumption at a certain level (Morgan, 1988). Obviously due to the scale of public health consequences, in some countries this issue was more concerning than others (Tulchinsky and Varavikova, 1996). A variety of policies deployed had rather modest or even a neglected impact to the sales and consumption of alcohol in many countries, particularly in the youth and adolescent population (Foster et al., 2006; Anderson et al., 2009).

Published evidence has clearly shown that regular consumption of spirits, beer, wine, or cider, presents a core risk factor for the occurrence of major non-communicable diseases (Forouzanfar et al., 2016). Clinical evolution of alcohol-attributable illnesses has been thoroughly studied and was the field of extensive medical knowledge development. It led to the rise of several distinguished classification of stages of alcohol addiction and abuse such as Clonninger, Babor, LAT and few others. Some of these, like LAT typology and its associated clinical software based guidelines were even documented to be capable of inducing cost savings in large university hospital settings (Jakovljevic et al., 2014b). Distinctively different cultural patterns of alcohol abuse have created a myriad of local conditions whose diversity in Europe has been well documented (Jakovljevic et al., 2013). A particularly concerning fact is that social cost of alcohol reached a scale that severely threatens financial sustainability of both Western and Asian health systems like the French one (Fenoglio et al., 2003), Canadian (Single et al., 1998), Californian (Rosen et al., 2008), Swedish (Jarl et al., 2008), New Zealand's' (Devlin et al., 1997), Indian (Benegal et al., 2000; Benegal, 2005) and many others. Preventive public health interventions were historically the first response option after policy makers awareness reached its maturity (Glasgow et al., 1999). However these strategies were either misunderstood or poorly supported by capacity building and resource allocation in many world regions (Room et al., 2002). Therefore curative, hospital based care for the medical consequences of neglected alcoholism became an option of choice for many communities (Jovanovic and Jakovljevic, 2011). This expensive, late stage solution raised the issue of affordable evidence based care of alcohol addicts both in psychiatric and internal medicine clinics (Jakovljevic et al., 2014a). Diagnostics, treatment and rehabilitation of alcohol dependent patients have proven to be major cost drivers (Jakovljević et al., 2013). Once again a variety of cost-effectiveness estimation efforts were put in place to rationalize resource allocation in this domain (Anderson et al., 2009). And once again strategic thinkers were more convinced that a long term measures targeted to make alcohol beverages less accessible to the ordinary citizen were probably the best solution to release this burden (Baumberg and Anderson, 2008). Reducing the affordability of alcohol by raising prices seems to lead to a reduction in alcohol consumption and associated harms—one of the successful policies is so called Minimum Unit Pricing, which consists of defining a level below which retailers cannot sell alcohol depending on the number of units per beverage (Institute of Alcohol Studies n.d.). It has been shown that 1% increase in the price of alcohol may lead to 0.96% reduction in alcohol consumption for the overall population of drinkers (Byrnes et al., 2016). However, it should be noted that rather than simply lowering consumed quantity in response

to price increase, drinkers may as well be willing to switch to lower-cost brand in order to maintain their consumption (Gruenewald et al., 2006).

DATA REPORT METHODS

Official data released by World Health Organization's Global Health Observatory Data Repository (European Region and broader (Russian) Commonwealth of Independent States observed) were downloaded from the links provided beneath: http://apps.who.int/gho/data/node.main-euro.A1113?lang=en&showonly=GISAH (World Health Organization n.d.). The data refer to the several key indicators of alcohol beverage industry revenues such as: Alcoholic beverage tax revenue as a per cent of government revenue; Annual revenues from alcohol excise tax in millions US$; Alcohol expenditure as a per cent of total household expenditure; Revenues from taxes on consumption (excise duties and similar charges) other than Value Added Tax (VAT)—ethyl alcohol in millions EUR; Revenues from taxes on consumption (excise duties and similar charges) other than VAT—intermediate products in millions EUR; Revenues from taxes on consumption (excise duties and similar charges) other than VAT—still wine in millions EUR. Extraction of selected data from this public repository is provided in **Tables 1, 2**. Another source of data was the European Commission's Taxation and customs union, Legislation section on Excise duties—Alcoholic beverages: http://ec.europa.eu/taxation_customs/business/excise-duties-alcohol-tobacco-energy/excise-duties-alcohol/excise-duties-alcoholic-beverages_en (European Commission n.d.). Data were synthesized in a comparable manner with emphasis on first and last historically reported value to the transnational authorities such as WHO and European Commission for European Union countries. Incremental gains and losses were calculated as annual and total net changes. Largest possible time horizon available was adopted and it ranged from 6 to 23 years on the set of total of 69 countries of Europe and broader CIS Region. There was a large amount of missing data and therefore conclusions refer to a limited set of countries providing sufficiently detailed data for comparison. Extraction and synthesis of aforementioned public registries on alcohol is archived as an excel sheet at FigShare link: https://figshare.com/articles/Alcohol_beverage_household_expenditure_taxation_and_government_revenues_in_European_and_CIS_countries/4245296.

ALCOHOL BEVERAGE TAXATION AND GOVERNMENT REVENUES IN THE EUROPEAN REGION AND BROADER COMMONWEALTH OF INDEPENDENT STATES

Natural response of the national authorities to the huge medical and socioeconomic burden of alcohol use was a tightened control over its manufacturing and distribution (Levine and Reinarman, 1991). Many nations adopted the strategy targeted at limiting access to alcoholic drinks by making them effectively more expensive to final consumer. Among a variety of polices developed to tackle these issues we decided to observe taxation approach and consecutive changes in governmental/budgetary revenues.

We may notice several distinct trends taking place in Europe over the past two and a half decades. Household expenditure on alcohol expressed in percentage terms, was slightly growing since the early 2000s in only three countries with Ireland on the lead (+1.7%). Most data on this indicator come either from the Russian Commonwealth of Independent States (CIS) nations or post-2004 Eastern EU members. This share of family spending was steadily falling in all of these nations (Stroev et al., 1999). Surprisingly the most prominent decrease was noticed in Russian Federation, Lithuania, Belarus, UK, Poland in order of appearance with Romania topping the list with bottom—10.6% net change over 22 years. Due to tightened tax policies annual revenues from alcohol excise tax expressed in millions US$, grew significantly in most European nations. These amounts were exceptionally high in several large nations and Norway ranging from even + US$ 8,388.05 million, in the UK to only + US$ 2.86 million, in Malta. Only five countries recorded contraction of such income to the public budget and these were: Portugal, Germany, Romania, Iceland and Austria at the bottom with loss of even—US$ 243.54 million over 7 years. Unlike these amounts in absolute terms, in relative terms alcoholic beverage tax revenue contribution as a per cent of government revenues was steadily falling over the same period. This was effectively due to the stronger impact of other sources of budgetary revenues. Contraction of these revenues share was ranging from −7% in Estonia to −0.2% in Iceland. Total net increase in revenues from taxes on consumption such as excise duties and similar charges *(other than VAT) recorded a bold growth upwards particularly in some Western European, EU-15 traditional free-market economies. This is clearly visible in ethyl alcohol, intermediary products, beer, sparkling wine and still wine official turnover and sales statistics. In all of these domains the UK is clearly dominating revenue growth. Probably the most notable example is their still wine income to public resources which surmounted to €1,142.06 million. The only major exception is beer industry and consumption in France whose taxation heavily increased putting France ahead of others. This meant + €560.63 million budgetary gains or almost €95 million annual growth over the 6 year time span 2008–2014. Some countries remained in certain sense outliers of this mainstream trend of harsher alcohol taxation polices in Europe. Their excise and similar taxes and consecutive national revenue rates remained rather constant and slowly decreasing over the past decade or more. This was the case with Portugal, Germany, Romania, Iceland and an extreme case of Austria who even lost −US$ 243.54 million, since 2005. If we observe the European landscape in revenues from taxes other than VAT, on ethyl alcohol we shall notice a number of countries with huge net losses. Bottom line ones are Lithuania, Ireland, Germany, Poland and Spain leading the picture with −€154.92 million of total losses since 2008.

Increase in annual revenues from alcohol taxes was also noted in the United States. Increase was substantial: from US$ 8.14

TABLE 1 | Alcohol beverage taxation and government revenues—general.

Country	Alcoholic beverage tax revenue as a per cent of government revenue					Annual revenues from alcohol excise tax in millions US$					Alcohol expenditure as a per cent of total household expenditure				
	First reported value	Last reported value	Total change	Time span (years)	Annual increment	First reported value	Last reported value	Total change	Time span (years)	Annual increment	First reported value	Last reported value	Total change	Time span (years)	Annual increment
United Kingdom	2.8^{1990}	2.2^{2013}	−0.6	23	−0.03	$7{,}722.12^{1991}$	$16{,}110.17^{2013}$	8,388.05	22	381.28	6.5^{1990}	1.6^{2012}	−4.9	22	−0.22
France	1.8^{1990}	1.5^{2007}	−0.3	17	−0.02	$2{,}573.1^{2002}$	5706.25^{2013}	3,133.15	11	284.83	1.4^{2006}	N/A	N/A	N/A	N/A
Poland	N/A	N/A	N/A	N/A	N/A	$2{,}228.88^{2005}$	$3{,}271.75^{2012}$	1,042.87	7	148.98	8.5^{1990}	0.8^{2012}	−7.7	22	−0.35
Norway	2.1^{1996}	1^{2012}	−1.1	16	−0.07	869.02^{1990}	$3{,}243.53^{2011}$	2,374.51	21	113.07	4.6^{1990}	2.6^{2011}	−2	21	−0.10
Turkey	N/A	N/A	N/A	N/A	N/A	$1{,}060.78^{2003}$	$1{,}557.91^{2010}$	497.13	7	71.02	N/A	N/A	N/A	N/A	N/A
Sweden	1.8^{1996}	1.6^{2012}	−0.2	16	−0.01	$1{,}206.96^{2002}$	$1{,}794.99^{2012}$	588.03	10	58.80	3.7^{1992}	2.8^{2012}	−0.9	20	−0.05
Finland	8.4^{1990}	5^{2012}	−3.4	22	−0.15	$1{,}063.39^{1999}$	$1{,}739.81^{2012}$	676.42	13	52.03	7^{1991}	4.4^{2012}	−2.6	21	−0.12
Italy	0.6^{1996}	N/A	N/A	N/A	N/A	751.58^{2002}	$1{,}249.95^{2012}$	498.37	10	49.84	1.1^{1990}	0.7^{2010}	−0.4	20	−0.02
Netherlands	1^{1996}	N/A	N/A	N/A	N/A	970.2^{2002}	$1{,}273.44^{2012}$	303.24	10	30.32	N/A	N/A	N/A	N/A	N/A
Spain	1.8^{1996}	N/A	N/A	N/A	N/A	$1{,}160.62^{2002}$	$1{,}444.94^{2012}$	284.32	10	28.43	1.3^{1992}	N/A	N/A	N/A	N/A
Czech Republic	N/A	N/A	N/A	N/A	N/A	380.25^{2005}	566.65^{2012}	186.4	7	26.63	N/A	N/A	N/A	N/A	N/A
Greece	N/A	N/A	N/A	N/A	N/A	271.01^{2002}	511.51^{2012}	240.5	10	24.05	0.9^{2000}	0.9^{2009}	0	9	0.00
Belgium	1.1^{1996}	N/A	N/A	N/A	N/A	533.69^{2000}	799.49^{2012}	265.8	12	22.15	N/A	N/A	N/A	N/A	N/A
Ireland	5^{1996}	1.7^{2010}	−3.3	14	−0.24	761.83^{1994}	$1{,}066.01^{2012}$	304.18	18	16.90	6^{2000}	7.7^{2012}	1.7	12	0.14
Estonia	10^{1995}	3^{2012}	−7	17	−0.41	59.83^{2000}	277.45^{2013}	217.62	13	16.74	1.7^{1996}	3^{2012}	1.3	16	0.08
Lithuania	N/A	N/A	N/A	N/A	N/A	206.86^{2005}	314.04^{2012}	107.18	7	15.31	6.1^{1990}	2.4^{2012}	−3.7	22	−0.17
Slovakia	N/A	N/A	N/A	N/A	N/A	215.24^{2005}	321.4^{2012}	106.16	7	15.17	N/A	N/A	N/A	N/A	N/A
Bulgaria	N/A	N/A	N/A	N/A	N/A	101.45^{2006}	171.63^{2012}	70.18	6	11.70	N/A	N/A	N/A	N/A	N/A
Latvia	N/A	N/A	N/A	N/A	N/A	114.792^{2005}	182.01^{2012}	67.218	7	9.60	2^{1994}	N/A	N/A	N/A	N/A
Slovenia	N/A	N/A	N/A	N/A	N/A	75.33^{2005}	117.1^{2012}	41.77	7	5.97	N/A	N/A	N/A	N/A	N/A
Switzerland	0.5^{1996}	N/A	N/A	N/A	N/A	244.38^{2007}	278.5^{2013}	34.12	6	5.69	N/A	N/A	N/A	N/A	N/A
Denmark	1.4^{1996}	0.3^{2012}	−1.1	16	−0.07	583.33^{2002}	613.63^{2012}	30.3	10	3.03	2.4^{1994}	1.1^{2012}	−1.3	18	−0.07
Hungary	N/A	N/A	N/A	N/A	N/A	339.59^{2005}	360.44^{2012}	20.85	7	2.98	1.1^{2006}	1^{2012}	−0.1	6	−0.02
Cyprus	N/A	N/A	N/A	N/A	N/A	25.11^{2005}	34.89^{2012}	9.78	7	1.40	0.6^{1991}	N/A	N/A	N/A	N/A
Luxembourg	0.6^{1996}	N/A	N/A	N/A	N/A	32.24^{2002}	41.53^{2012}	9.29	10	0.93	N/A	N/A	N/A	N/A	N/A
Malta	N/A	N/A	N/A	N/A	N/A	11.96^{2005}	14.82^{2012}	2.86	7	0.41	N/A	N/A	N/A	N/A	N/A
Portugal	0.9^{1996}	N/A	N/A	N/A	N/A	215.6^{2002}	211.51^{2012}	−4.09	10	−0.41	N/A	N/A	N/A	N/A	N/A
Germany	1.7^{1996}	0.6^{2013}	−1.1	17	−0.06	$3{,}433.49^{2002}$	$3{,}414.33^{2013}$	−19.16	11	−1.74	N/A	N/A	N/A	N/A	N/A
Romania	N/A	N/A	N/A	N/A	N/A	331.04^{2007}	298.37^{2012}	−32.67	5	−6.53	11^{1991}	0.4^{2013}	−10.6	22	−0.48
Iceland	2.4^{2003}	2.2^{2012}	−0.2	9	−0.02	182.98^{2007}	131.88^{2012}	−51.1	5	−10.22	3.4^{1990}	2.9^{2007}	−0.5	17	−0.03
Austria	1^{1996}	0.3^{2010}	−0.7	14	−0.05	647.09^{2005}	403.55^{2012}	−243.54	7	−34.79	1.7^{1995}	1.4^{2013}	−0.3	18	−0.02
Belarus	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	7.4^{1990}	2.5^{2013}	−4.9	23	−0.21

(Continued)

TABLE 1 | Continued

Country	Alcoholic beverage tax revenue as a per cent of government revenue					Annual revenues from alcohol excise tax in millions US$					Alcohol expenditure as a per cent of total household expenditure				
	First reported value	Last reported value	Total change	Time span (years)	Annual increment	First reported value	Last reported value	Total change	Time span (years)	Annual increment	First reported value	Last reported value	Total change	Time span (years)	Annual increment
Republic of Moldova	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	2.6^{1990}	1.9^{1995}	−0.7	5	−0.14
Russian Federation	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	5^{1990}	1.7^{2012}	−3.3	22	−0.15
Ukraine	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	3.7^{1990}	1.5^{2012}	−2.2	22	−0.10
Croatia	N/A	N/A	N/A	N/A	N/A	37.91^{2008}	N/A	N/A	N/A	N/A	1.6^{2005}	1.5^{2011}	−0.1	6	−0.02
The former Yugoslav Republic of Macedonia	N/A	N/A	N/A	N/A	N/A	24^{2007}	N/A	N/A	N/A	N/A	1.3^{2006}	1.2^{2011}	−0.1	5	−0.02
Armenia	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	4^{1990}	1.5^{2012}	−2.5	22	−0.11
Azerbaijan	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1.3^{1990}	0.5^{2012}	−0.8	22	−0.04
Georgia	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1.3^{1990}	1.1^{1991}	−0.2	1	−0.20
Kazakhstan	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	5^{1990}	2.5^{1995}	−2.5	5	−0.50
Kyrgyzstan	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	3.9^{1990}	1.9^{1995}	−2	5	−0.40
Tajikistan	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1.8^{1990}	0.1^{2011}	−1.7	21	−0.08
Turkmenistan	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	3.4^{1990}	4^{1994}	0.6	4	0.15
Republic of Uzbekistan	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	2.9^{1990}	1.9^{1995}	−1	5	−0.20

TABLE 2 | Alcohol beverage taxation and government revenues—specific.

Country	Revenues from taxes on consumption (excise duties and similar charges) other than VAT—ethyl alcohol in millions EUR					Revenues from taxes on consumption (excise duties and similar charges) other than VAT—intermediate products in millions EUR					Revenues from taxes on consumption (excise duties and similar charges) other than VAT—still wine in millions EUR				
	First reported value	Last reported value	Total change	Time span (years)	Annual increment	First reported value	Last reported value	Total change	Time span (years)	Annual increment	First reported value	Last reported value	Total change	Time span (years)	Annual increment
United Kingdom	3,357.62[2008]	3,928.21[2014]	570.59	6	95.10	326.45[2008]	415.38[2014]	88.93	6	14.82	3,226.04[2008]	4,368.1[2014]	1,142.06	6	190.34
France	2,001[2008]	2,239.47[2014]	238.47	6	39.75	106[2008]	76.15[2014]	−29.85	6	-4.98	85[2008]	90.38[2014]	5.38	6	0.90
Belgium	230.05[2008]	291.58[2014]	61.53	6	10.26	27.6[2008]	25.54[2014]	−2.06	6	-0.34	114.05[2008]	139.5[2014]	25.45	6	4.24
Austria	123.98[2008]	171.6[2014]	47.62	6	7.94	1.31[2008]	5.7[2014]	4.39	6	0.73	0[2008]	0[2014]	0	6	0.00
Croatia	22.59[2013]	30.37[2014]	7.78	1	7.78	N/A	N/A	*N/A*	N/A	N/A	0[2013]	0[2014]	0	1	0.00
Italy	554.67[2008]	600.26[2014]	45.59	6	7.60	N/A	N/A	*N/A*	N/A	N/A	0[2008]	0[2014]	0	6	0.00
Estonia	109.86[2008]	144.1[2014]	34.24	6	5.71	0.96[2008]	1.34[2014]	0.38	6	0.06	14.12[2008]	17.32[2014]	3.2	6	0.53
Bulgaria	66.08[2008]	95.74[2014]	29.66	6	4.94	0.0012[2008]	0.172[2014]	0.1708	6	0.03	0[2008]	0[2014]	0	6	0.00
Greece	257.46[2008]	282.31[2014]	24.85	6	4.14	N/A	N/A	*N/A*	N/A	N/A	0[2008]	0[2014]	0	6	0.00
Finland	415.35[2008]	430.11[2014]	14.76	6	2.46	16.84[2008]	17.7[2014]	0.86	6	0.14	227.95[2008]	336.18[2014]	108.23	6	18.04
Luxembourg	26.94[2008]	35.76[2014]	8.82	6	1.47	1.1[2008]	0.98[2014]	−0.12	6	-0.02	0[2008]	0[2014]	0	6	0.00
Slovenia	15[2008]	21.33[2014]	6.33	6	1.06	0.09[2008]	0.16[2014]	0.07	6	0.01	0[2008]	0[2014]	0	6	0.00
Cyprus	17.38[2008]	20.96[2014]	3.58	6	0.60	0.15[2008]	0.16[2014]	0.01	6	0.00	0[2008]	0[2014]	0	6	0.00
Portugal	92.8[2008]	96.11[2014]	3.31	6	0.55	12.95[2008]	10.99[2014]	−1.96	6	-0.33	0[2008]	0[2014]	0	6	0.00
Malta	9.786[2008]	11.426[2014]	1.64	6	0.27	N/A	N/A	*N/A*	N/A	N/A	0[2008]	0[2014]	0	6	0.00
Slovakia	199.9[2008]	200.314[2014]	0.414	6	0.07	0.404[2014]	N/A	*N/A*	N/A	N/A	0[2008]	0[2014]	0	6	0.00
Denmark	156[2008]	154.82[2014]	−1.18	6	−0.20	3.05[2008]	3.94[2014]	0.89	6	0.15	133.54[2008]	212.04[2014]	78.5	6	13.08
Hungary	182.69[2008]	175.07[2014]	−7.62	6	−1.27	2.55[2008]	1.19[2014]	−1.36	6	-0.23	0.46[2008]	2.1[2014]	1.64	6	0.27
Romania	98.65[2008]	88.98[2014]	−9.67	6	−1.61	29.6[2008]	0.38[2014]	−29.22	6	-4.87	0[2008]	0.26[2014]	0.26	6	0.04
Latvia	117.56[2008]	107.63[2014]	−9.93	6	−1.66	2.07[2008]	2.92[2014]	0.85	6	0.14	7.44[2008]	10.07[2014]	2.63	6	0.44
Sweden	441.63[2008]	430.09[2014]	−11.54	6	−1.92	20.32[2008]	16.65[2014]	−3.67	6	-0.61	413.95[2008]	532.14[2014]	118.19	6	19.70
Netherlands	338.94[2008]	322.09[2014]	−16.85	6	−2.81	37.49[2008]	26.75[2014]	−10.74	6	-1.79	239.07[2008]	319.19[2014]	80.12	6	13.35
Czech Republic	268.64[2008]	245.37[2014]	−23.27	6	−3.88	2.71[2008]	1.06[2014]	−1.65	6	-0.28	N/A	N/A	N/A	N/A	N/A
Lithuania	218.88[2008]	173.16[2014]	−45.72	6	−7.62	13.77[2008]	15.13[2014]	1.36	6	0.23	12.42[2008]	17.75[2014]	5.33	6	0.89
Ireland	350.92[2008]	301.78[2014]	−49.14	6	−8.19	66.46[2008]	67.33[2014]	0.87	6	0.15	213.25[2008]	332.78[2014]	119.53	6	19.92
Germany	2,125.93[2008]	2,059.66[2014]	−66.27	6	−11.05	27.11[2008]	14.67[2014]	−12.44	6	-2.07	0[2008]	0[2014]	0	6	0.00
Poland	1,632.94[2008]	1,536.27[2014]	−96.67	6	−16.11	N/A	N/A	N/A	N/A	N/A	126.26[2008]	86.2[2014]	−40.06	6	−6.68
Spain	981.82[2008]	826.9[2014]	−154.92	6	−25.82	19.96[2008]	19.56[2014]	−0.4	6	-0.07	N/A	N/A	N/A	N/A	N/A

billion in 2000 to US$ 9.64 billion in 2015, with a forecast to continue in a similar manner to US$ 10.18 billion in 2021 (Statista n.d.). About 3% per cent of government revenue in the United States comes from excise tax on the sales of alcohol, tobacco and fuel (Center on Budget Policy Priorities, 2016).

ALCOHOL BEVERAGE INDUSTRY TAXATION POLICIES IN FUTURE

As witnessed by this short analysis of public datasets we may see that there has been a variety of strategies across the European region and broader Commonwealth of Independent States countries. We may see that a number of Western European EU-15 traditional free-market economies recorded tightened governments' grip on alcohol industry inclusive of double taxation of manufacturers, distributors and the final consumer. This example led by the UK obviously succeeded to gain huge net revenues into the public funds either at the regional or national level. Many other large countries such as Germany, Romania, and Spain did not adopt such policies. Their alcohol beverage taxation rates remained rather constant or even slightly contracted over past few decades. Due to large populations and alcohol consumption being deeply rooted as a part of popular culture and way of life, this led to the strong contraction of public revenues coming from this source of income. The case with the Russian Federation was marked with several positive developments (Rechel et al., 2013). Its household expenditure on alcohol severely shrank from 5% back in 1990 to only 1.7% in 2012 over the span of 22 years. At the same time rate of road traffic accidents involving alcohol per 100,000 inhabitants decreased from 47.18 in 1990 to 11.16 in 2009 over 19 years. Other not less effective polices were advertising bans on alcohol beverages deployed in some countries (Fieldgate et al., 2013). Investigation of the efficiency frontier and public health gains achieved with these measures goes well beyond the scope of this Data Report. Seeking at least partial answer we had insight into the road traffic accidents involving alcohol per 100,000 inhabitants presented in the original data (please see FigShare repositorium link) (Ruhm, 1996). Here it is clear that few nations managed to significantly reduce these rates with prominent cases of Denmark, Iceland, Russian Federation, Andorra and Luxembourg each cutting its own rates approximately for 30–45% since 1980s. Another angle of view could be taken while observing mortality issues—standardized death rates (SDR) attributable to the selected alcohol-related causes expressed per 100,000 inhabitants. These data are available for most countries since 1980s or even late 1970s. Here vast majority of nations made a huge advance with some of them decreasing these mortality rates for even more than 70% such as Spain, Turkmenistan, Italy, Hungary, Austria, Portugal, and France (Dee, 1999). Here it is worthy to mention few important outliers coming mostly from CIS region (Stickley et al., 2007). These are Kazakhstan, Belarus, Ukraine, Turkey, Tajikistan, and San Marino who all substantially increased their alcohol-attributable mortality with Kazakhstan on the lead with 84% in the 1991–2003. Due to the fact that some of these referral values are significantly outdated we should stay short of premature conclusions on contemporary momentum on alcohol in these regions (Shleifer and Treisman, 2005). Improved methods of the Global Health evaluation (Global Burden of Disease), strong epidemiologic evidence, improved knowledge of the alcohol harm bring together solid base for a change in Health policy toward the alcohol consumption. At the policy level, the hypothesis of health benefits from moderate drinking should no longer play a role in decision making (Chikritzhs et al., 2015). The number of nations across EU, CIS and intermediary regions, were decently successful in employing and persisting with alcohol industry taxation policies. The tendency to make the alcohol drinking habit expensive luxury good (Babor, 2010) in many countries appears to be quite effective distraction against heavy drinking patterns (Wilk et al., 1997). The long term consequences of these efforts remain yet to be seen in the upcoming years.

AUTHOR CONTRIBUTIONS

MJ, EV, HW, AW, AP, OL all contributed essentially to the definition of research questions, study design and writing of the final manuscript thus fulfilling the ICMJE requirements for full authorship.

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Observed and Normative Discount Functions in Addiction and other Diseases

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The aim of this paper is to find a suitable discount function able to describe the progression of a certain addiction or disease under treatment as a discounting process. In effect, a certain indicator related to a disease decays over time in a manner which is mathematically similar to the way in which discounting has been modeled. We analyze the discount functions observed in experiments which study addictive and other problematic behaviors as well as some alternative hyperbola-like discount functions in order to fit the patience exhibited by the subject after receiving the treatment. Additionally, it has been experimentally found that people with addiction display high rates of discount (impatience) and preference reversals (dynamic inconsistency). This excessive discounting must be correctly modeled by a suitable discount function, otherwise, it can become a trans-disease process underlying addiction and other disorders. The (generalized) exponentiated hyperbolic discount function is proposed to describe the progression of a disease with respect to the treatment, since it maintains the property of inconsistency by exhibiting a decreasing discount rate after an initial period in which the opposite occurs.

Keywords: delay discounting, addiction, disease, hyperbolic discounting, (generalized) exponentiated hyperbolic discounting, hazard rate

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1. INTRODUCTION

In a recent paper, Bickel et al. (2012) state that drug-dependent individuals, and people with other diseases such as obesity, gambling problems, diagnosed ADHD (Attention Deficit Hiperactivity Disorder) or schizophrenia, discount delayed reinforcers more rapidly than individuals not having these addictions or diseases. It could be said that these individuals are more impulsive or impatient than individuals belonging to the control group (people not suffering from the studied addiction or disease). After an extensive review of the literature on addictive behavior and discounting of delayed rewards, a similar conclusion is drawn by MacKillop et al. (2011) who found strong evidence of greater discounting in individuals with addictive behavior. On the other hand, there are empirical studies in which only (mainly hypothetical) monetary rewards are discounted. Most of these experiments can be found in MacKillop et al. (2011). However, there are also empirical works which compare the discounting of monetary and non-monetary rewards by people with and without addictive behavior. Hypothetical amounts of cigarettes (e.g., Bickel et al., 1999), heroin (e.g., Madden et al., 1997), crack/cocaine (e.g., Coffey et al., 2003), and alcohol (e.g., Petry, 2002) have been used as non-monetary rewards. As a general conclusion, all these substances of abuse

were discounted more steeply than money by their consumers. Furthermore, a higher discount was applied to monetary rewards by the group of substance abuse consumers.

According to Prelec (2004), "the core meaning of impatience is a preference for something to happen sooner rather than later." Some papers (Takahashi et al., 2007) use the term impulsivity as a synonym for impatience[1]. Although Bickel and Marsch (2001) broadly call them "personality assessments," we will refer to impulsivity in the context of delay discounting.

Another interesting idea, proposed by Bickel et al. (2012), is the consideration of excessive discounting as a trans-disease process underlying addiction and other disorders as well as disease-related behavior. For example, high discount rates appear in smokers and ADHD. This was also pointed out by Green and Myerson (2004) who stated: "Such findings raise the possibility that differences in impulsivity may underlie these behavioral problems[2] and that assessment based on behavioral discounting measures may be able to predict who is at risk and who is most likely to benefit from interventions." In a similar fashion, Bickel et al. (2012) propose that "[...] understanding the commonalities in comorbid disorders may inform treatment approaches for multiple disorders." They also suggest that the relation between disorders and discount rates may be additive and, for example, individuals with two or more disorders could show higher discount rates than individuals with only one disorder. In the same vein, Petry and Casarella (1999) found that the discount rates displayed by people with two disorders, namely gambling and substance abuse, were three times higher than the rates of non-gambling substance abusers. As these disorders additively affected discount rates, we are going to consider an aggregated discount function in this work which takes into account higher discount rates due to more than one disease or addiction. In summary, we will take into account that people with addiction:

1. Have high rates of discount (Bickel et al., 2012, refer to it as excessive rates of discount).
2. Have preference reversals. "These preference reversals are a hallmark feature of individuals suffering from addiction, as they often express a desire to abstain when drugs are not immediately available, but may reverse this preference when the opportunity to use is more proximal [...]" (Bickel et al., 2012).
3. Could have a propensity to developing other diseases in which high discount rates are an underlying process.

Indeed, the aforementioned characteristics will help us to find a suitable discount function able to describe these addiction situations. To this end, this paper is organized as follows: In Section 2 we are going to describe a disease or an addiction as a discounting process. Following that, in Section 3, we will first study the discount functions that best fit the behavior of the diseases and their properties. Then, in Section 4, we will analyze some properties of time discounting which may be helpful in the design of the disease therapy. Section 5 proposes excessive discounting as a trans-disease process underlying addiction and other disorders, and explains it through the concept of hazard rate. Finally, Section 6 provides a summary and conclusion.

2. ADDICTION AND ILLNESSES AS DISCOUNTING PROCESSES

Usually, the term *discounting* is applied to contexts involving delay (delay discounting), or probability (probability discounting). However, several kinds of quantifiable processes may also be viewed as discounting phenomena (Rachlin, 2006). **Table 1** shows these processes and introduces the behavioral and psychopharmacological treatment of addictions and diseases which can be considered discounting processes as well. The variable to be discounted (i.e., the original quantity), the discounted quantity and the variable involved in the discounting process is specified for every discounting process in this table. We can distinguish between temporal and non-temporal variables involved in the discounting. In this regard, delay discounting and memory exhibit temporal variables involved in the discounting process, namely, delay to reward and time between learning and recall, respectively. On the other hand, an example of a non-temporal discounting variable would be the social distance from a person in the case of discounting "generosity." In their experiment, Jones and Rachlin (2006) applied a social discounting equation from Rachlin and Raineri (1992) which included a parameter measuring the social distance (from 1 to 100) between the participants and the person who would be sharing the money, 1 being the closest. The participants had to decide whether to forgo a hypothetical amount of money for themselves in order to give $75 to another person and the amount of money forgone varied with the perceived social closeness to the beneficiary.

As indicated, in **Table 1** we have introduced another process, the behavioral and psychopharmacological treatment of addictions and diseases, which can be considered as a discounting process. In actual fact, all addictions involve the involuntary consumption of an increasing amount of a certain substance. For example, cigarettes (smokers), drugs (drug addicts), and money (compulsive gamblers), among others. The level of an addiction can be defined as the amount of substance which can be consumed in a given period of time (for example, a day). Analogously, for a disease we can assume that an individual is affected by a microbial population. This justifies a joint consideration of addictions and diseases (see **Chart 1**).

It is well known that many diseases cannot be completely cured. In that situation, treatment attempts to improve or neutralize the problem, especially in chronic diseases. However, this paper is about the subset of treatments which reverse diseases completely or end medical problems permanently. More specifically, we will analyze the diseases treated with a regular dose able to reduce the concentration of pathogens in the patient.

[1]For a formal definition of impatience (impulsivity), see Cruz Rambaud and Muñoz Torrecillas (2016).

[2]For example, they refer to substance abusers.

TABLE 1 | Different types of discounting processes.

Application of discounting to	Original quantity Discounted quantity Involved variable
Delay of reward	Absolute reward value Current value Delay to reward
Probability of reward	Absolute reward value Value of probabilistic reward Probability of reward
Generosity	Money you have Money you give to another person Social distance from that person
Energy	Source of energy (e.g., light, sound) Energy distant from source Distance from source
Memory	Original learning Memory Time between learning and recall
Addiction or disease	Level of addiction Current level Regular dose/time frequency

Source: Rachlin (2006) and own elaboration.

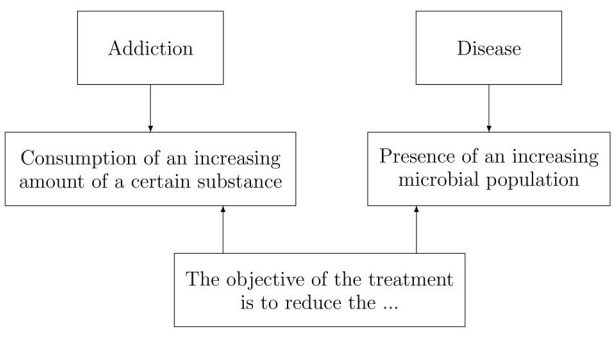

Chart 1 | Parallelism between addictions and diseases. Source: own elaboration.

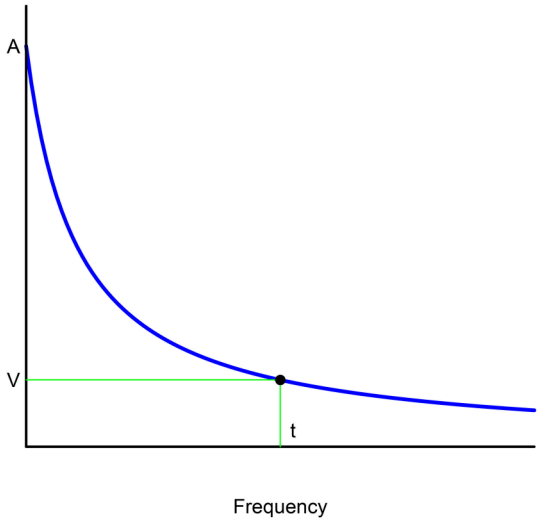

Figure 1 | Hyperbolic discounting.

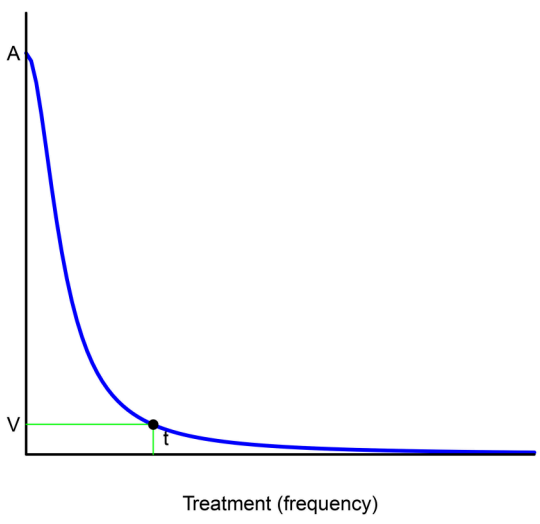

Figure 2 | Exponentiated hyperbolic discounting.

3. THE DISCOUNT FUNCTIONS FITTING ILLNESS OR ADDICTION PROCESSES

Many experimental studies have shown that the monetary discounting exhibited by people with certain addictions or diseases is best fitted to a hyperbolic discount function (see **Figure 1**). Accordingly, MacKillop et al. (2011) offer an extensive review of the literature on addictive behavior (addiction to alcohol, tobacco, and gambling, among others) related to discounting of delayed rewards. From the 64 experimental comparisons[3] reviewed by MacKillop et al. (2011), 70% used Mazur's (1987) hyperbolic discount function. In effect, a simple hyperbola-like is used in the majority of cases to describe the discount in this framework:

$$V = \frac{A}{1 + it}, \tag{1}$$

where $i > 0$ is a constant discount rate, and t is the interval between A (the value of the reward to be discounted for t periods) and V (the value of the reward at instant 0).

Our paper is also in line with the work by Augenblick et al. (2015) who suggest that individuals exhibit hyperbolic

[3]Comparisons between a group with addiction and a control group.

discounting for non-monetary goods, but exponential discounting for money. More specifically, the decay in effort is exponential, not hyperbolic, in the delay. This finding is consistent with the evidence of non-present bias on monetary payments (Andreoni and Sprenger, 2012), as opposed to real effort (DellaVigna and Pope, 2017).

According to Bernheim and Rangel (2005), addicts are sometimes allowed to consume involuntarily. To all intents and purposes, this paper introduces five important patterns of addictive behavior: (1) unsuccessful attempts to quit, (2) cue-triggered recidivism, (3) self-described mistakes, (4) self-control through precommitment, and (5) self-control through behavioral and cognitive therapy. Our paper lies in the context of this last group with the implementation of "successful behavioral therapies" able to "teach cue-avoidance, often by encouraging the adoption of new lifestyles and the development of new interests," as opposed to item 4 where addicts exhibit a "tendency to make mistakes by voluntarily removing or degrading future options."

Story et al. (2014) assimilate the progression of an illness to a discounting process when stating: "Individuals who are willing to accept a more severe illness occurring after a delay over a less severe immediate illness are said to discount future illness." According to Ganiats et al. (2000), health evolution can be described as an improvement in health from an initial state of illness, where individuals prefer immediate over delayed health improvement. More specifically, the discounting process is hyperbolic in the way that individuals are willing to accept a smaller-sooner improvement in health over a larger-later improvement. Going beyond this idea, "high discount rates for money (and in some instances for food or drug rewards) are associated with several unhealthy behaviors and markers of health status, establishing discounting as a promising predictive measure" (Story et al., 2014).

This section provides an approach toward justifying the exponentiated hyperbolic discount function as a new discounting model better able to describe the illness processes. This is because the shape of the discount function underlying the medical treatment of an illness or an addiction is very important as the mathematical expression of this function can influence wrong treatment and so itself become a trans-disease factor. As such, **Figure 2** can also be interpreted in the following way: if an individual suffers an addiction or an illness at a level A, a certain frequency t can reduce this level as far as V.

That said, under this interpretation, the function displayed in **Figure 2** can better represent the progression of a certain disease with respect to the treatment (dosage or frequency) for the following reasons:

1. The decrease in the level of addiction or disease must have a lower improvement rate at the beginning, which later starts increasing. This can be best described by stating that a future discount function must verify that V and consequently $\ln V$ are convex in a neighborhood of 0. On that note, we must clarify that this paper focuses on the types of diseases whose symptoms disappear after a period of time in which a dose of medicine has been administered to the patient. Nevertheless, there are some diseases, in particular chronic ones, which are excluded from the work. A chronic disease is a persistent, or otherwise long-lasting, disease whose effects persist over a long period. A chronic course is further distinguished from a recurrent course as recurrent diseases relapse repeatedly, with periods of remission in between. However, a chronic disease may be progressive, result in complete or partial disability, or even lead to death. The expected improvement in the patient is low in the first instants of his disease but it is also logical that the curve regarding the level of the disease can decay as the number of administered doses increases. This is the particular form of the decay function we are going to analyze in this paper.
2. Following Takahashi (2006), abstinent drug addicts may be more susceptible to relapse when an abstinence period is presented as a series of divided shorter time-blocks. In terms of intertemporal choice, abstinence implies choosing larger later rewards (i.e., successful recovery from drug addiction) instead of smaller sooner ones (i.e., immediate drug intake). He points out: "My present hypothesis states that this subadditivity may result from perception of the time-interval following Weber-Fechner law. Therefore, medical and behavioral treatments which help abstinent addicts precisely perceive time-duration of abstinent period is expected to be effective." In delay discounting, subadditivity[4] implies that the cumulative discounted value is smaller (and the discount higher) for more subdivided intervals. For example, the discount function for 1 month will be greater than the product of the corresponding discount function values for each day. Conversely, superadditive discounting means that the discounted value is greater (and the discount smaller) when the interval is divided into subintervals.

Let us apply these concepts to our proposed discount function. If $F(t)$ represents the concentration of pathogens in a patient when administering a treatment every t hours, it is possible that a dose level of reference t_0 exists such that the disease can get worse if the medicine is administered every $t_0/2$ hours and so on. This property is known as *superadditivity* which can be expressed as follows:

$$F(t_0/2)F(t_0/2) > F(t_0). \tag{2}$$

In other words, the illness/addiction gets worse by partitioning the administration of tablets/drugs. Similarly, it is possible that drug administration can improve the disease if the subintervals are greater than or equal to t_0. For instance,

$$F(t_0)F(t_0) < F(2t_0). \tag{3}$$

This property is known as *subadditivity*. As we are considering behavioral and/or psychopharmacological treatment for certain diseases or addictive behavior (pathological gambling, psychiatric disorders, smoking and drugs abuse, among others), we can also represent the medicine dosage on the x-axis, but in the case of behavioral/psychological treatment we could represent, for

[4]For more detailed reading on subadditive discounting, see Cruz Rambaud and Muñoz Torrecillas (2014).

example, a sequence of actions over the course of time. Similar reasoning could be performed by considering a dose of reference, d_0, instead of the time of administration, such that:

- $F(r)F(s) > F(d_0)$, whether $r + s = d_0$ (superadditivity).
- $F(r)F(s) < F(r + s)$, provided that r and s are greater than or equal to d_0 (subadditivity).

Observe that r and s can be different. This reasoning reinforces the argument whereby the function is convex in a neighborhood of 0. However hereinafter, we will focus on the dose as time frequency.

Our objective now is to find a suitable family of discount functions satisfying the two former items. This approach was introduced by Cruz Rambaud and Ventre (2014, 2015) when searching for a family of discount functions $F(t)$ such that the following property holds:

P: There is a certain period of time, t_0, such that the behavior of the discount function changes from subadditivity/superadditivity into superadditivity/subadditivity, i.e.:

$$F(t_1)F(t_2)\cdots F(t_n) < F(t), \tag{4}$$

if $t_1 + t_2 + \cdots + t_n = t \leq t_0$ (which, of course, implies that all numbers t_k are less than t_0, for $k = 0, 1, \ldots, n$), and

$$F(t_1)F(t_2)\cdots F(t_n) > F(t), \tag{5}$$

if $t_1 + t_2 + \cdots + t_n = t$ and $\min\{t_1, t_2, \ldots, t_n\} > t_0$ (which, of course, implies that t and all values t_k are greater than t_0, for $k = 0, 1, \ldots, n$).

As we are focusing on the disease as a delay discounting process, we will first assume that impatience as a function of delay follows the trend described in the former paragraphs. However, we are going additionally to take into account the following points:

1. If the dose must be administered every t hours, usually dividing in two could prove better, but this subdivision reaches a limit. In effect, there is a maximum partition for which the treatment is not efficient. In this regard, an exponentiated hyperbolic discount function (Rachlin, 2006):

$$V = \frac{A}{1 + it^k},\ k > 1 \tag{6}$$

or even a generalized exponentiated hyperbolic discount function:

$$V = \frac{A}{(1 + it^k)^\alpha},\ k > 1,\ \alpha > 0, \tag{7}$$

(see **Figure 2**) may be more adequate to describe an expected increasing discount rate at the beginning of the treatment, followed by a decrease in the rate. Note that i, k and α in Equations (6) and (7) represent a constant.

Observe that function (7) is a special case of a more general q-exponential time discounting model (Cajueiro, 2006; Takahashi, 2007; Cruz Rambaud and Muñoz Torrecillas, 2013) with psychological time following the well-known Stevens's power law ($\tau = t^s$), where $q = 0$:

$$V = \frac{A}{\exp_q(it^k)} = \frac{A}{[1 + (1 - q)it^k]^{1/(1-q)}},\ i > 0,\ k > 1. \tag{8}$$

This model is compatible with a sharp decrease in the discount function. Indeed, **Figure 3** shows a comparison of the hyperbolic discounting of monetary rewards for people with certain addictions or diseases with the exponentiated discount function representing the decrease of the disease with respect to time. Note that, for the same value of i, the exponentiated hyperbolic discount function (in green) is steeper than the simple hyperbola (in blue).

2. An argument which reinforces the choice of exponentiated against simple hyperbolic discounting is the so-called sequence effect as described in the experimental work by Hofmeyr et al. (2010) in the following manner: "The propensity of smokers to prefer small short-term rewards over larger delayed rewards may be mitigated, over a sequence of decisions of this kind, by encouraging or forcing them to think of the sequence as a whole."

Focusing on a disease, let us consider a microbial population of size N. An *external (exposure) dose* is the amount of an agent or chemical administered to an experimental animal or human (containing this population) in a controlled experimental setting by some specific route at some specific frequency (World Health Organization, 2009). Irrespective of the *internal dose* (the external dose is that which is absorbed and enters general circulation), the dose is determined by its *frequency* and *duration*: for example, mg/kg body weight per day over a given period of time. In this context, a *dose-response curve* is a plot of the fraction of surviving organisms as a function of the exposure intensity (Peleg et al., 1997).

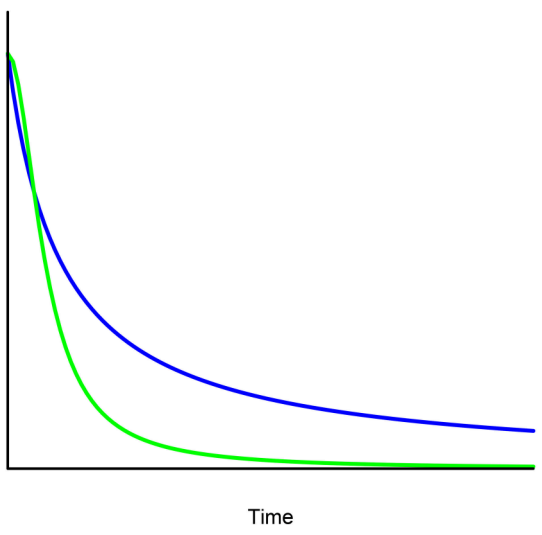

Figure 3 | Comparison between exponentiated and simple hyperbolic discounting for the same value of parameter i.

A *uniform effective dose* in pharmacology is the dose or amount of a drug which produces a therapeutic response or desired effect in a certain fraction of the subjects taking it. Hereinafter, we will represent the regular dose amount as x (in mg) and the time between two consecutive doses as t (in hours). Thus, the effective dose will be denoted by (x_0, t_0), where x_0 represents the effective dose amount and t_0 the time after which the drug has produced the desired effect. In some experimental studies about the possible doses for the treatment of certain diseases (for instance, Krober et al., 1990), patients were randomly selected to receive doses of x mg of a medicine m times per day, $x/2$ mg $2m$ times per day, $x/4$ mg $4m$ times, and so on. As a result, they obtained a recommended (optimal) medicine treatment. In general terms, let x be an amount of drug or tablets to be administered and assume that the optimal time frequency remains constant. If $F(y, x)$ denotes the surviving population after administering x, t times per day, to an initial population of size y, it can be supposed that:

$$F(y, x) = yF(1, x) = yF(x), \tag{9}$$

where $F(1, x)$ has been denoted by $F(x)$. As (x_0, t_0) is the optimal dose, one has:

$$\underbrace{F\left(\frac{x_0}{m}\right) F\left(\frac{x_0}{m}\right) \cdots F\left(\frac{x_0}{m}\right)}_{m \text{ times}} > F(x_0) \tag{10}$$

and

$$\underbrace{F(x_0)F(x_0) \cdots F(x_0)}_{m \text{ times}} < F(mx_0). \tag{11}$$

An alternative way of dealing with this issue could have been as follows. Essentially, let t be the frequency of administration (in hours) of the drug and assume that the optimal drug amount remains constant. Of course, a multiple kt of the frequency implies the same multiple of the amount to be administered for this time. If $F(y, t)$ denotes the surviving population after administering an amount x_0 with a frequency t over an initial microbial population of size y, it can be supposed that:

$$F(y, t) = yF(1, t) = yF(t), \tag{12}$$

where $F(t) := F(1, t)$ is the ratio of surviving microbes after administering x_0 with a frequency t.

As (x_0, t_0) is the effective (periodic and constant) dose, one has:

$$\underbrace{F\left(\frac{t_0}{n}\right) F\left(\frac{t_0}{n}\right) \cdots F\left(\frac{t_0}{n}\right)}_{n \text{ times}} > F(t_0) \tag{13}$$

and

$$\underbrace{F(t_0)F(t_0) \cdots F(t_0)}_{n \text{ times}} < F(nt_0). \tag{14}$$

By considering F as a function of t, these conditions are satisfied if F is superadditive to the left of t_0 and subadditive to the right of t_0. To be more precise, we can assume that the instantaneous discount rate of F, defined as:

$$\delta(t) = -\left.\frac{\mathrm{d} \ln F(z)}{\mathrm{d}z}\right|_{z=t} \tag{15}$$

increases to the left of t_0 and decreases to the right of t_0. An example of such a function could be (Peleg et al., 1997):

$$S(x) = \frac{1}{1 + \exp\{(x - x_c)/a\}}, \tag{16}$$

where x_c is a measure of the individual organism's resistance to the particular lethal agent, and a is an arbitrarily small numerical value. On the other hand, Altshuler (1981) proposes the following cumulative probability function representing the fraction of responders with time-response less than or equal to a time t when administering a dose d:

$$P(t, d) = 1 - \exp\left\{-adt^k\right\}, \tag{17}$$

where a is a constant and k is determined by a background response. In any case, the shape of the dose-response curve is shown in **Figure 4**.

Nevertheless, we are going to derive a discount function belonging to a well-known family of discount functions. To do this, we have to take into account the following result:

Theorem (Cruz Rambaud and Ventre, 2017). Let $F(t)$ be a subadditive discount function and let us consider its corresponding new discount function $G(t)$ using the time deformation $D(t) = t^k$, with $k > 1$. A necessary and sufficient condition for $G(t)$ to satisfy superadditivity and then subadditivity is that the equation:

$$\frac{k-1}{kt^k} = \delta_H(t^k), \tag{18}$$

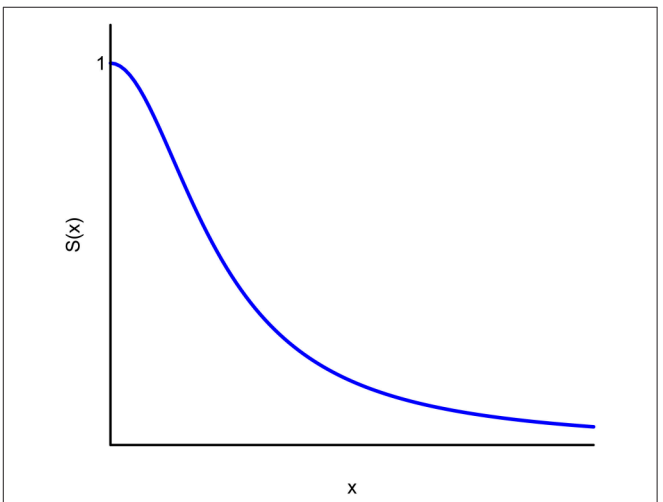

Figure 4 | Standard dose-response curve.

where $H(t) := \frac{\delta(t)}{\delta(0)}$, has a finite number of solutions.

As an application, the q-exponential discount function (Equation 8) $F_q(t)$ is subadditive for certain values of q. Consequently, by introducing the deformation $D(t) = t^k$, $k > 1$, we can obtain a family of partially superadditive and subadditive discount functions in which we can highlight the exponentiated hyperbolic discount function (Rachlin, 2006) (Equation 6) and the generalized exponentiated hyperbolic discount function (Equation 7). Both functions are suitable for describing the progression of the level of an addiction or an illness. In summary, there are three possibilities for the variable which best describes the discounting process for the level of an addiction or illness:

1. The time frequency of the drug or therapy administration.
2. The regular amount of drug or therapy dose.
3. The delay to a certain reward that the patient can receive, once discounted, depending on the waiting time. Observe that, in this case, the discounting is applied, not to the disease or addiction, but to an original reward amount, resulting in the first row of **Table 1**.

4. SOME MATHEMATICAL PROPERTIES OF THE EXPONENTIATED DISCOUNT FUNCTION

The so-called exponentiated discount function is not the only model to describe the progression of an addiction or disease under treatment. The advantage of this inverse S-curve time discount function is that it can be obtained from hyperbolic discounting by distorting time with a given power. It is noteworthy to highlight the relevance of Takeuchi's (2011) contribution since we need to introduce a new discount function able to describe the transition from an increasing to a decreasing instantaneous discount rate. In this section, we are going to introduce some mathematical properties which will be necessary to use the exponentiated hyperbolic discount function hereinafter. First, for the sake of simplicity, we will work with the mathematical expression of the exponentiated discount function for a \$1 reward. This expression is as follows:

$$F(t) = \frac{1}{1+it^k},\ i > 0,\ k > 1. \tag{19}$$

Let us calculate the instantaneous discount rate of this discount function:

$$\delta(t) := -\frac{\mathrm{d}\ln F(t)}{\mathrm{d}t} = \frac{ikt^{k-1}}{1+it^k}. \tag{20}$$

Next, we question whether $\delta(t)$ increases or decreases. To do this, we will calculate its derivative:

$$\frac{\mathrm{d}\delta}{\mathrm{d}t} = ik\frac{t^{k-2}(k-1-it^k)}{(1+it^k)^2}. \tag{21}$$

Therefore, solving the equation $\frac{\mathrm{d}\delta}{\mathrm{d}t} = 0$, we obtain the following two solutions: $t_1 = 0$ or $t_1 = \left(\frac{k-1}{i}\right)^{1/k}$. Obviously, the first solution makes no sense, meaning only the second one is consistent. Moreover, observe that $\delta(t)$ increases in the interval $]0, t_1[$ and decreases in the interval $]t_1, +\infty[$[5]. Therefore, $F(t)$ is superadditive in the interval $]0, t_1[$ and subadditive in the interval $]t_1, +\infty[$, i.e., the exponentiated discount function satisfies the property **P** defined in Section 3.

We now question whether every point (t_1, x_1) can be chosen as the maximum of $\delta(t)$. The answer is positive since (t_1, x_1) must satisfy the following system of equations:

$$x_1 = \frac{1}{1+it_1^k} \tag{22}$$

and

$$t_1 = \left(\frac{k-1}{i}\right)^{1/k}. \tag{23}$$

Simple algebra shows that $k = \frac{1}{x_1}$ and $i = \frac{k-1}{t_1^k}$. Observe that the obtained values of both k and i are consistent because $k > 1$ and $i > 0$. Finally, using the generalized exponentiated hyperbolic discount function (7), the instantaneous discount rate is:

$$\delta(t) = \frac{\alpha ikt^{k-1}}{1+it^k}. \tag{24}$$

while its derivative is:

$$\frac{\mathrm{d}\delta}{\mathrm{d}t} = \alpha ik\frac{t^{k-2}(k-1-it^k)}{(1+it^k)^2}. \tag{25}$$

From this, the maximum of $\delta(t)$ has the same abscissa as in the case of the exponentiated hyperbolic discount function, its ordinate being different. Summarizing, the (generalized) exponentiated hyperbolic discount function is a good candidate for describing the progression of illnesses or addictions with respect to their treatment as hypothesized at the beginning of this paper. In this regard, Becker and Murphy (1988) pointed out that "[p]ermanent changes in prices of addictive goods may have a modest short-run effect on the consumption of addictive goods. [...] However, we show that the long-run demand for addictive goods tends to be more elastic than the demand for nonaddictive goods." They added: "Indeed, rational persons end strong addictions only with rapid and sometimes discontinuous reductions in consumption." As such, the dose frequency of drug administration can be adapted to the particular situation of a patient, showing the utility of equations from (22) to (25) when choosing the suitable frequency for each addict.

In the following section, we are going to show that impatience or excessive discounting as a trans-disease process can be explained by the fact that the corresponding discount rate is obtained from the hazard rate of the sum of two or more random times.

[5] According to Takeuchi (2011), $F(t)$ is an inverse S-curve.

5. JUSTIFYING TRANS-DISEASE PROCESSES

In order to explain our findings, we need the following definitions and results. A *hazard function* mathematically describes the effect that increases in waiting time have on the risk that something will happen to prevent an event from occurring (Gross and Clark, 1975). In the framework of temporal discounting, the fail represents the probability of an event occurring at t that will prevent the receipt of a reward, divided by the probability of the event not occurring until t, that is, the conditioned probability of fail. We can build a discount function based on *system reliability*: the discount function at t will be the reliability of the system at time t (denoted by $R(t)$), i.e., the probability that the life of the system will be greater than t (Cruz Rambaud and Muñoz Torrecillas, 2005):

$$R(t) = 1 - F(t) = \exp\left\{-\int_0^t h(x)\mathrm{d}x\right\}, \tag{26}$$

where $F(t)$ is the distribution function, valued at instant 0, of the random useful life of the system, and $h(x)$ the instantaneous hazard rate at instant x ($0 \leq x \leq t$).

To all intents and purposes, we can consider that, at instant 0, n elements work and that the useful life of each component is a random variable T. As a consequence of the fails that happen as time passes, the number of components that still work, $N(t_1), N(t_2), \ldots, N(t_n)$, decreases. Thus, we could determine the reliability and non-reliability of the system in the interval $[0, t]$ as:

$$R(t) = \frac{N(t)}{N(0)} \text{ and } F(t) = 1 - \frac{N(t)}{N(0)}, \tag{27}$$

respectively. We can define the *instantaneous hazard rate* of a component at instant t, as:

$$h(t) = -\lim_{\Delta t \to 0} \frac{\Delta N(t)/N(t)}{\Delta t} = -\frac{N'(t)}{N(t)} = -\frac{R'(t)}{R(t)} = -\frac{\mathrm{d}}{\mathrm{d}t}\ln R(t). \tag{28}$$

Taking into account that:

$$R(t) = \int_t^\infty f(x)\mathrm{d}x \text{ and } F(t) = \int_0^t f(x)\mathrm{d}x \tag{29}$$

(f being the density function of T), one has:

$$h(t) = \frac{f(t)}{1 - F(t)}, \tag{30}$$

that represents the proportion of units that fail in the interval $]dt, t + \mathrm{d}t[$ with respect to the units that continue working at time t.

We are going to make the hazard rate of the random variable T, defined in the interval $[0, +\infty[$, equal to the instantaneous rate of a discount function (Takeuchi, 2011). The justification of our approach can be found in Cruz Rambaud and Muñoz Torrecillas (2005) in the context of systems failure. In our case, we will consider the system fail as a relapse of the substance abuser in an abstinence period.

Finally, several random variables could be considered, but for the sake of simplicity only two random variables were chosen, namely, T_1 and T_2 with distribution functions $F(t_1)$ and $F(t_2)$, respectively. For example, assume that T_1 denotes the time in which the treatment of a smoker fails, and T_2 the time corresponding to a pathological gambler. In this case, experiments can describe impatience due to the aggregation of the two addictions, $T_1 + T_2$. It is well known that the hazard rate corresponding to the sum of two (whether independent or not) random variables is greater than the hazard rate of each summand (Barlow and Proschan, 1996). Let us remind ourselves that the hazard rate is the instantaneous discount rate of the discount function describing the impatience of patients, but the treatment of the first disease needs a smaller dose. This justifies that the slope of certain discount functions can be very steep and this does not only correspond to the effect that the treatment may have in the illness since there could be a trans-disease process affecting the shape of these discount functions.

6. CONCLUSION

In this paper we have described the progression of illnesses and addictions in connection with their treatment as discount functions by considering that the "discounted disease" depends on three possible explanatory variables, viz the level of dose, the frequency of administration and the time to assess the (non)monetary rewards, all other things being the same. The level of disease is superadditive for an interval and subadditive otherwise.

Essentially, if x^* and x_0 denote, respectively, the maximum and the optimal dose of medicine per day, the function representing the progression of the disease behaves as a discount

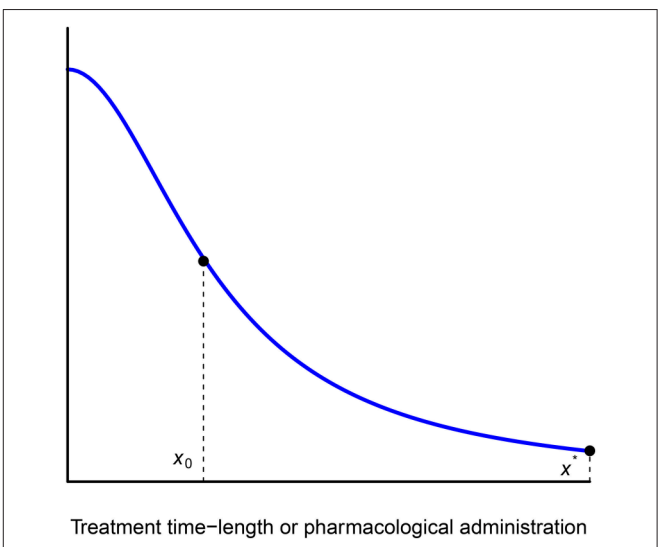

Figure 5 | Plotting the progression of a disease.

function with a bounded domain $[0, x^*]$ where the x-axis now represents regular doses of the medicine or time frequencies (see **Figure 5**). If $n := \lfloor \frac{x^*}{x_0} \rfloor$, then the following inequalities hold (for every integer h and k such that $k < n$):

$$\underbrace{F\left(\frac{x_0}{h}\right) F\left(\frac{x_0}{h}\right) \cdots F\left(\frac{x_0}{h}\right)}_{h \text{ times}} > F(x_0)$$

and

$$\underbrace{F(x_0)F(x_0) \cdots F(x_0)}_{k \text{ times}} < F(kx_0).$$

As such, despite the fact that in most experiments about illnesses and addiction processes data are fitted to hyperbolic discounting, we propose that the suitable adjustment must be to the so-called exponentiated hyperbolic discount function. This reasoning can be reinforced by the idea that most medical treatments are designed to follow a regular dosage, and this would justify the shape of the discount function. In this case, the instantaneous discount rate will be increasing up to a level of the independent variable and decreasing otherwise. An explanation of this situation is provided because in most occasions impatience is measured in patients who exhibit two or more addictions, and their impulsiveness is due to two or more diseases. Consequently, if a psychopharmacological treatment for an addiction or disease is administered based only on the impatience level shown by a patient, there could be a problem of excessive dosage. This is because impatience or excessive discounting is a trans-disease process (as indicated by Bickel et al., 2012) underlying addiction and other disorders and disease-related behavior which needs to be correctly assessed.

It should be noted that our study is a complement to the conventional economic theory of addiction (Becker and Murphy, 1988) in that our model proposes more bio-psychologically plausible characteristics for the decay of the biological influences of drug consumption after "cold turkey" (abstinence) proposed as exponential "depreciation" processes in Becker's model.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Health Economic Data in Reimbursement of New Medical Technologies: Importance of the Socio-Economic Burden as a Decision-Making Criterion

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Background: Assessment and appraisal of new medical technologies require a balance between the interests of different stakeholders. Final decision should take into account the societal value of new therapies.

Objective: This perspective paper discusses the socio-economic burden of disease as a specific reimbursement decision-making criterion and calls for the inclusion of it as a counterbalance to the cost-effectiveness and budget impact criteria.

Results/Conclusions: Socio-economic burden is a decision-making criterion, accounting for diseases, for which the assessed medical technology is indicated. This indicator is usually researched through cost-of-illness studies that systematically quantify the socio-economic burden of diseases on the individual and on the society. This is a very important consideration as it illustrates direct budgetary consequences of diseases in the health system and indirect costs associated with patient or carer productivity losses. By measuring and comparing the socio-economic burden of different diseases to society, health authorities and payers could benefit in optimizing priority setting and resource allocation. New medical technologies, especially innovative therapies, present an excellent case study for the inclusion of socio-economic burden in reimbursement decision-making. Assessment and appraisal have been greatly concentrated so far on cost-effectiveness and budget impact, marginalizing all other considerations. In this context, data on disease burden and inclusion of explicit criterion of socio-economic burden in reimbursement decision-making may be highly beneficial. Realizing the magnitude of the lost socio-economic contribution resulting from diseases in question could be a reasonable way for policy makers to accept a higher valuation of innovative therapies.

Keywords: health technology assessment, reimbursement, decision-making, cost-effectiveness, burden of disease, socio-economic burden, cost-of-illness, rare diseases

INTRODUCTION

The balance between the value of a health technology and the effective access to it represents an important issue of today's health policy. Assessment and appraisal of new medical technologies is a debate of political priorities, health system specifics and societal expectations. In all countries, choices in the allocation of resources are necessary. Health technology assessment (HTA) has been introduced as a concept to address rising health care costs and growing fiscal concerns (Iskrov and Stefanov, 2016). Health economic data play a crucial role in this process and the subsequent reimbursement decision-making (Jakovljevic and Getzen, 2016).

Health technology assessment systematically explores the properties and effects of a health technology, evaluating direct, and intended effects, as well as indirect and unintended consequences. These factors include safety, efficacy, effectiveness, cost, cost-effectiveness, as well as expected social, legal, ethical, and political impacts. There is a growing consensus on the importance of balancing all these criteria, which are determining the impact of a health technology on the healthcare system. In this context, the progress in medical research and development requires innovation of HTA process too. HTA should be updated in order to respond to such challenges, as innovative health technologies pose new critical factors, which affect patients, payers and providers (Panzitta et al., 2015).

OBJECTIVE

This perspective paper discusses the socio-economic burden of disease as a specific reimbursement decision-making criterion and calls for the inclusion of it as a counterbalance to the cost-effectiveness and budget impact criteria. The current limitations of the latter in HTA of innovative therapies are outlined. We focus on addressing these concerns through cost-of-illness studies. This is illustrated through rare diseases and orphan drugs as a paradigm of innovative health technologies.

COST-EFFECTIVENESS IN REIMBURSEMENT DECISION-MAKING

Cost-effectiveness is a leading consideration in priority setting and resource allocation. It is a utilitarianism-inspired idea, aiming to achieve the biggest possible benefits to the widest range of users. Its rationale is clear, as growing number of innovative health technologies are available while budget resources are limited. Cost-effectiveness is usually denoted as an incremental cost-effectiveness ratio (ICER). ICER is defined as the ratio of the change in costs of a therapeutic intervention (compared to the alternative) to the change in effects of the intervention (Eichler et al., 2004). In other words, it is the ratio of the extra costs to the extra effects. Meeting this criterion is the most important objective from health economic perspective. In practice, however, few innovative health technologies tend to be cost-effective. Appraisal is very often a choice between more costs and more effects or less costs and less effects.

Incremental cost-effectiveness ratio is not a new concept. Despite political will and public demand for transparent and objective reimbursement decisions on new medical technologies, there are very few examples of officially accepted and applied ICER thresholds. UK's National Institute for Health and Care Excellence (NICE) is often mentioned as using, albeit implicitly, ICER thresholds. Nevertheless, this institution has repeatedly denied such statements. ICER does offer a range of theoretical advantages, including reduced burden on decision-makers, consistency and effectiveness of reimbursement decisions (Eichler et al., 2004). However, this criterion remains a politically and morally dividing issue. The implementation of an explicit ICER threshold requires various comparisons and rankings under strictly defined settings, which do not always exist in real world. Moreover, there is no constant, context-independent willingness to pay for each gained unit of health effect (McCabe et al., 2008). Payers and society as a whole tend to give different priority to different health technologies. In many occasions, there is a need for flexibility and inclusion of *ad hoc* considerations in these decisions. Furthermore, the single universal focus on ICER as a reimbursement decision-making benchmark is detrimental. ICER has been criticized for limiting patient choice and health care rationing (Schnipper et al., 2015). Finally, any positive ICER, no matter how appealing, represents additional spending which may not be always affordable or sustainable.

BUDGET IMPACT IN REIMBURSEMENT DECISION-MAKING

The overall reimbursement decision on a new medical technology requires a budget impact analysis. Opportunity costs are the main reason for implementing this criterion. While various economic analyses allow decision makers to assess the effectiveness of health technologies, budget impact analysis is measuring the financial impact of the adoption and use of a new medical technology within the health system. Given the increasingly stringent budgetary frameworks, regulators and payers demand information on the impact that a new technology would have on their limited budget (Niezen et al., 2009). In other words, this indicator represents an assessment of the accessibility of a new medical technology. Economic analyses provide the basis for a favorable reimbursement decision and budget impact analysis ultimately determines what resources would be needed to actually implement this decision.

It is not surprising that budget impact considerations are sometimes blamed for undermining the rational application of the cost-effectiveness criterion (Niezen et al., 2009). Budget impact is a substantial issue because health authorities attach great importance to the sustainability of the health care system. With regard to new medical technologies, they fear that the costs of these innovative therapies would be significant and may cause changes in resource allocation. In fact, studies showed that health technologies with a high budget impact are much more likely to be rejected for reimbursement or to be subject of access restrictions than technologies with a limited impact

(Mauskopf et al., 2013a,b). Furthermore, budget impact analysis is posing some practical challenges for new medical technologies. Especially in the case of highly innovative therapies, data on the size of patient population, secondary costs, degree of market penetration are difficult to estimate. Use of health care information is traditionally fragmented and this is additionally exacerbating the problem. Health care costs are usually divided into several different budgets. Reimbursement decisions are often taken at product level, without considering the spillover effect. For example, an innovative drug may significantly increase the costs for treatment, but at the same time it could also reduce the costs for other health and social services (Iskrov and Stefanov, 2014).

EXTENSION OF THE SCOPE AND USE OF HEALTH ECONOMIC DATA IN REIMBURSEMENT DECISION-MAKING

Health economic data and their use could significantly affect subsequent reimbursement decisions (Jakovljevic and Getzen, 2016). It is important that all relevant costs and outcomes of the medical technology in question are identified and measured. Direct and indirect costs should be included. The same goes for positive and negative outcomes. Added societal value must be considered as well. The choice of comparator is crucial and has to be guided only by the evidence-based medicine. When a new medical technology belongs to a well known therapeutic class, this comparison is easily done. Nevertheless, many innovative therapies represent a new therapeutic class themselves. In this case, there is an additional risk for bias in the comparison (Iskrov and Stefanov, 2014).

Reimbursement decision-making is not only about cost-effectiveness and budget impact (**Figure 1**). Assessment and appraisal of new medical technologies require a balance between the interests of different stakeholders. Final decision should take into account the societal value of new therapies. HTA itself does not determine whether a new medical technology worth spending of public funds for its use. This decision is ultimately taken by health authorities and payers, who base their recommendations on a combination of other criteria as well, including political factors (Iskrov and Stefanov, 2016). Reimbursement decision-making is always a question of trade-off. In the case of new medical technologies, this issue is even controversial, as it consists of two opposing principles – beneficence and justice. This is why the role of health economic data in reimbursement decision-making should further expanded. A clearly defined and accepted use of socio-economic burden as a reimbursement criterion could counterbalance the domination of the cost-effectiveness and budget impact criteria.

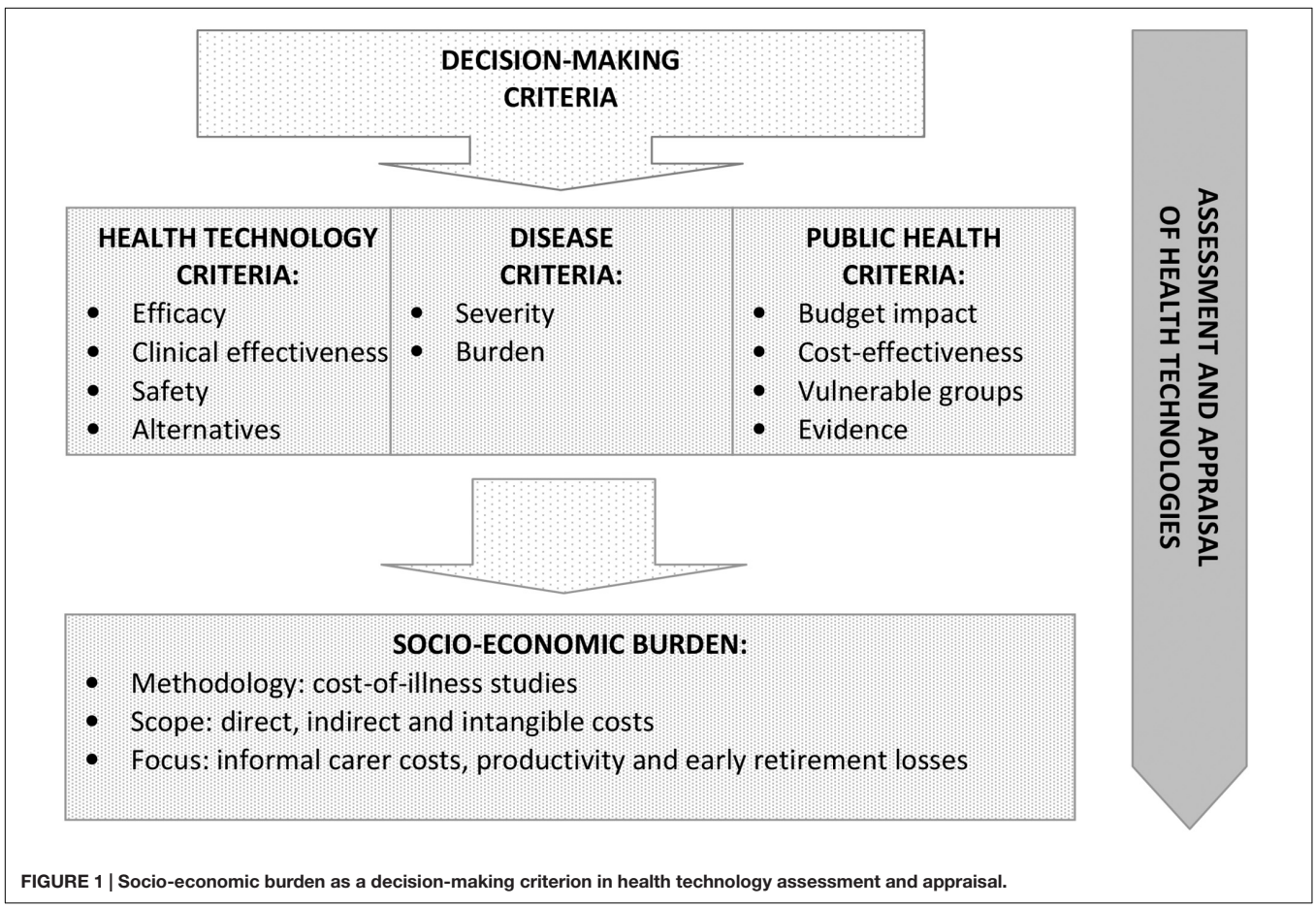

FIGURE 1 | Socio-economic burden as a decision-making criterion in health technology assessment and appraisal.

SOCIO-ECONOMIC BURDEN

Socio-economic burden is a decision-making criterion, accounting for diseases, for which the assessed medical technology is indicated (**Figure 1**). This measure is usually researched through cost-of-illness studies that systematically quantify the socio-economic burden of diseases on the individual and on the society. This is a very important decision-making consideration as it illustrates direct budgetary consequences of diseases in the health system and indirect costs associated with patient or carer productivity losses (Angelis et al., 2015b). While cost-effectiveness and budget impact are describing the health technology and its application, the socio-economic burden is characterizing the disorder. It is a crucial point in terms of unmet health needs and health inequalities. Accurate knowledge about socio-economic burden is essential to formulate and prioritize health care policies and technologies, as well as to allocate health care resources in accordance with budget constraints in order to achieve health policy efficiency (Jo, 2014).

There is no uniform definition for the burden of disease. High socio-economic burden of disease does not necessarily mean acute condition or frequent hospitalization. This indicator and its values are more related to the degree, by which physical and social symptoms affect the ability of patients to lead a normal life and perform daily activities. It incorporates a high dependence on family, relatives and carers, as well as frequent follow-up by expert medical professionals. Despite being health economic by nature, it is very important to engage clinicians when defining this criterion and its scope (Jakovljevic et al., 2016). Knowledge on disease epidemiology, morbidity and prognosis is crucial. To understand socio-economic burden and to use it efficiently in reimbursement decision-making, it is important to analyze how socio-economic costs are defined, classified and measured. Traditional paradigm of cost-of-illness studies puts costs into three categories: direct, indirect and intangible costs. Nevertheless, the decision-making focus is greatly on the first two groups, as intangible costs are difficult to quantify. Furthermore, the criterion of socio-economic burden of disease represents the potential benefits of a new medical technology if it had eradicated the disease. This type of health economic research is closely related with the concept of disability-adjusted life years, which encompass health care costs, as well as lost socio-economic contribution resulting from premature death or disability (Jo, 2014).

SOCIO-ECONOMIC BURDEN OF DISEASES AND HEALTH TECHNOLOGY ASSESSMENT

New medical technologies, especially innovative therapies, present an excellent case study for the inclusion of socio-economic burden in HTA and reimbursement decision-making. Innovative therapies are usually seen as recently introduced or modified health technologies with unproven effect or side effect undertaken in the best interest of the patient. They could be anything from an innovation with no precedent to using a conventional treatment in a different context. Assessment and appraisal of these therapies tend to be one of the most complicated tasks for health authorities and payers. It has been acknowledged that, while regulatory incentives have stimulated research and development of innovative therapies on a global level, equitable and timely access to market approved ones remains an issue. HTA has been heavily promoted a health policy tool to ensure sustainability and credibility of the reimbursement decision-making process. Despite best efforts, there are legitimate concerns among medical professionals, patients and industry that access to innovative therapies is greatly delayed (Iskrov and Stefanov, 2014). It should not be forgotten that HTA is only an instrument. Assessment and appraisal of new medical technologies have been greatly concentrated so far on cost-effectiveness and budget impact, marginalizing all other considerations. It is important to underline that reimbursement-decision making is perceived as fair and legitimate, when this process leads to a balance and agreement among different stakeholders' interests. Reimbursement policy must recognize public health priorities and fiscal constraints, but it should also respect the individual health care right of each patient (Iskrov and Stefanov, 2016).

These assumptions are particularly strong in the field of rare diseases and orphan drugs. Rare diseases pose a unique challenge to health authorities and payers, as they represent life-threatening or chronically debilitating conditions with a low prevalence and a high level of complexity. It is estimated that between 5 000 and 8 000 distinct rare diseases exist today, affecting between 6 and 8% of the population in the course of their lives. In other words, the total number of people affected by rare diseases in the EU is between 27 and 36 million. Because of their low prevalence, their specificity and the high total number of people affected, rare diseases call for a global approach based on special and combined efforts to prevent significant morbidity or avoidable premature mortality and to improve the quality of life and socio-economic potential of affected persons (European Union, 2009).

Methods for health economic evaluation have their own specifics when it comes to rare disease-related orphan medicinal products. Orphan drugs are unable to meet the standard ICER threshold. Moreover, health authorities and payers have strong concerns about the increasing budget impact of those therapies. These two considerations have historically had a negative impact on the assessment and appraisal of orphan drugs (Rosenberg-Yunger et al., 2011; Iskrov and Stefanov, 2014). In this context, data on rare disease burden and inclusion of explicit criterion of socio-economic burden in reimbursement decision-making may be highly beneficial. Realizing the magnitude of the lost socio-economic contribution resulting from rare disease premature death or disability could be a reasonable way for policy makers to accept a higher valuation of innovative therapies. Generation of such evidence is crucial for the timely access to these products.

The EU-funded BURQOL-RD project (Social Economic Burden and Health-Related Quality of Life in Patients with Rare Diseases in Europe) should be highlighted as the very successful first step toward this objective. BURQOL-RD studied both direct and indirect costs for 10 rare diseases in 8 EU

Member States. While there were important differences between countries depending on the degree of development of formal care provided by social services, informal care was found to be the main social resource involved in the care of people with rare diseases (López-Bastida et al., 2016). Results from this project showed the importance of studying the economic consequences of rare diseases from a societal perspective and interpreting the outcomes in a global framework. Burden of disease data from BURQOL-RD provided insights into the distribution of rare disease costs and their impact on national health system expenditure, as well as on patient and family income (Angelis et al., 2015a; López-Bastida et al., 2016). More importantly, this study demonstrated that while direct costs for rare diseases were significant, other indirect societal costs, such as informal care, productivity loss and early retirement, were even higher. In short, rare diseases represent considerable invisible costs to the society and this should be taken into account when making a reimbursement decision about orphan drugs and innovative therapies for rare diseases.

CONCLUSION

Assessment and appraisal of new medical technologies is a debate of political priorities, health system specifics and societal expectations. Health economic data and their use could significantly affect subsequent reimbursement decisions. Reimbursement decision-making is not only about cost-effectiveness and budget impact. Socio-economic burden quantified through cost-of-illness studies is an important and essential benchmark in health policy. By measuring and comparing the socio-economic burden of different diseases to society, health authorities and payers could benefit in optimizing priority setting and resource allocation.

Generation of such evidence goes far beyond clinical trials and requires multi-stakeholder cooperation and coordination. Early constructive dialog and elaboration of disease-tailored research tools could set the scene for ongoing accumulation of evidence, as well as for proper and timely assessment and appraisal of new medical technologies. Burden of disease data need to be updated to understand the economics of diseases and their changing cost structures. This will enable policymakers to better understand the factors that impact on disease-related expenditure, and will also enable a better-informed distribution of resources.

AUTHOR CONTRIBUTIONS

All authors listed, have made substantial, direct and intellectual contribution to the work, and approved it for publication.

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REVIEW
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Overcoming Barriers to the Market Access of Biosimilars in the European Union: The Case of Biosimilar Monoclonal Antibodies

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Background: In 2014, six of the top ten blockbuster medicines were monoclonal antibodies. This multibillion-dollar market with expiring patents is the main driver for the development of biosimilar mAbs. With the ever-increasing cost of healthcare and the economic pressure to reduce or sustain healthcare expenses, biosimilars could be instrumental in reducing costs for medication and increasing patient access to treatment.

Objectives: The aim of this study is to identify and describe the barriers to market access of biosimilar mAbs in the European Union and to analyze how these barriers could be overcome.

Methods: A narrative literature review was carried out using the databases PubMed, Embase, and EconLit. Studies were published in English or Dutch. Additionally, the reference list of the articles was checked for relevant studies. Articles and conference papers known to the authors were included as well. Articles were also identified by searching on the website of the Generics and Biosimilars Initiative (GaBI) journal.

Results: Six barriers were identified based on available literature: The manufacturing process, the regulatory process, intellectual property rights, lack of incentive, the impossibility of substitution, and the innovator's reach. These six barriers are presented as a possible framework to study the market access of biosimilar mAbs. Based on the literature search, recommendations can be made to overcome these barriers: (i) invest initially in advanced production processes with the help of single-use technology, experience or outsourcing (ii) gain experience with the regulatory process and establish alignment between stakeholders (iii) limit patent litigation, eliminate evergreening benefits, build out further the unitary patent and unified patent litigation system within the EU (iv) create demand-side policies, disseminate objective information (v) change attitude toward biosimilar switching/substitution, starting with physician, and patient education (vi) differentiate the biosimilar by service offerings, use an appropriate comparator in cost-effectiveness analyses.

Conclusions: Barriers to the market access of biosimilar mAbs could be reduced when more transparency and communication/education is used in all steps toward market access in order to increase the trust in biosimilar mAbs by all stakeholders. Only then biosimilar mAbs will be able to fully capture their cost saving potential.

Keywords: biosimilar, monoclonal antibody, market access, European Union, literature review

INTRODUCTION

Biotechnology has been widely adopted by large pharmaceutical companies in the development of new medicines. Medicines produced using biotechnology, biological medicines or biologics, represent a growing share of all medicines worldwide. In 2012, they accounted for 18% of the global market. In 2007, this was 15%, and in 2002 this was only 11% (Rickwood et al., 2013). Monoclonal antibodies (mAbs) are a great contributor to this growth. Today they represent a multibillion-dollar industry of medicines used mainly in treatment of autoimmune diseases and cancer. In 2014, eight of the top ten blockbuster medicines in Europe were biological medicines, six of these were mAbs (Dolan, 2015). Due to the complex and costly manufacturing process and often unique therapeutic value, biological medicines are more expensive than small molecule chemical medicines. The high prices and the success of biological medicines put pressure on healthcare expenses, and this cost pressure may lead to a decrease in patient access to medicines (McCamish and Woollett, 2012; Rickwood and Di Biase, 2013).

Following expiry of patent and other exclusivity rights, the market may open to non-innovator versions of biological medicines, so-called biosimilar medicines or biosimilars, which tend to be less expensive due to a lower research and development (R&D) cost and possible impact of competition. In the European Union, the European Medicines Agency (EMA) has established a regulatory framework for registration of biosimilars since 2005. The EMA defines a biosimilar as follows: *"A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorized original biological medicinal product (reference medicinal product) in the European Economic Area (EEA). Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise needs to be established."* (EMA, 2014) Later, product specific biosimilar guidelines were developed, e.g., for products containing monoclonal antibodies (EMA, 2012a). In September 2013, the first biosimilar mAb for infliximab developed by Celltrion was approved by the EMA as Inflectra® (by Hospira) and Remsima® (by Celltrion). These products could not enter the greater part of the European market until February 2015 due to prolongation of market exclusivity of the innovator medicine Remicade®. In 2014 global sales of the originator product Remicade® accounted for $9.8 billion (2014 Sales of Recombinant Therapeutic, Antibodies and Proteins, 2015). Even a limited price discount of 30% would create a substantial cost-saving per treatment.

With the ever-increasing cost of healthcare and the economic pressure to reduce or sustain healthcare expense, biosimilars could be instrumental in reducing cost for medication and increasing patient access to treatment (McCamish and Woollett, 2012; Rickwood and Di Biase, 2013). Especially the cost for cancer treatment is becoming unaffordable, even for wealthy countries, due to higher prevalence of cancer and more expensive biological and targeted therapies (Cornes, 2012). This results in a huge market potential for biosimilars.

The advancement in technology makes biosimilars possible and the pressure on healthcare budgets makes them desirable. Therefore, both a technological push and a market pull mechanism are facilitating biosimilar mAb development. In comparison to earlier introduced biosimilars, e.g., filgrastim biosimilars, biosimilar mAbs are more complex in structure and mode of action. In addition, competition from innovative products is fierce, and the regulatory requirements for biosimilar mAbs are more complex than for smaller biosimilars (Declerck, 2013; Mellstedt, 2013). The huge market potential nevertheless resulted in many pharma companies investing in biosimilar mAb development.

Although multiple patents of mAbs are expired (e.g., rituximab, trastuzumab; GaBI, 2015), so far only one biosimilar mAb received marketing authorization, i.e., a biosimilar of infliximab (European Medicines Agency, 2016a). Biosimilar etanercept was approved early 2016 and is regarded by many as a mAb. However, etanercept in a strict sense is not a mAb, but a TNF receptor fusion protein. It was assessed by EMA according to the same principles as mAbs (European Medicines Agency, 2015a). We expect the same uptake barriers for biosimilar etanercept. Furthermore, earlier biosimilars have seen slow uptake in European markets (GaBI, 2012; Farfan-Portet et al., 2014). With the slow emergence and uptake of biosimilar mAbs, we perceive that market access of biosimilar mAbs is hindered by several barriers.

The aim of this study is to (a) identify the barriers to market access of biosimilar mAbs in the European Union (EU), and (b) analyze how these barriers could be overcome.

This manuscript is based on the MBA thesis of one of the authors, Clara Jonker-Exler (Jonker-Exler, 2014). To the best of the authors' knowledge, this is the first study that (a) reviews the literature on market access of a significant class of new medicines, i.e., biosimilar mAbs, (b) uses a framework to identify and discuss barriers to market access of biosimilar mAbs, and (c) proposes clear recommendations to reduce or remove such barriers.

METHODS

This study is based on a narrative literature review. Relevant studies were identified by searching PubMed, Embase and

EconLit up to November 2015. The following search terms were used: "biosimilar monoclonal antibody," "biosimilar market entry." Studies could be published in English or Dutch. Additionally, the reference list of the articles was checked for other relevant studies. Articles known to the authors were included as well and conference papers were scrutinized for relevant information. An additional source was the website of the Generics and Biosimilars Initiative (GaBI) journal, GaBI Online.

Published literature was analyzed while the biosimilar mAb market is developing faster than studies can be carried out and published. The barriers may resolve or change over time and there will possibly be differences between different types of biosimilar mAbs. Even though only one biosimilar mAb is currently on the market, patents expired for some of the highest sold biologicals (rituximab, trastuzumab) or will expire in the next few years (**Table 1**), allowing more biosimilar mAbs to enter the market. Currently (March 2016), four dossiers for biosimilar mAbs [infliximab (one), rituximab (one) and adalimumab (two)] are under review at the EMA (European Medicines Agency, 2016c).

RESULTS AND DISCUSSION

Barriers to Market Access

Since literature on the market access of biosimilar mAbs is not abundant, this paper describes the market access barriers for biosimilars in general in case specific information on biosimilar mAbs was not available.

With a view to undertaking a structured analysis of barriers to biosimilar market access, this paper draws on the framework proposed by Aaron (Ronny) Gal and the hurdles that he identified (Gal, 2014; Gal et al., 2015). Gal's framework was adapted based on the available literature to develop our own framework that allows to analyze barriers to market access of biosimilar mAbs. Six barriers were identified based on available literature and hurdles described by Aaron (Ronny) Gal (Gal, 2014; Gal et al., 2015): The manufacturing process, the regulatory process, intellectual property rights, lack of incentive, the impossibility of substitution, and the innovator's reach. (**Table 2**) These six barriers are presented as a possible framework to study the market access of biosimilar mAbs.

An Expensive and Complex Manufacturing Process

The barrier of scale and experience is high in the biotech pharma industry, mainly because of high investment requirements for manufacturing processes and learning curve effects (Simoens, 2009).

Not only the cost, but also the complexity of the manufacturing process hinders biosimilar mAb development. Biosimilar developing companies have no access to the original biological expression system that was used for the innovative reference product and therefore need to take a reverse engineering approach (Mellstedt, 2013). Thus, full knowledge of the production process of the innovator medicine is not available as it is mainly protected by trade secret. Contrary to highly predictable chemical processes, the biological production process is more difficult to control (Lepage-Nefkens et al., 2013), and quality attributes of the product are highly influenced by changes in the production process, e.g., different expression system, growth conditions,... (Declerck, 2013). This complicates the reverse engineering of biological medicines, and therefore the production of a highly similar biological medicine.

Once the reverse engineering of the biosimilar mAb is finished, and the development and testing is successful, the company will need to upscale production and possibly open new facilities to meet market demand. Every change in production, including upscaling, may affect one or more quality attributes of the product, and managing the manufacturing process will be a continuous challenge for the biosimilar developer. Hence, access to manufacturing technologies may be restricted to those companies who have been investing in biologic manufacturing platforms throughout the years (Calo-Fernández and Martínez-Hurtado, 2012).

TABLE 1 | Exclusivity expiration dates monoclonal antibodies in the European Union (EU) (GaBI, 2015; European Medicines Agency, 2015c).

INN	Reference product	Exclusivity expiration EU	Biosimilar	Year of EMA approval
Infliximab	Remicade	2015		1999
			Inflectra	2013
			Remsima	2013
Adalimumab	Humira	2018	/	2003
Etanercept*	Enbrel	2015		2000
			Benepali	2016
Rituximab	Rituxan	2013	/	1998
Trastuzumab	Herceptin	2014	/	2000
Bevacizumab	Avastin	2022	/	2005
Cetuximab	Erbitux	2014	/	2004
Ranibizumab	Lucentis	2022	/	2007

**Not a real mAb.*

TABLE 2 | Barriers to market access of biosimilar monoclonal antibodies in the European Union.

Manufacturing process	• Expensive • Complex
Regulatory process	• Uneven contribution and acceptation by stakeholders
Intellectual property rights	• Innovator patents • Prolongation of exclusivity rights • Patent disputes
Lack of incentive	• Difficult to differentiate • Limited price discounts • Limited knowledge and acceptance • Burden of change
Impossibility of substitution	• No interchangeability • Little to no policies in favor of switching and substitution
Innovator's reach	• Strong ties with physicians and patients • Competitive rebates

A Regulatory Process with Uneven Contribution and Acceptation by Stakeholders

The EMA guideline for biosimilar mAbs was approved in 2012 (EMA, 2012a). Until that time, biosimilar developers were unsure about the final regulatory requirements for biosimilar mAbs. In 2009, EMA started with providing individual protocol assistance and scientific consultations to companies to avoid slowdown of the development of biosimilar mAbs (European Medicines Agency, 2015b). Even with the published guideline, the evaluation is very much case-by-case and the developer has the opportunity to propose novel study techniques (Schellekens and Moors, 2010; EMA, 2012a).

During the public consultation period of the EMA guideline on biosimilar mAbs, industry and regulatory representatives made comments, while the medical profession did not take this opportunity to be involved in designing the guidelines (Ebbers et al., 2012a). This uneven contribution to the guidelines by different stakeholders has led to uneven commitments of medical professionals, patients and industry to the outcome of the guideline. This may have contributed to concerns raised by medical professionals and patients/patient organizations, subsequently hindering uptake of biosimilars in the market (Aapro, 2011).

Innovator Patents, Prolongation of Exclusivity Rights, and Patent Disputes

The earliest market entry date for a biosimilar is the latest expiration date of relevant patents as well as data and market exclusivity rights, but in most cases patents are the determinant blocking market entry (Rader, 2013). Patent protection is a legal restraint on new market entry of biosimilars, but patent protection and market exclusivity are tools for innovator biologicals to recover the R&D expense.

While the patent for a product, which claims the specific amino acid sequence of the medicine, blocks market entry of biosimilars, innovator patents on production processes and mAb applications complicate the development of biosimilars. Patents on manufacturing processes can be used to prevent manufacturers of biosimilars from using the same production processes as innovators. On the other hand, biosimilar developers will never know the details of the production process, since these are kept as a trade secret. Choosing or adapting different production processes may lead to differences in the end product, which then need to be shown as not having an effect on efficacy and safety in patients. This adds to the burden and cost of manufacturing process design of biosimilars and validation after manufacturing.

The first approved biosimilar mAb, an infliximab biosimilar, could not directly enter the greater part of the European market due to an extension of market exclusivity of the innovator medicine Remicade® of 6 months, granted in return of filing an extra indication for pediatric use (GaBI, 2013). The possibility of prolongation of exclusivity rights, as a reward for e.g., licensing pediatric indications, makes the date for market entry of the biosimilar more uncertain. In addition, patents are territorial in scope, therefore patent expiration dates may differ across countries, which further complicates market entry.

The first company to launch a biosimilar will likely need to resolve patent disputes and this could explain why some companies have halted their trials (Rader, 2013; Malkin, 2015). This leads to a complicated trade-off between postponement of the launch date, investing high budgets in new production processes and subsequent validation, or risking the cost and possible loss of a patent dispute.

With the slow uptake of existing biosimilars and the difficulties in developing biosimilar mAbs, the abrupt drop in sales or patent cliff that innovators face is much less sharp and acute for biologics than in the case of generic small molecules (Calo-Fernández and Martínez-Hurtado, 2012). Nevertheless, with the high revenues of biologics threatened by biosimilar competition, the innovator companies are expected to fight off and delay this competition.

Difficulties to Differentiate a Biosimilar, Low Price Discounts, Limited Knowledge and Acceptance, and the Burden of Change Lead to a Lack of Incentive

After marketing authorization is granted, the uptake of biosimilars is influenced by incentives for healthcare payers, physicians, pharmacists and patients to promote, prescribe, dispense, and use these biosimilars.

The possible strategy of differentiation leads to the importance of providing a biosimilar product with a greater perceived value than the originator biological product. Where innovative biologics are highly branded it is more difficult to differentiate biosimilars and use this to incentivize buyers.

With the high cost of development, the biosimilar can only be introduced on the market with a limited discount compared to the originator. They are usually priced at a discount of only 10–35% (Farfan-Portet et al., 2014). Absolute cost savings could still be substantial because of the high price and high volume of the reference medicines (Declerck and Simoens, 2012).

Physicians are hesitant to accept biosimilars as equal to the reference product (Aapro, 2011) and they generally do not directly benefit from the lower cost. There is a need for an incentive to facilitate biosimilar introduction and transition from prescribing the familiar and trusted reference product, to prescribing a biosimilar mAb with its inherent uncertainties, and to compensate for the effort it will take to explain to their patients the switch to a cheaper alternative. Patients will follow the advice of their physician and patient associations, and are influenced by reports in general media.

Physicians are mainly concerned about patient safety and need to choose the right treatment, based on available information (Schellekens, 2009). The overall slow uptake of currently available biosimilars in Europe is mainly ascribed to low physician knowledge and acceptance of the concept of biosimilarity (Aapro, 2011; European Commission, 2013; Rickwood and Di Biase, 2013).

No Interchangeability, and Little to No Policies in Favor of Switching and Substitution

Another barrier biosimilar mAbs face is the impossibility of substitution in most European countries. Substitution is the act of replacing the innovator medicine with the biosimilar, or

one biosimilar for the other, at the pharmacy level, without the previous consent of the prescribing physician (Boone et al., 2013). Substitution is the reason generic medicines can gain market share rapidly.

In Europe, the national authorities are responsible for the legislation on substitution. So far, few countries, e.g., France and Germany, have explicitly allowed a restricted form of biosimilar substitution (Drozd et al., 2014; GaBI, 2014) and therefore market share in Europe will need to be gained by costly marketing or high discounts.

The decision on interchangeability lies as well with the national authority of the EU member states. The evaluation by the EMA does not include a statement on interchangeability of biosimilars on an individual level (EMA, 2012b). Interchangeability of the biosimilar is a prerequisite for substitution. It could be argued that if a biosimilar is approved in Europe, it is deemed interchangeable with its reference product on a population level (Ebbers et al., 2012b). Even though this is applicable to treatment-naïve patients, uncertainties still exist about switching for patients during their treatment.

Switching is prescribing or dispensing a biosimilar to a patient who was previously using the innovator medicine, or vice versa. To enable track and trace, repeated switching and substitution without consent of the prescribing physician are not advised (Weise et al., 2012). A company can only live up to its post-authorization safety study requirements if accurate track and trace is guaranteed, so an adverse event can be traced to the exact product causing it (Vermeer et al., 2015). It should be noted that this is further complicated by the delay of certain adverse events such as immunogenicity. If more biosimilars of the same molecule enter the market, the issue is further complicated, as a biosimilar is similar to a reference product, and similarity to another biosimilar has not been studied.

Without the possibility of substitution, biosimilars are offered as a choice for new patients or as a one-time switch for stable patients only. This market segmentation makes the size of the potential market for the biosimilar a fraction of the total market of the reference product, especially for those products used in long-term treatments (Rickwood and Di Biase, 2013).

Strong Ties of the Innovator Company with Physicians and Patients, and Offering of Competitive Non-transparent Rebates

As mentioned before, the innovator company is likely to undertake steps to protect its market share against biosimilar mAb competition (Morisot et al., 2013), and has a better position to offer a differentiated product. The innovator companies protect their market share not only by patent strategies but also through strong ties with physicians and patients.

The innovator companies often have a long lasting relationship with the physicians, sponsoring clinical research or offering practical support. Also patient associations often have strong ties with innovator companies that sponsor their meetings and offer educational materials.

For many European hospitals, the procurement of medications is done by a group of hospitals through extensive negotiation with the pharmaceutical industry (Lepage-Nefkens et al., 2013). High rebates or interesting research sponsoring can be given when procurement of medication is concentrated to a few companies. This can make it difficult for a biosimilar developer who might not offer as complete a package and is not able to give the rebate. The extent of the rebates, and other favorable agreements with hospitals, is often unknown to the third party payer (Lepage-Nefkens et al., 2013). For mAbs that are mainly used inside the hospital, it may therefore, depending on the funding model of the hospital, be profitable for the hospital to procure the innovator medicine, even if the biosimilar has a lower list price (and subsequent lower reimbursement rates). High-cost cancer medication like mAbs, are often not discounted, because many have no therapeutic alternative and they are not likely to be continued for outpatient use (Vogler et al., 2013). This can change when biosimilar mAbs enter the market offering a lower cost therapeutic alternative. The innovator company will likely lower the price of the innovator medicine and therefore biosimilar mAbs cannot rely on price competition alone but will need to offer a differential advantage through marketing and service offerings (Bocquet et al., 2014).

Overcoming the Barriers

Based on the literature review, the following recommendations are proposed to overcome barriers to the market access of biosimilar mAbs (**Table 3**).

Invest Initially in Advanced Production Processes with the Help of Single-Use Technology, Buy-in of Experience, or Outsourcing

Technological advances have led to more efficient cell lines that produce an increased amount of antibody while using more standardized, less expensive media and thus creating a higher yield at a lower cost (Calo-Fernández and Martínez-Hurtado, 2012; Gal et al., 2015). The innovator company is bound by the validated original processes, while the biosimilar developer can use modern techniques from the start.

TABLE 3 | Recommendations to overcome barriers to market access of biosimilar monoclonal antibodies in the European Union.

Barrier	Recommendation
Manufacturing process	• Invest initially in advanced production processes with the help of single-use technology, buy-in of experience or outsourcing
Regulatory process	• Gain experience with the regulatory process and establish alignment between stakeholders
Intellectual property rights	• Limit patent litigation • Eliminate evergreening benefits • Build out further the unitary patent and unified patent litigation system within the European Union
Lack of incentive	• Create demand-side policies • Disseminate objective information
Impossibility of substitution	• Change attitude toward biosimilar switching/substitution, starting with physician and patient education
Innovator's reach	• Differentiate the biosimilar by service offerings • Use an appropriate comparator in cost-effectiveness analyses

The availability of single-use (i.e., disposable) technology in the development stage of biosimilars may lower the cost involved in the early development stage (Whitford, 2012).

Further development cost and time savings can be realized through buy-in of manufacturing experience and outsourcing. Initial investment in a technically advanced production process will keep production costs low in the future and lead to a better competitive position when the biosimilar market becomes generic like with competition based on price (Rader, 2013).

With the ongoing technological advances in analysis and manufacturing of biosimilars, this barrier will decrease over time.

Gain Experience with the Regulatory Process and Establish Alignment between Stakeholders

The EMA guidelines evolved as a compromise between the different industrial parties, innovator vs. biosimilar, and the regulatory body. Regulatory authorities need to ensure patient safety and encourage both competition and innovation in the biopharmaceutical industry (Blackstone and Fuhr, 2013; European Medicines Agency, 2016b). The EMA guidelines are supportive of biosimilar development and it is up to the company developing the biosimilar to use it to the greatest advantage and to reduce the need for large and expensive clinical trials.

The historical market approval of biosimilars shows a case-by-case approach and approval of the marketing authorization application based on the available test data and the intellectual judgment of the EMA (Schellekens and Moors, 2010). Profound knowledge of and experience with the regulatory requirements, in combination with EMA Scientific advice/Protocol assistance, will help a company to adjust the biosimilar mAb development process to these requirements and overcome this barrier for the EMA regulatory pathway.

Greater alignment between the medical community and the regulators can lead to greater trust in the regulatory process (Ebbers et al., 2012a).

Limit Patent Litigation, Eliminate Evergreening Benefits, Build Out Further the Unitary Patent and Unified Patent Litigation System within the EU

Innovator companies have protected their mAbs with a myriad of patents and will likely challenge infringement of these patents by biosimilar developers. The outcome of these patent disputes will provide jurisprudence for future cases.

Dylst et al. provide a list of recommendations to enhance market access of generic medicines (Dylst et al., 2012). Of these recommendations the following are equally applicable to biosimilars: (a) Grant patents only for truly innovative medicines, thereby eliminating evergreening benefits (i.e., follow-on patents on existing products for non-significant therapeutic improvements), (b) Create a unitary European Union patent, and (c) Unified patent litigation within the European Union. Plans for a unitary patent and unified patent litigation are already made (EPO, 2016). Several EU member states signed the Agreement on a Unified Patent Court (EU, 2013).

Create Demand-Side Policies, Disseminate Objective Information

Positive experience with available biosimilars (Vulto and Crow, 2012) is increasing confidence with payers and physicians and will positively influence uptake. Not all physicians are familiar with the concept of biosimilars, neither are they confident about their safety and efficacy, but awareness has increased over the years (Noaiseh and Moreland, 2013). Providing objective information about the characteristics of biosimilars is key in increasing physician acceptance (Lepage-Nefkens et al., 2013). Improved communication to physicians, payers, and patients about the rigor of oversight for biosimilars will improve market uptake (Schneider et al., 2012). The positive experiences should strengthen reimbursement authorities, physicians, pharmacists, and patients to have a positive attitude toward biosimilars and trust in the EMA biosimilar pathway.

It is argued that a high discount strategy will not overcome the lack of physician confidence and might easily be countered by the originator company. The absence of demand-side policies for biosimilars in many EU member states restricts the potential price difference between originator and biosimilar (Simoens and Huys, 2013).

The inclusion of a biosimilar in treatment guidelines, e.g., filgrastim biosimilar in European Organization for Research and Treatment of Cancer (EORTC) guidelines (Aapro et al., 2016) and infliximab biosimilar in National Institute for Health and Care Excellence (NICE) guidance (NICE, 2016), will increase uptake.

The lack of incentive and burden of change barrier will become less high with the increase of experience and knowledge of biosimilars and the growing pressure on healthcare budgets.

Change Attitude toward Biosimilar Switching/Substitution, Starting with Physician, and Patient Education

Two possible ways are proposed to change the attitude toward biosimilar switching and substitution. First the realization and publication of more head-to-head studies with the reference product, and second strict regulations on biosimilar exchange quota (Haustein et al., 2012). The Norway Ministry of Health funded NOR-SWITCH to compare the biosimilar infliximab in all granted indications with its reference product Remicade® after switching from the reference product (Asbjørn, 2015). The rationale behind setting quota, that the prescription of biosimilar mAbs to a new patient or the one time switch for an existing patient may be considered as a low risk, will need to be clearly communicated, e.g., the position paper of the Finnish medicines agency (Fimea, 2015). This education is best done through pharmacists and physicians, who can function as ambassadors. This communication may cause an increased uptake apart from the subsequent quota introduction (Lepage-Nefkens et al., 2013). Information about biosimilars needs to be better spread to all concerned to raise confidence in the biosimilar development model. Members of the EMA Biosimilars Working Party have published two papers with a clear message that biosimilars can be considered therapeutic alternatives to the reference product (Weise et al., 2012, 2014).

However, it is unclear in view of the current knowledge whether back and forth switching may jeopardize patient safety. For now, it seems that introduction of biosimilars will be largely limited to new patients, or stable patients where a judiciously made one-time switch initiated by the prescriber can be made,

making this barrier most relevant for those biosimilar mAbs with indications for long-term chronic use like rheumatoid arthritis.

Differentiate the Biosimilar by Service Offerings, Use an Appropriate Comparator in Cost-Effectiveness Analyses

Biosimilars may be positioned as late-entrant branded products rather than generics. The biosimilar developers may need to develop strategies to differentiate products on the basis of branding and corporate identity by providing services linked to the brand identity (Ellery and Hansen, 2012). An optimized formulation (with e.g., better stability, less painful injections, more convenient storage conditions) and packaging variants and sizes are other ways a biosimilar developer can positively differentiate its biosimilar.

From a health-economic perspective, several aspects need to be considered. First, with a view to quantifying the value of second or third generations of biologics using the efficiency frontier approach (Cleemput et al., 2012), cost-effectiveness needs to be calculated versus the previous most cost-effective alternative. This alternative can be a first generation biologic or the biosimilar. Second, given that pharmaceutical companies (can) offer discounts/rebates on biologics and biosimilars, prices of biologics and biosimilars used in a cost-effectiveness analysis should be prices net of discounts/rebates. Third, economic pressure can result in lower incremental cost-effectiveness ratio (ICER) threshold limits (Cleemput et al., 2008). Therefore, second or third generation biologics will have to prove highly efficacious or cannot ask a premium price when a biosimilar or a first generation biologic is used as comparator in the cost-effectiveness analysis.

However, with the long development time and slow market uptake, the risk remains that an innovative treatment replaces the competitive power of a biosimilar mAb before the biosimilar has become profitable (Declerck, 2013).

Although brand manufacturers will still defend their reference products and compete with other biosimilar developers, they are now producing biosimilars as well. It is thus not in their interest to campaign indiscriminately against the concept of biosimilars. An example is how the acquisition of Hospira by Pfizer led to marketing of biosimilars via their Established Products Division, which is an independent competitive business unit. The innovator will still have a competitive advantage over other biosimilar developers, since biosimilar mAbs that are developed by innovator companies can benefit from the company's network and reputation.

The strong ties that innovator companies have with physicians through supporting investigator initiated trials can be challenged when the biosimilar developer has enough credibility, product and resources to facilitate these trials. This reach of innovator barrier will become less relevant once biosimilar mAbs are more accepted as therapeutic alternatives, but will never cease to exist.

CONCLUSION

Our literature search found evidence that market access of biosimilar mAbs in the EU is hampered by six barriers: The manufacturing process, the regulatory process, intellectual property rights, lack of incentive, the impossibility of substitution and the innovator's reach. (**Table 2**)

All of the barriers mentioned above apply more or less to all biosimilars, which have accordingly seen slow uptake in European markets (GaBI, 2012; Farfan-Portet et al., 2014).

Based on the literature search the following recommendations can be done to overcome these barriers to the market access of biosimilar mAbs (**Table 3**):

1. Invest initially in advanced production processes with the help of single-use technology, buy-in of experience or outsourcing.
2. Gain experience with the regulatory process and establish alignment between stakeholders.
3. Limit patent litigation, eliminate evergreening benefits, build out further the unitary patent and unified patent litigation system within the EU.
4. Create demand-side policies, disseminate objective information.
5. Change attitude toward biosimilar switching/substitution, starting with physician and patient education.
6. Differentiate the biosimilar by service offerings, use an appropriate comparator in cost-effectiveness analyses.

In addition to the recommendations above, the authors believe that within the group of biosimilar mAbs, products of which the mode of action is better understood, and/or of which the risk of immunogenicity is thought to be less, the competition is high, and which are used in short-term treatments, are expected to be accepted by the market more easily. They are thus expected to experience faster uptake than products for which the opposite is valid.

Since biosimilars are approved on a European level, it would be a good idea to make recommendations on interchangeability on a European level as well, to support national authorities in policy development and decision making.

Future research could investigate market dynamics, since the market is evolving rapidly. Not only the relationship innovator/biosimilar can be studied, also differences with second-generation innovator products. Barriers to the market access of biosimilar mAbs could be reduced when more transparency and communication/education is used in all steps toward market access in order to increase the trust in biosimilar mAbs by all relevant stakeholders. Only then biosimilar mAbs will be able to fully live up to their cost saving potential.

AUTHOR CONTRIBUTIONS

EM and CJ reviewed the literature and drafted the initial version of the manuscript. SS, IH, PD, and AV revised the manuscript critically and contributed to the interpretation of the identified barriers and recommendations to overcome these. All authors read and approved the final manuscript.

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The Systemic Changes to Improve Efficiency in Polish Primary Health Care

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Primary health care is an important part of any health care system. In highly developed countries it secures the population's most elementary health needs, with particular emphasis on preventive care and early intervention. Polish PHC model is currently undergoing a thorough transformation, associated with the need to adapt to standards designated based on the WHO's criteria, and with reference to the experience of other European countries. The paper describes the process of changes being carried out, in the context of previous experiences of reform relating to the sphere of organization, processes and efficiency. A review and systematization has been made, with regard to the undertaken activities in the field of deregulation and change of legal provisions, which are aimed at achieving the improvement of the efficiency of treatment and resource allocation. A set of recommendations based on expert's discourse have also been provided, with respect to future directions of Polish PHC transformation.

Keywords: primary health care, health care reform, efficiency, health management, Poland

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INTRODUCTION

In developed countries, primary health care (PHC) protects most of the population's health needs, having laid special emphasis on preventive care and early intervention. Similar is its role in Polish health care system, which is however subject to a process of change, including a transition from the model of budgetary financing to a mixed one, inspired by the experiences of other European countries and WHO recommendations[1].

On the level of primary health care in Poland there are acknowledged physicians of different specialties, not only family medicine specialists, auxiliary staff, which includes nurses, midwives, receptionists, therapists and other medical professionals with different levels of experience. Additionally, health measures in PHC are conducted with the use of patchy technical equipment of facilities, diversified rules of work organization, as well as heterogeneous ownership structure, which includes private providers (currently dominant), along with public and social ones. Inconsistent is also legal environment, since part of the provisions, such as those arising of Labor Code (Ustawa z dnia 26 czerwca, 1974), or the Law on Medical Activity (Ustawa z dnia 15 kwietnia, 2011) applies to all providers, while other laws are applied only to public institutions or those, which have signed a contract with the National Health Fund (NHF) and are obliged to respect

[1] WHO Conferences: Ałma-Ata 1978, Bordeaux 1983, Copenhagen 1991, Copenhagen, 1999.

the provisions of the Law on Health Services Funded from Public Resources (Ustawa z dnia 27 sierpnia, 2004).

Although many changes have been made in the area of primary care, the satisfying level of efficiency has not been achieved so far, the more that until now, not a single institutionalized tool of measuring the effectiveness of treatment in the primary care has been applied. As a natural consequence—the level of financing of the individual providers has not been connected with its level of efficiency in any way, except for the negligible mechanism of increasing by 1.35% on average of the capitation rates for units ordering, and reporting in details, more laboratory tests (provision enforced in November 2015., and now suspended to equalize rates for all providers). Additionally NHF grant some extra points in the process of contracting services for units having voluntary quality management certificate.

Most importantly—no improve of the effectiveness of treatment, in conjunction with a favorable change in health indicators and cost effectiveness, has been assured, which, to some extent, is a similar phenomenon, as observed in other post-communist countries (Jakovljevic et al., 2016). At the moment, PHC in Poland is experiencing repeating attempts to reform, aimed at improving the rationality of public spending, while taking into account the expectations of patients regarding the availability, quality, comprehensiveness and continuity of care.

Attempts to modify the system of the service provision, according to health care experts should use internationally proven tools to evaluate the effectiveness of treatment, which should then be a basis for remuneration of individual providers. With high probability, however, representatives of providers will harshly criticize this direction of change, as they used to do several times in previous years, when Poland had to face strikes paralyzing the system of primary care. At the same time, the activities of the Ministry of Health and NHF aim to shift further responsibilities to the primary care sector. This is due to financial and organizational constraints, as PHC is the least expensive level of health service provision. The result has so far been some increase in capitation rates, which is the basis for the financing of this level of care, in exchange for the inclusion among PHC tasks new duties related to the oncological treatment (Seifert et al., 2008; Holecki and Romaniuk, 2015), widening the powers of midwives in gynecology and nurses in terms of the ordination of drugs.

This paper refers to the broad context of the functioning of PHC in Poland, consisting of critical analysis of the sources and causes of the current state of affairs. We review the previous reform experiences and their functional consequences. Eventually, based on the latest literature sources and a review of official acts, we outline the likely scenario of further changes.

SYSTEMIC CAUSES OF LOW EFFICIENCY OF PHC IN POLAND

Among the most primordial reasons for the insufficient organizational capacity of PHC in Poland, there are problems of mentality, ingrained in the awareness of all stakeholders responsible for the shape and functioning of the health system. That problem arises from many years of experience of communism and habits that grown of Semashko model implemented in Poland's health system after the Second World War. This paradigm remained a basis for the organization of the system actually until the very end of the Twentieth century. Among the elements that characterized this model was a domination of hospital treatment, based on an extensive infrastructure and high prestige of doctors of clinical specialties. This was additionally strengthened with free access to specialists, not requiring a patient to have a referral from general practitioner, who, in such circumstances, had been perceived as a doctor of inferior significance, useful only in case of minor health issues.

Funding was carried out on the basis of the estimated global budgets, in isolation from the criteria of efficiency. Additionally, until 1999 patients were secured with access to PHC based on their place of residence, having no right to choose provider, which eliminated any possibility of developing mechanisms of competition (Tomasik et al., 2013). Moreover, what it is typical for all the economies operating under a deficit, the model has developed a system of socially tolerated corruption. This became one of the causes of failure of reforms in the last decade of the Twentieth century, where reform leaders had to deal not only with the objective constraints, like the lack of funds for maintenance and development of the system, or the general turbulence of the economy in transition, but also the reluctance to change. Until now in common use there is a term "health service," assuming a disinterested and non-for-profit help to another person, which is opposed to the concept of "health care market" as a commercial solution, and thus exclusive and socially unjust.

Conceptual schemes ingrained in the minds of health system participants, connected with the lack of political determination, complexity and consistency in the implementation of the assumed solutions, resulted in preservation of the specific state of inertia. It is also worth noting that the educational gap characteristic for the post-communist society, which manifested itself particularly strongly in a deep ignorance of managerial mechanisms and basic market rules, contributed to the organizational failure of the whole health sector, which for years has been fitted into a "developmental drift."

Another cause of indolence of Polish PHC must be clearly emphasized against the rules of political correctness. It is the insufficient level of competence of primary care physicians, in conjunction with staff shortages. This is a clear derivative of the system imperfections, particularly the difficulties in getting access to specialty trainings. This, in turn, results of the caste structure deeply rooted in the medical community. A consequence of this specific mechanism of professional exclusion was a situation, where whole groups of young medical professionals were pushed out to the margins of the health care system.

The first real attempt to reform the system have been taken in the 90's of the Twentieth century. The assumption was to transform primary care into a British-like model (Krztoń-Królewiecka et al., 2013). A new specialty in family medicine had been implemented, assumed to become commonly popular (Przekształcenia podstawowej opieki zdrowotnej. Strategia

realizacji leków, 1994). Young doctors were proposed to achieve specialization under a three-year residency. First such a training program was launched in 1994. For the experienced PHC doctors, a so-called "short educational path" had been offered, lasting for only 6 months. These activities were supported by World Bank's and pre-accession EU funds, and their effect was education of nearly 5000 family medicine specialists, up to the end of 2000 (Kosiek, 1997). This policy temporary filled the employment gap, but no guarantee of the persistence of the trend was ensured, as the acquired specialization was perceived as of low prestige, and did not translate into wage growth. Consequently, the issue of staff shortage is still a problem, which in turn results in an excessive work burden on doctors. This is confirmed by the official upper limits of patients per one general practitioner in Poland, which are the highest in CEE region (Oleszczyk et al., 2012). This, in turn, has a negative impact on doctors' psycho-physical work conditions, as well as reduces the quality of services and causes a negative perception of the PHC system by patients (Coulter and Jenkinson, 2005).

In financial terms, almost entire accounting system used in PHC is based on capitation rate, which is a monthly fee for the care of the group of patients declared to the doctor, nurse and midwife. Such a solution significantly simplifies the remuneration system, but at the same time deprives the positive financial incentives and strengthens the mechanism of pushing patients to specialist care.

CURRENT REFORMS IN PHC IN POLAND

It is unacceptable to keep tolerating the lack of uniform standards, effective motivational tools and clear criteria for evaluation of medical staff in Polish PHC. In case of further avoidance of adequate solutions, in conjunction with the demotivating factors and limitations of the system, the system will experience further persistence of the low service quality (Tomasik et al., 2013), late, inadequate and incomplete response of general practitioners to changing guidelines for the treatment of certain diseases, and significantly lower effectiveness of provided treatment.

An objective for decision makers initiating the change should be to create effective systemic mechanisms, which would allow not only a diverse valuation of benefits in connection with their actual quality, but also to facilitate choices made by individual patient. The development and application of standardized assessment tools should be the first step toward improving the quality of services. Currently, despite declarations, no major standardization tools, or measurements of the patients' satisfaction and effectiveness of treatment have been applied. The only exceptions are voluntary instruments linked to the implementation of the quality management systems.

The applied rules of contracting services are definitely outdated and inadequate, not only to the needs but also to the existing possibilities. Capitation method is an effective mechanism only for cost containment (Kowalska et al., 2015), having no impact on the efficiency of treatment. At the same time it intensifies the efforts of providers and doctors to maximize their own income, which is achieved by increasing the number of patients declared with a doctor, along with restrictions on access to diagnostic services or shifting costs to the sector of specialist care.

In financial terms, we observe insufficient resources combined with their incorrect allocations. In this area, there is also the issue of the lack of mechanisms connecting the amount of funds for individual provider with his operational effectiveness. Adopted solutions disable the PHC physicians from taking the assumed role of coordinator of the process of treating their patients, being rather an incentive to reduce their own responsibility than to increase it. Existing solutions do not address factors encouraging general practitioners to systematically improve their professional qualifications, which in practice leads to a depreciation of their competence.

Currently PHC in Poland is in a situation of waiting for a thorough change, the scope of which is to cover three dimensions of its operation: the structure, processes and results. In January 2016, on behalf of the Ministry of Health, a preparations of the project of complex changes has started. A panel of experts, including representatives of all organizations of family doctors, is expected to prepare the assumption of the new law until June 2016, along with the PHC development plan for further years. Members of the panel proposed a set of possible solutions, like remuneration for the effects. In such a case the capitation rate would represent only part of the PHC providers incomes (as assumed—80% at a maximum). The remaining part would be dependent on keeping patients in good health, or applying a widely defined preventive measures, which currently is strongly neglected. Among the likely indicators to be used, there are: fasting blood glucose or glycated hemoglobin (HbA1c) in patients with diabetes, targeted blood pressure or cholesterol in patients with cardiovascular diseases, body weight reduction in patients with obesity and overweight. In case of smokers, number of patients, who dropped permanently smoking might be awarded, as verified during the period of half a year, then the year and two. In general, indicators should relate to common diseases and measure the effects dependent on medical action at this level of care. Two other newly established panels should simultaneously work on changes related to deregulation in health system, and general remodeling of the health system[2].

The existing model of separate contracting of PHC doctor, nurse and midwife is to be replaced with the cumulative contract for the whole team under the supervision of a physician. It is also envisaged to supplement those teams with a psychologist. This contracting proposal met a very strong protest of nurses and midwives associated in professional self-government organizations. Supreme Council of Nurses and Midwives is in a position that the adopted proposals infringe the principle of economic freedom, as expressed in the Constitution (Konstytucja Rzeczypospolitej Polskiej z dnia 2 kwietnia, 1997). In particular, the proposal to create "medical and nursing teams" with the role of the physician as a primary care coordinator, and the lists of patients declared commonly to

[2]www.sluzbazdrowia.com.pl (Accessed: 8 May 2016); www.medexpress.pl (Accessed: 5 May 2016).

a doctor, nurse and midwife is being criticized. According to nurses and midwives, new solutions represent a threat to their professional independence (Ustawa z dnia 15 lipca, 2011). This opinion is so justified, that the current project is contrary to recent amendments, which gave nurses and midwives, in case of having an appropriate higher education of master's degree or specialization, a permission to independently prescribe medicines containing certain active substances and foods for particular nutritional uses. According to the law, this applies to some weaker drugs, the list of which has been defined in the Regulation of the Minister of Health of 20th October 2015 (Rozporządzenie Ministra Zdrowia z dnia 20 października, 2015). The list consists of 31 substances in 16 groups, e.g., antiemetics, different types of anti-infectives, anesthetics or painkillers. Furthermore, the proposal of common contracting and joint declaration of provider choice is inconsistent with the Law on Health Services Funded from Public Resources (Stanowisko nr 4, Naczelnej Rady Pielęgniarek i Położnych z dnia 8 marca, 2016).

A place of permanent dispute on competences and financial issues is also PHC cooperation with hospitals. Representatives of the inpatient sector are protesting against embarking them with a large part of the duties of PHC, which appears e.g. during the weekend and night duties, as PHC sector provides services only from Monday to Friday from 8.00 to 18.00. In such a situation, they believe increased PHC funding is unfair and needs to be corrected at the level of coordination between all elements of the health system.

Regardless of the announcement of thorough regulations of the issues of family medicine, the first minor changes are already being implemented. Regulations enforced by the NHF in 2015 (Zarządzenie nr 77/2015/DSOZ Prezesa NFZ z dnia 19 listopada, 2015), assuming better remuneration of doctors who prescribe more additional diagnostic tests, has been abandoned. Currently, a higher capitation rate will be paid to all doctors, and the reporting on selected specialized examination has been changed from quarterly to semi-annual, to be soon completely abolished. Nurses and midwives since January 2015 received wage growth, by addressing the PHC sector with a stream of "labeled" money just for this purpose from the regional NHF branches. Further salary increase have been announced for the next three consecutive years. While undoubtedly salary increase for the least paid PHC workers is a positive action, it is clear that this kind of central control deprived the health facilities managers of decisional abilities, although formally they are autonomous in decision making. Additionally the wage regulation omitted other PHC labor groups, like the receptionists or office nurses.

Improvements has been also announced in relation to the oncological package. The Ministry of Health proposes to replace the paper version of the card of oncological diagnosis and treatment (DiLO) with the sole electronic version. Additionally sanctions for over-sized level of incorrect cancer diagnoses are to be abandoned. Currently, if general practitioner refers a patient to the so-called "oncological fast track," and cancer is confirmed in less than 1 in 15 people, the doctor is excluded from the possibility of writing more such referrals. This type of punishment, along with the obligation to pass training courses for physicians, is not only a kind of stigma in the professional environment, but also gives rise to a number of risks associated with defensive behaviors when planning of oncological treatment.

The proposed deep changes in Polish PHC, which are being encouraged by the Minister of Health, on the one hand are strongly expected by experts and service providers, especially in the area of deregulation and simplification of existing rules, in particular those relating to the extensive reporting. On the other hand, although they are a chance to improve the effectiveness of treatment and management, they also conceal the seeds of conflict within the environment.

CONCLUSIONS

Reorganization of primary health care in Poland coordinated by the Ministry of Health involves efforts of many groups related to health care—the representatives of ministries and public payer, representatives of professional associations, providers associations, and organizations representing the interests of patients. An interdisciplinary panel of experts has been appointed at the beginning of 2016 to prepare a strategy for systemic solutions in PHC, which are the basis for further legislative changes (Zarządzenie Ministra Zdrowia z dnia 4 stycznia, 2016). As a result of the panel's work, on 5th April 2016 a draft of the amendment to the Law on Health Services Funded from Public Resources, the Law on Pharmaceutics (Ustawa z dnia 6 września, 2001), as well as the Law on the prevention and elimination of infections and communicable diseases (Ustawa z dnia 5 grudnia, 2008), has been sent for public consultation.

It should be clearly emphasized, that these actions must be conducted in a strategic perspective, and not just *ad hoc*, which requires reformers not only to have knowledge and commitment, but, above all, a comprehensive look at the entire health care system. This is important also because the initiated changes will penetrate extremely sensitive area of social life, centered on the human and civil rights to health.

According to the Spokesman for the Rights of Patients, PHC is especially lacking a complex, well prepared and consistently applied prevention, which is confirmed by the report of the Supreme Chamber of Control (Supreme Audit Office, 2015) showing that more than a half of the inspected providers not carried out their tasks in accordance with the range originally assigned to the PHC. Among the postulates submitted by family doctors, particularly important is long-awaited increase of their role in the system, followed by clear formal regulations and better financing. Public health market experts in turn to pay particular attention to the potential difficulties in developing and implementing a coherent model of PHC organization and financing, yet so universal to be suitable for all providers, in particular to improve coordination of care and cooperation between physicians, nurses and midwifes (Primary Health Care, 2016).

In addition, it should be remembered that the rebuilt PHC model is not only a component of the national health system, but also fits the coordinated health care of the European

Community[3], particularly with regard to the provisions of the Directive on cross-border health care[4]. Thus, the actions and tools taken from other health systems to improve efficiency should lead to sustained optimization of the provision of PHC services, which is currently devoid of any serious tools of organizational and financial motivation.

[3]Regulation (ec) No. 883/2004 of the European Parliament and of the Council of 29 April 2004 On the coordination of social security systems.

[4]Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 On the application of patients' rights in cross-border healthcare.

AUTHOR CONTRIBUTIONS

TH conceived the study and prepared draft of the paper and made the study. PR contributed to paper preparation and study. JW contributed to paper preparation and study.

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OPINION
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The Life Cycle of Health Technologies. Challenges and Ways Forward

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Keywords: disinvestment, life cycle assessment, health technology assessment, investment, innovation, reimbursement mechanisms, real world data

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Health care systems have considered the introduction of health technologies a linear process in which different stakeholders (innovators, manufacturers, regulators, health technology assessors, reimbursement bodies, health care providers, health care professionals, patients, and citizens) did interact in each of the steps of the process, but were not involved in a continuous dialogue and knowledge exchange. This step by step approach generates inefficiency in many cases by means of: the isolation of innovators from real health care needs, the introduction of health technologies of doubtful value, the generation of unnecessary variability in practice, the maintenance of practices of no-added value, and the disregard of knowledge out of the practice, among others. These circumstances suppose an inefficient allocation of resources and investment, a hole in the waterline of health care systems, and their sustainability and what is more, a non-direct correlation between expected or theoretical outcomes and real health outcomes. Different initiatives have been put in place in the last years in order to mitigate the effects of the aforementioned issues.

On the basis of the life cycle concept of health technologies (see **Figure 1**), this article will go through some of these initiatives and define the role that Health Technology Assessment could play in each step.

Health Technology Assessment (HTA) is "*the systematic evaluation of the properties and effects of a health technology, addressing the direct and intended effects of this technology, as well as its indirect and unintended consequences, and aimed mainly at informing decision making regarding health technologies. HTA is conducted by interdisciplinary groups that use explicit analytical frameworks drawing on a variety of methods*" HTAglossary (http://htaglossary.net).

HTA was used to act when decisions on reimbursement were required and thus was called the fourth hurdle or the fourth guarantee (safety, efficacy, effectiveness, and efficiency). However, having in mind its definition and privileged position, HTA activities have evolved to more constructive approaches from health technology inception to its obsolescence (Henshall et al., 2011). New concepts such as scientific advice (Jost et al., 2015), early dialogue, early awareness, and alert systems (Packer et al., 2012), post-introduction observation of health technologies (Varela-Lema et al., 2012), appropriateness, re-assessment, and disinvestment (Elshaug et al., 2007) have gained ground.

RESEARCH AND DEVELOPMENT

In the nineties of the 20th century, many countries in the world started policies on incentivizing the creation of innovation hubs and enterprises incubators in different sectors, especially energy, transport, and biosciences-health. These policies were followed by supporting innovators, universities, spin-offs, spin-outs, and small and medium enterprises (SMEs) both managerially

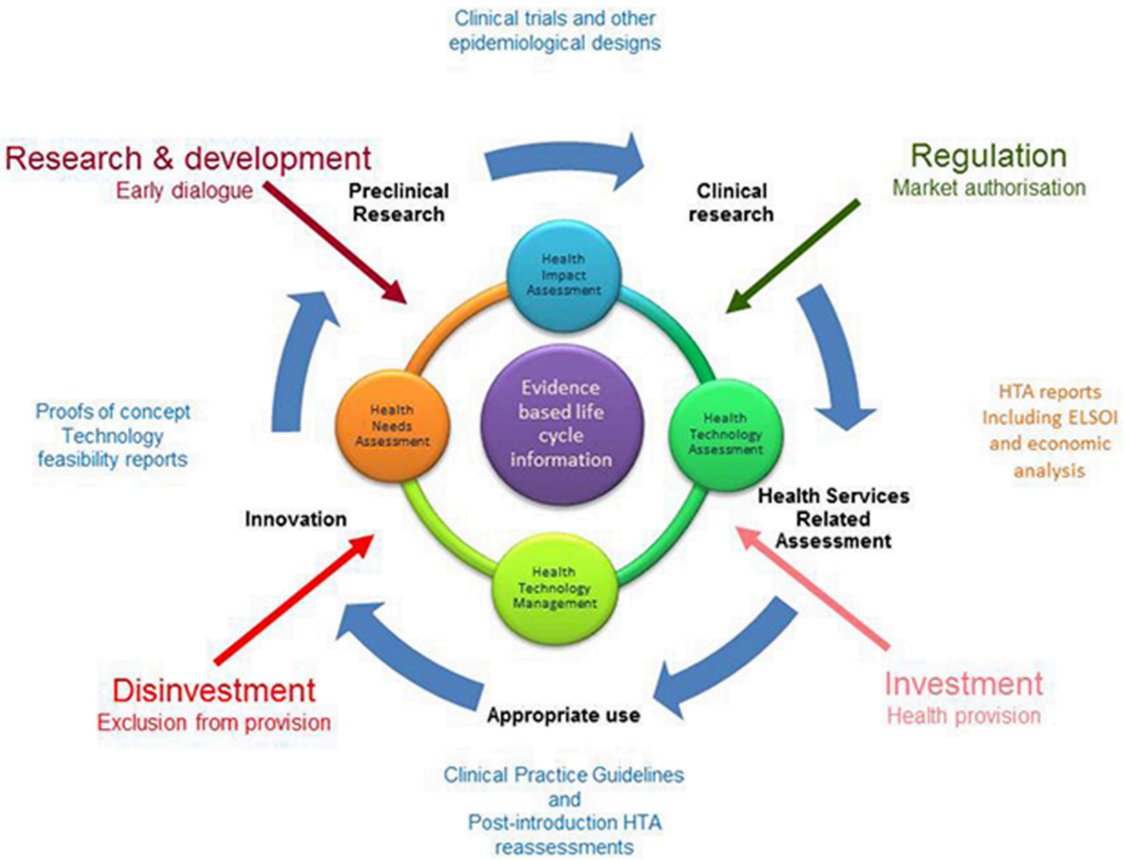

FIGURE 1 | The life cycle of health technologies concept. ELSOI (Ethical, Legal, Social and Organizational Issues).

and economically. These policies generated an increasing amount of initiatives and technological ideas. One of the challenges of those innovators were centered in convincing the health care systems on the added-value of their ideas and anticipating financial needs, especially regulators, and reimbursement requirements of evidence generation. Regulatory agencies including the European Medicines Agency (EMA) established focused policies to promote innovative solutions and especially the development of new drugs by SMEs. Furthermore, EMA launched in 2005 an "SME Office" to provide financial and administrative assistance to micro-SMEs (Carr, 2010).

Unfortunately, many of these initiatives failed, not linked to their possible value to health systems, but rather due to inadequate planning of the steps to be followed in the continuum from regulation to market access. This misalignment between innovators, regulators, and health care systems have generated that many laboratory discoveries have gone to the termed "valley of death," the so-called gap between bench research to health care application (Roberts et al., 2012). Moreover, as Roberts et al. (2012) described there are fewer scientists with a true understanding of clinical problems and health needs. The promotion of clinician-scientists is crucial to bridge the gap and avoid the valley of death at the early stages, as well as the contribution of "early dialogue" and scientific advice to define the characteristics of the patient and health care system to which the new technological solution will be targeted to. In fact, some highly sophisticated technological solutions such as many "point of care" diagnostics have not been successful due to an inadequate plan including the inexistence of companion treatments or the insufficient knowledge of the standard of care in different settings. However, there are examples of initiatives that have combined experts, health care providers, and HTA organizations and have become a reality such as the European Union (EU) funded projects AngeLab for non-invasive prenatal diagnosis (http://angelab-systems.eu/) or Discognosis, a Point-of-Care diagnostic device for malaria and other tropical diseases (http://www.discognosis.eu/).

Current initiatives to promote dialogue and funding at the early stages include the Innovative Medicines Initiative (IMI) that aims to facilitate and speed the access to the market and obviously, to the patients of innovative medicines, with an especial focus in areas where there is high unmet medical (e.g., rare diseases) or social need (https://www.imi.europa.eu/). IMI is a public-private joint action with the participation of the European Union (through the European Commission) and the European pharmaceutical industry represented by the European Federation of Pharmaceutical Industries and Associations (EFPIA).

REGULATION

Market authorization or regulation has been a necessary step that countries and health care systems have established to build trust on the products that are marketed authorized, in terms of safety and efficacy/performance. Developed countries have created well-structured and demarcated processes for market authorization, especially when they relate to health and environment. These necessary steps have been followed by the creation of independent institutions at the national (Food and Drug Administration and other national bodies) and international level (EMA) that have defined the rules and evidence requirements to ensure that the products that reach the market are safe and efficacious. Nevertheless, these regulatory processes and evidence requirements for market access are unequal for the different health technologies. We need to bear in mind that health technology definition embraces "*any intervention developed to prevent, diagnose or treat medical conditions; promote health; provide rehabilitation; or organize healthcare delivery. The intervention can be a test, device, medicine, vaccine, procedure, program or system*" (http://htaglossary.net/health+technology). Meanwhile, drug development and market access is well-defined and regulated in many countries in the world (at least in OECD countries), medical devices, diagnostics, procedures, programs, or systems do not currently follow such process. In fact, researchers and health technology assessors have claimed for a more robust and centralized system for medical devices in Europe (Eikermann et al., 2013) that could enhance not only the evidence generation necessary for decision making, but the competitiveness of European medical devices when accessing other markets. Another debate could be the possible evidence requirements of procedures and programs to ensure that only those that comply with high-quality standards are promoted to health care systems. An open area under discussion is public health interventions. Also here a higher level of evidence is demanded but due to the nature of the interventions, the tools and knowledge on how to handle evidence quality is lacking.

It is also worth noting that health care systems, services providers, and health technologies manufacturers are demanding an alignment of evidence requirements by regulators and reimbursement bodies. In this sense, regulators, industry, and HTA bodies have started common approaches to outcomes of interest definition, stakeholders' involvement, and possible comparators when designing trials for market authorization of drugs and medical devices. A pioneering initiative has been launched by the European network of Agencies for HTA (EUnetHTA; http://www.eunethta.eu/) as part of the Joint Action 3 funded by the EU. EUnetHTA has included a work package (WP5) that based on previous experience in Joint Action 2 (http://www.eunethta.eu/activities/EUnetHTA_Joint_Action_2_(2012-15)/eunethta-joint-action-2-2012--2015) promotes early-dialogue with industry and regulators on drugs and medical devices. This initiative tries to avoid further evidence generation requirements on safety and efficacy and choice of comparator when informing decision making on reimbursement. This is especially crucial when talking about SMEs that need to be efficient on evidence requirements and trials' design and are unable to afford further investments to answer HTA bodies and health care systems.

INVESTMENT

Health care providers and organizations need to decide on which services and technologies will be implemented into the Health Systems, and, simultaneously, to which extent those goods will be funded. In view of the scarce resources and the open-ended needs that put at risk Health Systems' sustainability, the investment in a concrete condition or pathology impedes the investment in other pathologies or processes, in which similar or higher value could be generated (cost-opportunity). Unluckily, health care providers invest in health technologies that are not tailored to their needs or the settings in which they are going to be applied. Likewise, the relative added value of some health technologies at the purchasing price does not justify their acquisition and generate tensions between health care providers, health technology suppliers, and patients. More than desirable, investments are not performed on the basis of priority needs or they do not consider systems and settings characteristics acquiring technologies that are more complex than required or unsuited to the context where they will be provided, demanding expensive maintenance, or very advanced capacity building to gain the benefit of the single technology. Additionally, the variability in practice, the irrational or inadequate use of health technologies, the wide range of health professionals, and the lack of required competencies to achieve the desired outcomes may also lead to an inefficient use of investments, a spendthrift of services, and the lack of funds vital for purchasing other more priority resources for Health Systems. HTA could be helpful at this stage by anticipating the possible impact and requirements of health technologies included in different health care systems, what it has been called "Early Awareness and Alert Systems" (Packer et al., 2012) and by promoting evidence generation post-marketing authorization and reimbursement decision (Varela-Lema et al., 2012). As previously mentioned, the value of health technologies in routine care differs from that promised in theory and according to trials in ideal conditions. That's why HTA bodies, regulators, payers, health professionals, and patients are claiming for the establishment of mechanisms that headed to the generation of evidence in real practice what has been called "real world data" (Schneeweiss et al., 2016). Real world data generation supports other actions such as: "Manage Entry Agreements" (Klemp et al., 2011), adaptive licensing for innovations market authorization (Schneeweiss et al., 2016), and public procurement and prices negotiation, based on comparative effectiveness, when demonstrated value. Even legal basis had changed so that reimbursement bodies are able to spend money into the development of real life evidence (Germany—GKV-VSG, 2015).

DISINVESTMENT

The linear concept of health technologies life cycle was a stop to the analysis of what happened in real practice. It seemed to be that once decisions on reimbursement were taken,

health technologies remained unassessed up to their disuse by health professionals. Actually, variability in practice has been a constant in health care systems. This variability could be due to the personalization of the management of individual patients or to the use of obsolete, superseded, or low-added value practices. The analysis of variability and the identification of low-added or no added-value practices has become a must. Different programs have tried to systematically identify obsolete technologies and promote disinvestment (Ibargoyen-Roteta et al., 2009; Leggett et al., 2012; Polisena et al., 2013). New initiatives like Choosing Wisely (USA http://www.choosingwisely.org/; Australia http://www.choosingwisely.org.au/home; Canada http://www.choosingwiselycanada.org/; UK http://www.choosingwisely.co.uk/; Spain http://www.msc.es/organizacion/sns/planCalidadSNS/cal_sscc.htm) promoted by systems, patients, and professional societies have achieved further attention in mass media. Notwithstanding, there is a need for further research on sources for the identification of obsolete technologies and their consequences in health care systems. The systematic, comprehensive, and accountable divestment of low added or no added value health technologies could be the basis for budget release that enables investment in innovations that seek greater value and better allocation of resources.

Future challenges are countless: from theoretical efficacy to effectiveness, from traditional "one size fits all" medicine to personalized medicine. To this evolving scenario, it must be added the limited financial resources that will force more than ever to select the best technology according to each concrete system and appropriate criteria. However, this will require stakeholders' involvement aimed at increasing quality and value of care (Stelfox et al., 2015).

AUTHOR CONTRIBUTIONS

IG design the concept of the paper and distributed the tasks among HD and MC. HD and MC contributed to the discussion and the review of two subsequent drafts. HD contributed to the area of investment and disinvestment and MC to the discussion and drafting of the area of reimbursement and innovation. Final submission was approved by the three authors.

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The New and Old Europe: East-West Split in Pharmaceutical Spending

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HIGHLIGHTS

- Since the geopolitical developments of 1989, former centrally planned economies of Eastern Europe followed distinctively different pathways in national pharmaceutical expenditure evolution as compared to their free market Western European counterparts.
- Long term spending on pharmaceuticals expressed as percentage of total health expenditure was falling in free market economies as of 1989. Back in early 1990s it was at higher levels in transitional Eastern European countries and actually continued to grow further.
- Public financing share of total pharmaceutical expenditure was steadily falling in most Central and Eastern European countries over the recent few decades. Opposed scenario were EU-15 countries which successfully increased their public funding of prescription medicines for the sake of their citizens.
- Pace of annual increase in per capita spending on medicines in PPP terms, was at least 20% faster in Eastern Europe compared to their Western counterparts. During the same years, CEE region was expanding their pharmaceuticals share of health spending in eight fold faster annual rate compared to the EU 15.
- Private and out-of-pocket expenditure became dominant in former socialist countries. Affordability issues coupled with growing income inequality in transitional economies will present a serious challenge to equitable provision and sustainable financing of pharmaceuticals in the long run.

Keywords: Eastern Europe, Western Europe, centrally-planned economy, free market economy, pharmaceuticals, expenditure, spending, transition

JEL codes: I11 Analysis of Health Care Markets, I18 Government Policy Regulation Public Health, P2 Socialist Systems and Transitional Economies, P1 Capitalist Systems, P51 Comparative Analysis of Economic Systems, F6 Economic Impacts of Globalization

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INTRODUCTION

Historical decades following WWII were marked with rapid industrialization and build-up of welfare states in most free-market economies. This trend was closely associated with health expenditures rising across 4% GDP threshold which remained quite stable throughout entire XIX and first half of XX century (Getzen, 1990). After this phenomenon was described in the US it became common elsewhere but most prominent in Western Europe, Japan and British Commonwealth countries. Over the next half a century health expenditure doubled or even tripled

in many of the richest OECD societies. Challenges to sustainability of health care funding gradually were more obvious and concerning for policy makers. Unlike capital investments in buildings, equipment, medical staff salaries etc. prescription and dispensing of pharmaceuticals soon was understood to be more manageable part of these costs (Carone et al., 2012).

European geopolitical destiny since the end of Cold War Era back in 1989 opened up many issues ultimately affecting costs of medical care provision. Large number of previously state controlled socialist economies have undergone profound health reforms adopting free-market model (Jakovljevic, 2013). Central and Eastern European Post-Semashko Soviet style health systems were characterized with higher number of (more) hospital beds, physician, and nursing staff densities compared to Western Europe (Semashko, 1934; Torosyan et al., 2008). Nevertheless, average length of hospital stay was much lengthier and these nations had curative, hospital based systems instead of preventive ones, driven by family medicine practices common in the West (Healy and McKee, 2002). The latter turned out to be far more effective in terms of resource use and health outcomes gained (Kornai and Eggleston, 2001).

Evidence based medicine and cost-effective resource allocation slowly became more common in Eastern European policy makers mindset (Jakovljevic et al., 2011). These changes were closely to the rapid growth of most CEE pharmaceutical markets since the middle 1990s and early 2000s (Jakovljevic et al., 2015a). Although drug acquisition costs clearly grew up in the old EU-15 pre-2004 members as well, this appears to have happened at the far slower pace (Nuijten et al., 2001). Basically similar upward trends in value based turnover and budget impact of medicines in East and West of European region were hiding distinctively different patterns. We decided to observe WHO issued European Health for All database (HFA-DB) in order to test this assumption.

DATA REPORT METHODS

Public Data Sources Used

WHO issued European Health for All database (HFA-DB) is a public registry with large number of data on demographics, health care resources and outcomes and medical service consumption data on all countries of the European Region (WHO, HFA-DB, 2015). It consists of regularly updated reports issued by WHO/European Office, the statistical office of the European Union (EUROSTAT), United Nations system, the Organization for Economic Cooperation and Development and data reported by the national authorities. Readers are free to access and reuse these publicly available data at the link provided beneath.

Data

Pharmaceutical spending is commonly defined as expenditures on prescription medicines and over-the-counter products without hospital consumption of pharmaceuticals (OECD Pharmaceutical Spending, 2013). Medical consumables are included in such data in many countries (approximately 5% of reported value) and pharmacists' salaries if these are accounted separately from the price of medicines. Ultimately calculated total pharmaceutical expenditure assumes wholesale and retail margins and value-added tax.

Selected pharmaceutical spending indicators in this study were: Pharmaceutical expenditure expressed as percentage of total health expenditure, public pharmaceutical expenditure expressed as percentage of total pharmaceutical expenditure and pharmaceutical expenditure per capita expressed in purchase power parity terms (international $). Time horizon observed was spreading from the earliest available evidence listed in HFA-DB back in 1970 to the last official updates in 2012.Targeted countries where were all 53 countries of the European Region divided in two groups based on their economic and health care historical legacies: free-market economies prior to 1989 (a total of 25dominantly Western European countries) and centrally planned socialist economies prior to 1989 (a total of 28dominantly Eastern European countries; Berend, 2006).Total of five nations among free-market economies and ten among former centrally planned economies were observed for missing relevant data and thus were excluded from observation.

RESULTS

Pharmaceutical expenditure (PE) percentage of total health expenditure used to be higher in centrally planned economies. Mean of historical bottom values was 20% growing toward 21.7% in recent years. This meant total +3.0% net increase per country over 14.7 years long time horizon on average. Mean annual growth was calculated to be +0.08%. Unlike these, we notice exactly the opposed trend in free market economies. Their arithmetic mean of historical baseline values was 16.2%. It felt toward 15.1% in contemporary period. Net change here was negative: average −0.7% decrease over 33.5 years long time horizon on average. Length of observation here was longer because OECD economies pioneered reporting these data to WHO during the Cold War Era. Their mean annual growth was eight times slower, approximately +0.01%.

Observing the landscape of public pharmaceutical expenditure percentage point share of total health expenditure we come to entirely different mirror-like reflection. Centrally planned economies tended to have lower public participation in drug acquisition and dispensing costs (arithmetic mean of earliest reported values of 43.3%) which was historically further falling toward 36.5% on average in recent years. This meant a total contraction of public spending on drugs of −6.8% on average. This huge change happened over the course of 10.6 years (mean time span between first and last reported values in Eastern European states).This accounts for mean annual −0.47% contraction of public spending on drugs. Free market nations recorded much higher average public share of 57.5% in earliest historical records back in 1970s. It has grown further up to 62.9% in recent years with a total net change of +5.4% over 32.3 years (mean time span between first and last reported values in Western, Southern and Northern European states). Annual net change was positive amounting to +0.16%. This huge disparity

presents the single most important finding of this data report (see **Figure 1**).

Pharmaceutical expenditure per capita expressed in purchase power parity (PPP) terms (international $) allows for international comparability and these values introduce another perspective. Back in early 1970s free market economies were spending on medicines modest average amount of $68 per capita which grew tremendously reaching mean value of $488 in recent years. This meant net gain of $420 on average with annual increment of +$12.30 over 34.1 years (**Table 1**). Among most of the former centrally planned economies such data were lacking almost until the late 1990s. Therefore, we have come to a slightly distorted picture of mean $190 per capita among the earliest reported values rising up to $427 in recent years. Total increment of some $237 was approximately twice lower compared to the West. Keeping in mind that this change refers to the average time span of 13.8 years between the earliest and last reported values, we come to the annual increment of +$16.89 per capita (**Table 2**).

DISCUSSION

Long term spending on pharmaceuticals expressed as percentage of total health expenditure was falling in mature economies (Mossialos and Oliver, 2005).Back in the late 1980s and early 1990s it was at higher levels in transitional Eastern European countries and actually continued to grow (Mrazek et al., 2004). Opposed to this trend, free market, predominantly Western, Southern and Northern European states continued to contract participation of medicines in their national medical spending pattern. This effectively meant that other medical technologies mostly related to hospital care, such as radiology diagnostics, advanced surgery, interventional radiology and radiation oncology, laboratory tests, rehabilitating and mental health related medical services and social support programs were participating more significantly to the structure of medical spending (Robinson, 1994; Ackroyd et al., 2006; Jakovljevic et al., 2013, 2014a, 2015b; Ranković et al., 2013).

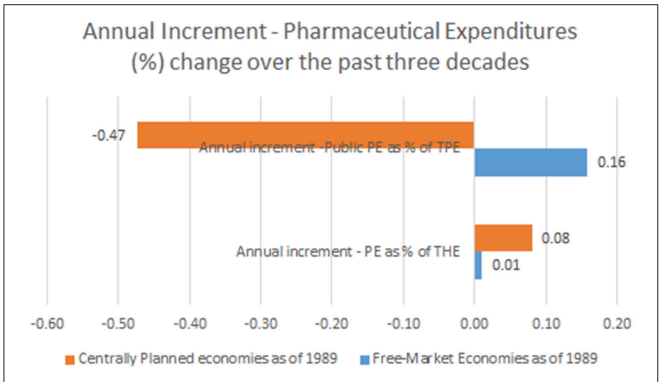

FIGURE 1 | Annual Increment—Pharmaceutical Expenditures (%) change (observation time span up to 22 years among former centrally planned and up to 42 years in free market economies).

Public financing share of total pharmaceutical expenditure was steadily falling in most Central and Eastern European countries (Gotseva, 2015). It was at far lower, approximately one-third level, compared to their Western counterparts back in Cold War era (Jakovljevic et al., 2015d). Today, such changes coupled with rising budget impact of drug acquisition costs point out to the strong growth of patient cost-sharing mechanisms throughout the CEE region (Iskrov and Stefanov, 2015; Tambor et al., 2015). Out-of-pocket expenses and risks of catastrophic illness-induced household expenditure add to the complexity of this challenge (Jakovljevic, 2014a,b).

Opposed scenario were EU-15 countries successfully struggling to maintain and increase their public funding of prescription medicines for the sake of their citizens. They achieved extension in population coverage with cost-effective drug reimbursement strategies (Rémuzat et al., 2015). Thus, these countries were reducing exposure of vulnerable social groups to the issues affecting access to medicines. Although success rates across EU-15 differ significantly, most countries have adopted responsible pharmaceutical polices. National authorities besides, proved mostly capable of withstanding diverse financial constraints. Some were temporary such as the global economic recession while others such as medical innovation led primarily by brand pharmaceutical industry posed difficulties in the long run (Higgins and Graham, 2009; Dagovic et al., 2015). Huge budget impact of novel medicines such as monoclonal antibodies remains particularly hot topic sparkling debate among policy makers (Jakovljevic, 2014b).Some of the solutions found to release such pressures were incentives for generic substitution of brand name medicines (Jakovljevic et al., 2014b). With more or less legislative obstacles generic share in local markets expanded significantly over time (Simoens and De Coster, 2006).

Per capita spending on pharmaceuticals expressed in purchased power parity terms, points out to the joint strong growth of overall costs of prescribed and dispensed medicines and OTC agents (Ess et al., 2003). With regards to the historical perspective there appears to be no distinct difference in spending patterns among the two regions. The obvious fact was lag in Eastern European drug acquisition costs back in the late 1980s (Rhodes et al., 1999). Rapid increase in pharmaceutical expenditure since the 1990s followed, being one of the recognized mile stones of transitional health care reforms (Krajewski-Siuda and Romaniuk, 2006). Notable transformation of local CEE markets is the expanded presence of brand name medicines and diversification of payment mechanisms (Petrusic and Jakovljevic, 2015). Informal payments and widening income gaps affecting affordability of medicines remain the key challenges across the region (Ensor, 2004; Jakovljevic et al., 2015c).

STUDY LIMITATIONS

Some countries did not report official data on pharmaceutical spending for either some indicators or years within the time span observed. These missing data refer to a total of 5 nations among free-market economies and 10 countries among former centrally planned economies. Most cases of partially or entirely missing data refer to the countries with relatively small population size in

TABLE 1 | Pharmaceutical expenditure indicators according to WHO issued HFA-DBdata for free-market economies in the European Region prior to 1989 (5 out of 25 countries lacking some relevant data from the official records).

	First available PE* as % of THE**	Last available PE as % of THE	Total change PE as % of THE	Time span (years)	Annual increment	First available public PE as % of TPE***	Last available Public PE as % of TPE	Total change public PE as % of TPE	Time span (years)	Annual increment	First available PE as PPP$ per capita	Last available PE as PPP$ per capita	Total change PE as PPP$ per capita	Time span (years)	Annual increment
Andorra	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Austria	9.6^{1990}	11.7^{2011}	+2.1	21	0.10	55.1^{1990}	67.6^{2011}	+12.5	21	0.60	$\$156.5^{1990}$	$\$533.1^{2011}$	+$376.6	21	$17.93
Belgium	28.1^{1970}	15.5^{2011}	−12.6	41	−0.31	58.5^{1970}	64.3^{2011}	+5.8	41	0.14	$\$41.9^{1970}$	$\$630.9^{2011}$	+$589.0	41	$14.37
Cyprus	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Denmark	N/A	6.8^{2011}	N/A	N/A	N/A	49.9^{1980}	49.2^{2011}	−0.7	31	−0.02	$\$53.8^{1980}$	$\$300.4^{2011}$	+$246.6	31	$7.95
Finland	12.6^{1970}	13.2^{2011}	+0.6	41	0.01	33.7^{1970}	55.9^{2011}	+22.2	41	0.54	$\$22.8^{1970}$	$\$446.2^{2011}$	+$423.4	41	$10.33
France	23.8^{1970}	15.6^{2011}	−8.2	41	−0.20	67.3^{1970}	68^{2011}	+0.7	41	0.02	$\$46.1^{1970}$	$\$641.1^{2011}$	+$595.0	41	$14.51
Germany	16.2^{1970}	14.1^{2011}	−2.1	41	−0.05	63.4^{1970}	75.6^{2011}	+12.2	41	0.30	$\$43.3^{1970}$	$\$632.6^{2011}$	+$589.3	41	$14.37
Greece	25.5^{1970}	28.5^{2011}	+3.0	41	0.07	60^{1970}	73.7^{2011}	+13.7	41	0.33	$\$40.8^{1970}$	$\$673.4^{2011}$	+$632.6	41	$15.43
Iceland	17.1^{1970}	15.4^{2011}	−1.7	41	−0.04	43.2^{1970}	42.1^{2011}	−1.1	41	−0.03	$\$29.9^{1970}$	$\$508.3^{2011}$	+$478.4	41	$11.67
Ireland	13.7^{1975}	17.5^{2011}	+3.8	36	0.11	43.4^{1975}	78^{2011}	+34.6	36	0.96	$\$37.3^{1975}$	$\$647.7^{2011}$	+$610.4	36	$19.96
Israel	15.5^{1995}	14.7^{2011}	−0.8	16	−0.05	39.3^{2006}	43.7^{2010}	+4.4	4	1.10	N/A	N/A	N/A	N/A	N/A
Italy	21.8^{1988}	15.7^{2012}	−6.1	24	−0.25	61.5^{1988}	45.5^{2012}	−16.0	24	−0.67	$\$247.2^{1988}$	$\$482.2^{2012}$	+$235.0	24	$9.79
Luxembourg	19.7^{1970}	9.1^{2008}	−10.6	38	−0.28	83.5^{1970}	84^{2008}	+0.5	38	0.01	$\$229.1^{1995}$	$\$406^{2008}$	+$176.9	13	$13.61
Malta	23.69^{2001}	27.98^{2012}	+4.29	11	0.39	43.61^{2001}	41.2^{2012}	−2.41	11	−0.22	N/A	N/A	N/A	N/A	N/A
Monaco	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Netherlands	10.3^{1972}	9.4^{2011}	−0.9	39	−0.02	60.1^{1972}	78.4^{2011}	+18.3	39	0.47	$\$32.3^{1972}$	$\$479.3^{2011}$	+$447.0	39	$11.46
Norway	7.8^{1970}	6.6^{2012}	−1.2	42	−0.03	35.8^{1970}	54.5^{2012}	+18.7	42	0.45	$\$11.2^{1970}$	$\$390.4^{2012}$	+$379.2	42	$9.03
Portugal	13.4^{1970}	17.9^{2011}	+4.5	41	0.11	68.7^{1970}	55.1^{2011}	−13.6	41	−0.33	$\$6.3^{1970}$	$\$469^{2011}$	+$462.7	41	$11.29
San Marino	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Spain	21^{1980}	17.4^{2011}	−3.6	31	−0.12	64^{1980}	71^{2011}	+7.0	31	0.23	$\$76^{1980}$	$\$535.8^{2011}$	+$459.8	31	$14.83
Sweden	6.6^{1970}	12.1^{2011}	+5.5	41	0.13	62.9^{1970}	58.3^{2011}	−4.6	41	−0.11	$\$20.5^{1970}$	$\$474^{2011}$	+$453.5	41	$11.06
Switzerland	11.3^{1985}	9.4^{2011}	−1.9	26	−0.07	53.3^{1995}	68.9^{2011}	+15.6	16	0.98	$\$164.9^{1985}$	$\$530.7^{2011}$	+$365.8	26	$14.07
Turkey	10.7^{1981}	26.6^{2000}	+15.9	19	0.84	100^{1981}	60.2^{2000}	−39.80	19	−2.09	$\$9.1^{1981}$	$\$120.7^{2000}$	+$111.6	19	$5.87
United Kingdom	14.7^{1970}	11.4^{2008}	−3.3	38	−0.09	59.4^{1970}	84.7^{2008}	+25.3	38	0.67	$\$23.4^{1970}$	$\$374.6^{2008}$	+$351.2	38	$9.24
MEAN	16.2	15.1	−0.7	33.5	0.01	57.5	62.9	5.4	32.3	0.16	$68.0	$488.2	$420.2	34,1	$12.30
ST DEV	6.2	6.2	6.3	10.1	0.25	15.6	13.8	16.3	11.7	0.68	$74.0	$136.0	$150.5	9,2	$3.18
MIN	6.6	6.6	−12.6	11.0	−0.31	33.7	41.2	−39.8	4.0	−2.09	$6.3	$120.7	$111.6	13	$5.87
MAX	28.1	28.5	15.9	42.0	0.84	100.0	84.7	34.6	42.0	1.10	$247.2	$673.4	$632.6	42	$17.93
MEDIAN	15.1	14.7	−1.1	38.5	−0.04	59.4	64.3	5.8	38.0	0.23	$40.8	$482.2	$447.0	39	$11.67

**PE, Pharmaceutical expenditure.*

***THE, Total health expenditure.*

****TPE, Total pharmaceutical expenditure.*

TABLE 2 | Pharmaceutical expenditure indicators according to WHO issued HFA-DBdata for former centrally-planned socialist economies in the European Region prior to 1989 (10 out of 28 countries lacking some relevant data from the official records).

	First available PE* as % of THE**	Last available PE as % of THE	Total change PE as % of THE	Time span (years)	Annual increment	First available public PE as % of TPE***	Last available Public PE as % of TPE	Total change public PE as % of TPE	Time span (years)	Annual increment	First available PE as PPP$ per capita	Last available PE as PPP$ per capita	Total change PE as PPP$ per capita	Time span (years)	Annual increment
Armenia	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Azerbaijan	N/A	26.2^{2010}	N/A	N/A	N/A	32.9^{2000}	20.4^{2009}	−12.5	9	−1.39	N/A	N/A	N/A	N/A	N/A
Belarus	12.1^{1990}	21^{2012}	+8.9	22	0.40	20.4^{1990}	44.8^{2012}	+24.4	22	1.11	N/A	N/A	N/A	N/A	N/A
Bosnia and Herzegovina	8.9^{1980}	27.4^{2011}	+18.5	31	0.60	52.5^{2009}	56.7^{2011}	+4.2	2	2.10	N/A	N/A	N/A	N/A	N/A
Bulgaria	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Croatia	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Czech Republic	21^{1990}	20^{2011}	−1.0	21	−0.05	89^{1990}	62.5^{2011}	−26.5	21	−1.26	$\$115.2^{1990}$	$\$394.2^{2011}$	+$279.0	21	$13.29
Estonia	19.5^{1999}	21.5^{2012}	+2.0	13	0.15	40.8^{1999}	49.2^{2012}	+8.4	13	0.65	$\$100.4^{1999}$	$\$279.8^{2011}$	+$179.4	12	$14.95
Georgia	45.6^{2000}	41.2^{2011}	−4.4	11	−0.40	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Hungary	27.6^{1991}	33.4^{2011}	+5.8	20	0.29	79.3^{1991}	49^{2011}	−30.3	20	−1.52	$\$158.6^{1991}$	$\$564^{2011}$	+$405.4	20	$20.27
Kazakhstan	6.8^{1991}	2.8^{2000}	−4.0	9	−0.44	8.3^{1991}	1.6^{1997}	−6.7	6	−1.12	N/A	N/A	N/A	N/A	N/A
Kyrgyzstan	10.9^{1990}	11.2^{2002}	+0.3	12	0.03	9.9^{1992}	9.9^{1992}	0	0	N/A	N/A	N/A	N/A	N/A	N/A
Latvia	21.9^{2005}	24.2^{2010}	+2.3	5	0.46	31.3^{2005}	38.4^{2010}	+7.1	5	1.42	N/A	N/A	N/A	N/A	N/A
Lithuania	32.9^{2004}	24.92^{2011}	−7.98	7	−1.14	34.96^{2004}	34.22^{2011}	−0.74	7	−0.11	N/A	N/A	N/A	N/A	N/A
Montenegro	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Poland	28.4^{2002}	22.5^{2011}	−5.9	9	−0.66	38.4^{2002}	39.4^{2011}	+1.0	9	0.11	$\$207.9^{2002}$	$\$326.3^{2011}$	+$118.4	9	$13.16
Republic of Moldova	7.94^{1991}	32.9^{2012}	+24.96	21	1.19	9.1^{1993}	6.4^{2012}	−2.7	19	−0.14	N/A	N/A	N/A	N/A	N/A
Romania	N/A	20^{1998}	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Russian Federation	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Serbia	11.83^{1998}	31.3^{2011}	19.47	13	1.50	50.4^{2003}	44.7^{2011}	−5.7	8	−0.71	N/A	N/A	N/A	N/A	N/A
Slovakia	34^{1999}	27.4^{2011}	−6.6	12	−0.55	76.2^{1999}	69.4^{2011}	−6.8	12	−0.57	$\$203.8^{1999}$	$\$525^{2011}$	+$321.2	12	$26.77
Slovenia	20.9^{2002}	19.5^{2011}	−1.4	9	−0.16	61.5^{2002}	55.9^{2011}	−5.6	9	−0.62	$\$355.3^{2002}$	$\$471.3^{2011}$	+$116.0	9	$12.89
Tajikistan	13^{1991}	10.5^{2003}	−2.5	12	−0.21	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
TFYR Macedonia	13.8^{1980}	14.9^{2004}	+1.1	24	0.05	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Turkmenistan	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ukraine	N/A	4.2^{2009}	N/A	N/A	N/A	95.3^{1993}	34.9^{2005}	−60.4	12	−5.03	N/A	N/A	N/A	N/A	N/A
Uzbekistan	N/A	11.6^{2001}	N/A	N/A	N/A	6.4^{1993}	3.4^{1999}	−3.0	6	−0.50	N/A	N/A	N/A	N/A	N/A
MEAN	20.0	21.7	3.0	14.7	0.08	43.3	36.5	−6.8	10.6	−0.47	$190.2	$426.8	$236.6	13.8	$16.89
ST DEV	10.6	9.6	9.4	6.9	0.64	28.9	21.2	18.6	6.6	1.60	$92.1	$112.4	$117.7	5.3	$5.58
MIN	6.8	2.8	−8.0	5.0	−1.14	6.4	1.6	−60.4	0.0	−5.03	$100.4	$279.8	$116.0	9.0	$12.89
MAX	45.6	41.2	25.0	31.0	1.50	95.3	69.4	24.4	22.0	2.10	$355.3	$564.0	$405.4	21.0	$26.77
MEDIAN	20.2	22.0	0.7	12.5	0.04	38.4	39.4	−3.0	9.0	−0.53	$181.2	$432.8	$229.2	12.0	$14.12

***PE, Pharmaceutical expenditure.*

***THE, Total health expenditure.*

****TPE, Total pharmaceutical expenditure.*

respective groups. Notable exceptions from this rule are Romania and Russian Federation. Russia was classified as a high income economy by the World Bank since August 2013 and as one of top performing emerging BRICS markets (The World Bank, 2015; Jakovljevic, 2016). Due to these facts we would like to limit our results and conclusions on the rest of Eastern European region as thus there is higher degree of homogeneity. Countries presented in the observed sample (20 of historical free market and 18 of centrally planned economies) are geographically scattered throughout the respective European regions. Therefore, we still regard observed sample of countries to be representative of broad long term trends in pharmaceutical spending in the European Region.

CONCLUSION

The two observed broad groups of countries, former centrally planned and free market economies, share profoundly different historical legacies in medicines provision and financing mechanisms (Mossialos et al., 2004). This data report provides insight into the existence of two distinctively different pathways in spending on drugs over past several decades in the East and West of Europe. National policies sharing public reimbursement, insurance based mechanisms and out-of-pocket spending appear to be headed in two different directions (Mackenbach, 2006). Eastern European states struggle with affordability issues and unequal access to medicines mostly determined by household income groups. Single most concerning fact is that transitional economies contracted their public share of pharmaceutical expenditure for almost half of percentage over the long course of years. Traditional free market economies, primarily EU-15 states mostly achieved better protection for their poor and vulnerable patient groups including those suffering from rare diseases and those requiring expensive treatment strategies (Iskrov et al., 2012). Nevertheless, we must point out the huge progress that was made in Eastern Europe providing access to the innovative medicines to the broad layers of population (Putrik et al., 2014). Pace of annual increase in per capita spending on medicines in PPP terms, was at least 20% faster in Eastern Europe compared to their Western counterparts. During the same years CEE region was expanding their pharmaceuticals share of health spending in eight fold faster annual rate compared to the EU 15. Current difficulties to withstand pressures arising from population aging and prosperity diseases remain primary challenge for sustainable funding of medicines provision in all of Europe (Ogura and Jakovljevic, 2014; Jakovljevic and Milovanovic, 2015; Jakovljevic and Laaser, 2015). Although differences remain we believe that at some point in future, these regions will converge increasing social welfare and affordability of medicines to the ordinary citizens (Deacon, 2000).

AUTHOR CONTRIBUTIONS

MJ and TK developed research questions, designed the study and drafted most of the manuscript. ML and OM took part in data acquisition, mining and analysis and prepared the tables and figure. All four authors revised draft and contributed essentially to the final appearance of the manuscript.

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The Market of Biopharmaceutical Medicines: A Snapshot of a Diverse Industrial Landscape

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Background: Biopharmaceutical medicines represent a growing share of the global pharmaceutical market, and with many of these biopharmaceutical products facing loss of exclusivity rights, also biosimilars may now enter the biopharmaceutical market.

Objectives: This study aims to identify and document which investment and development strategies are adopted by industrial players in the global biopharmaceutical market.

Methods: A descriptive analysis was undertaken of the investment and development strategies of the top 25 pharmaceutical companies according to 2015 worldwide prescription drug sales. Strategies were documented by collecting data on manufacturing plans, development programs, acquisition and collaboration agreements, the portfolio and pipeline of biosimilar, originator and next-generation biopharmaceutical products. Data were extracted from publicly available sources.

Results: Various investment and development strategies can be identified in the global biopharmaceutical market: (a) development of originator biopharmaceuticals, (b) investment in biotechnology, (c) development of next-generation biopharmaceuticals, (d) development of biosimilars, (e) investment in emerging countries, and (f) collaboration between companies. In the top 25 pharmaceutical companies almost every company invests in originator biopharmaceuticals and in biotechnology in general, but only half of them develops next-generation biopharmaceuticals. Furthermore, only half of them invest in development of biosimilars. The companies' biosimilar pipeline is mainly focused on development of biosimilar monoclonal antibodies and to some extent on biosimilar insulins. A common strategy is collaboration between companies and investment in emerging countries.

Conclusions: A snapshot of investment and development strategies used by industrial players in the global biopharmaceutical market shows that all top 25 pharmaceutical companies are engaged in the biopharmaceutical market and that this industrial landscape is diverse. Companies do not focus on a single strategy, but are involved in multiple investment and development strategies. A common strategy to market biopharmaceuticals is collaboration between companies. These collaborations can as well be used to gain access in regions the company has less experience with. With

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patents expiring for some of the highest selling monoclonal antibodies, this snapshot highlights the interest of companies to invest in the development of these molecules and/or enter into collaborations to create access to these molecules.

Keywords: Off-patent biological medicine, biosimilar medicine, investment and development strategies, biopharmaceutical market, pharmaceutical industry

INTRODUCTION

Totaling US$ 228 billion in global sales in 2016 (Troein, 2017), biopharmaceutical medicines represent a growing share of the global pharmaceutical market. With many of these biopharmaceutical products facing loss of patent protection and other exclusivity rights, also non-innovator versions of these molecules, biosimilars, may now enter the market, resulting in a shift of market shares (IMS Health, 2016), revision of strategies of companies and attraction of new players to the biopharmaceutical market. Due to lower research and development costs and increase in competition, biosimilars offer a lower cost alternative to expensive biopharmaceutical therapies. By adopting biosimilars, health care systems can expand patient access, offer more treatment options to physicians and have a new tool to control increasing health care expenses (IMS Institute for Healthcare Informatics, 2016). Overall, large investments have been made by companies to compete on the biopharmaceutical market.

These developments are also reflected in the industrial players in this market. Although there does not exist a classification system of companies active in this market, one could distinguish between big pharmaceutical companies, biotechnological companies, generics companies, new entrants, and companies from emerging countries. Big pharmaceutical companies are companies like Pfizer, Merck, and J&J, which originally focused on chemically developed medicines, and now target the biopharmaceutical market. On the biopharmaceutical market, there are as well biotechnological companies, like Amgen, whose focus has been on the development of biopharmaceutical medicines, be it initially originator medicines and in a later phase biosimilar medicines. Generics companies, companies originally focusing on generics, have also entered the biosimilar market (e.g., Sandoz). New entrants are new biotechnological companies, such as Celltrion and Samsung Bioepis. Companies from emerging countries, like Biocon and Dr. Reddy's, are companies in fast-developing economies.

The aim of this original research article is to identify and document which investment and development strategies are adopted by industrial players in the global biopharmaceutical market. To this effect, we distinguish between various investment and development strategies, and exemplify these strategies for the top 25 pharmaceutical companies. In 2012, Calo-Fernández et al. identified different players active in the biosimilar industry and core capabilities to enter this market, supported by three case studies (Calo-Fernández and Martínez-Hurtado, 2012). To the best of the authors' knowledge, our study is the first to provide a comprehensive snapshot of the industrial landscape of the biopharmaceutical and biosimilar market as of December 2016. It should be realized however that the landscape is rapidly evolving.

METHODS

A descriptive analysis was undertaken of the investment and development strategies of the top 25 pharmaceutical companies according to 2015 worldwide prescription drug sales (Evaluate Pharma, 2016; Pharm Exec, 2016). Identification of various investment and development strategies was based on previous research (Meuwissen, 2016). Identified strategies were further documented by collecting data on manufacturing plans, development programs, acquisition and collaboration agreements, the portfolio and pipeline of biosimilar, originator and next-generation biopharmaceutical products of these companies. Data were extracted from multiple, publicly available sources, including a review of the literature in PubMed and Embase over the last 5 years up to March 2016, a search of the reference list of included articles for other relevant studies, articles known to the authors, the website of the Generics and Biosimilars Initiative (GaBI) journal, GaBI Online, company and news websites. A detailed list with references consulted for each company is available from the authors on request.

RESULTS

Based on our analysis of industrial players in the global biopharmaceutical market, we distinguished between the following investment and development strategies: (a) development of originator biopharmaceuticals, (b) investment in biotechnology, (c) development of next-generation biopharmaceuticals, (d) development of biosimilars, (e) investment in emerging countries, and (f) collaboration between companies. **Table 1** shows the investment and development strategies of the top 25 pharmaceutical companies. It shows whether the company is an originator company, whether they invest in biotechnology via investment in their own development program, via acquisition of biotechnological companies, or both. The table also shows involvement in development of next-generation biopharmaceuticals. A next-generation biopharmaceutical is created by modifying the structure of an existing biological molecule (via e.g., pegylation, glycosylation) to alter pharmacokinetic or pharmacological properties, such as half-life or bioavailability or to improve its safety profile e.g., by reducing immunogenicity. This definition of next-generation biopharmaceuticals does not include new dosage forms. Subsequently, the table shows involvement in biosimilar development. Importantly, the term biosimilar is only applicable when strict regulatory requirements (European Medicines Agency (EMA), Food and Drug Administration (FDA) guidelines) are in place in the region in which it has been approved. **Table 1** also shows, the presence and investment of

TABLE 1 | Top 25 pharmaceutical companies ranked by 2015 worldwide prescription drug sales and examples of their investment and development strategies in the global biopharmaceutical market as of December 2016.

Rank (6, 7)	Company	Strategy biopharmaceutical market						
		(a) Development of originator biopharmaceuticals	(b) Investment in biotechnology		(c) Development of next-generation biopharmaceuticals	(d) Development of biosimilars	(e) Investment in emerging countries	(f) Collaboration and co-marketing
			Own development program	Acquisition				
1	Pfizer	◦ Genotropin®/ Genotonorm®-somatropin ◦ Prevnar 13®	◦ Investment in Global Biotechnology Center China ◦ Investment in new biologics clinical manufacturing facility (expansion existing site) in Andover (US) ◦ Plans expansion biologics plant Dublin (Ireland) ◦ Expansion plant Adelaide (Australia) to produce biosimilar pegfilgrastim	◦ Medivation (2016) ◦ Hospira (2015) ◦ Wyeth (2009)	◦ Development of next-generation human growth hormone in collaboration with OPKO	◦ Via Hospira: ◦ Epoetin zeta (Retacrit®) ◦ Filgrastim (Nivestim®) ◦ Infliximab (Inflectra®) ◦ Pipeline: adalimumab, bevacizumab, infliximab (outside EEA), rituximab, trastuzumab, pegfilgrastim (via Hospira) biosimilars	◦ Production facilities and sale China (biosimilars), Russia	◦ Celltrion (biosimilar infliximab) ◦ Merck KGaA (avelumab) ◦ OPKO (long-acting human growth hormone)
2	Novartis	◦ Lucentis®-ranibizumab ◦ Xolair®-omalizumab ◦ Simulect®-basiliximab ◦ Cosentyx®-secukinumab	◦ New biologics production plant Singapore ◦ Expansion Center of Biotechnology Huningue (France) ◦ Investment in biologics manufacturing sites Schaftenau and Kundel (Austria)	◦ Admune Therapeutics (2015)	– ◦ Albinterferon alfa-2b (Joulferon®) (withdrawn from market)	◦ Via Sandoz, the generics and biosimilars division of Novartis: ◦ somatropin (Omnitrope®) ◦ epoetin alfa (Binocrit®) ◦ filgrastim (Zarzio®/Zarxio®) ◦ etanercept (Erelzi®) ◦ Via subsidiary Hexal: ◦ epoetin alfa (Epoetin alfa Hexal®) ◦ filgrastim (Filgrastim Hexal®) ◦ Pipeline: infliximab (Sandoz acquired development and commercialization rights for EEA from Pfizer), rituximab, adalimumab, pegfilgrastim biosimilars	◦ Expanding presence in emerging markets of Asia, Africa and Latin America	◦ Genentech (development of Lucentis® and Xolair®) ◦ Xencor (bispecific antibodies)
3	Roche	◦ MabThera®/ Rituxan®-rituximab ◦ Avastin®-bevacizumab ◦ Herceptin®-trastuzumab ◦ RoActemra®-tocilizumab ◦ Perjeta®-pertuzumab ◦ Gazyva®-obinutuzumab	◦ Investment in increased manufacturing capacity at sites in Vacaville (Genentech) and Oceanside (US), and Penzberg (Germany) ◦ Construction antibody-drug conjugate manufacturing facility Basel (Switzerland)	◦ Adheron Therapeutics (2015) ◦ InterMune (2014) ◦ Genentech (2009)	◦ Methoxy polyethylene glycol-epoetin beta (Mircera®) ◦ Peginterferon alfa-2a (Pegasys®)	–	◦ China for, amongst others, oncology treatments ◦ The 'Blue Tree' cancer patient support initiative India ◦ Roche Pharma Africa Strategy to improve access to treatment in Sub-Saharan Africa, focus on hepatitis and cancer in women ◦	◦ Chugai Pharmaceutical (Japan) ◦ Pieris Pharmaceuticals (Cancer immunotherapy)

(Continued)

TABLE 1 | Continued

Rank (6, 7)	Company	Strategy biopharmaceutical market						
		(a) Development of originator biopharmaceuticals	(b) Investment in biotechnology		(c) Development of next-generation biopharmaceuticals	(d) Development of biosimilars	(e) Investment in emerging countries	(f) Collaboration and co-marketing
			Own development program	Acquisition				
4	Merck US (MSD)	○ Keytruda®-pembrolizumab ○ IntronA®-interferon alfa-2b ○ Several vaccines	○ Investment vaccine manufacturing site Carlow (Ireland) to produce oncology biologics (Keytruda®) ○ New biologics facility at site in Cork (Ireland) ○ New manufacturing facility in Hangzhou (China)	○ cCAM Biotherapeutics (2015)	○ Peginterferon alfa-2b (PegIntron®) ○ Corifollitropin alfa (Elonva®)	○ Pipeline: Via collaboration Samsung Bioepis, e.g., insulin glargine, adalimumab, trastuzumab biosimilars	○ Undertaking opportunities to expand in emerging markets (China, India, Brazil, Russia)	○ Samsung Bioepis (development of biosimilars, commercialization of infliximab biosimilar [worldwide ex-EU/Russia/Turkey] and etanercept biosimilar [worldwide ex-US/EU/Japan]) ○ J&J (commercialization Remicade®; Simponi® via Schering-Plough) ○ Ablynx (nanobodies) ○ Hanwha Chemical (development and commercialization etanercept biosimilar)
5	Sanofi	○ Lovenox®-enoxaparin ○ Lemtrada®-alemtuzumab ○ Zaltrap®-ziv-aflibercept ○ Vaccines (via Sanofi-Pasteur)	○ Expansion biologics site Geel (Genzyme, Belgium) to manufacture mAbs ○ Investment Genzyme production facility Framingham (US)	○ Shantha Biotechnics (2013) ○ Genzyme (2011)	○ Insulin glargine-Lantus® ○ insulin glulisine -Apidra®	○ Pipeline: insulin lispro biosimilar	○ Focus on China ○ Via acquisition of Shantha Biotechnics (focus vaccines) ○ Increasing insulin production in Russia	○ Regeneron (Zaltrap®-aflibercept)
6	Gilead Sciences	○ Macugen®-pegaptanib ○ Lexiscan®-regadenoson	○ Acquisition of biologics manufacturing plant in Oceanside (US) from Genentech	○ Arresto Biosciences (2011)	–	–	– ○ No specific efforts for biopharmaceuticals, focus on HIV treatments	– ○ Not for biopharmaceuticals, focus on HIV treatments
7	Johnson & Johnson	○ Remicade®-infliximab ○ Eprex®/Erypo®-epoetin alfa ○ Simponi®-golimumab ○ Stelara®-ustekinumab	○ Biologics manufacturing site Cork (Ireland) ○ Biologics manufacturing site Leiden (The Netherlands)	○ Crucell (2010) ○ Centocor (1999)	–	–	○ Global policy to support access in emerging markets as well	○ MSD (Remicade®, Simponi®) ○ Genmab (bispecific antibodies) ○ Bavarian Nordic (Ebola vaccine)
8	GlaxoSmithKline	○ Benlysta®-belimumab ○ Bexxar®-tositumomab ○ Multiple vaccins	○ Investment vaccines manufacturing site Tuas (Singapore) ○ Investments in UK manufacturing network ○ New US vaccines R&D center	○ GlycoVaxyn (2015) ○ Human Genome Sciences (2012) ○ CellZome (2011)	○ Albiglutide (Eperzan®/Tanzeum®)	–	○ Increasing investment in emerging markets, biggest areas of growth	○ Genmab (Arzerra®-ofatumumab; rights now transferred to Novartis) ○ OncoMed (development oncology drugs)

(Continued)

TABLE 1 | Continued

Rank (6, 7)	Company	Strategy biopharmaceutical market						
		(a) Development of originator biopharmaceuticals	(b) Investment in biotechnology		(c) Development of next-generation biopharmaceuticals	(d) Development of biosimilars	(e) Investment in emerging countries	(f) Collaboration and co-marketing
			Own development program	Acquisition				
9	AstraZeneca	◦ Synagis®-palivizumab ◦ Vaccines	◦ Construction biologics plant Södertälje (Sweden) ◦ Investment biologics production facility Frederick (US) ◦ Acquisition commercial biologics manufacturing site Boulder and supporting warehouse Longmont (US)	◦ Spirogen (2013) ◦ MedImmune (2007) ◦ Cambridge Antibody Technology (2006)	◦ Via biologics arm: MedImmune	◦ Pipeline: rituximab, bevacizumab biosimilars	◦ Area of focus, specifically China	◦ Samsung BioLogics (joint venture: Archigen Biotech, development rituximab biosimilar) ◦ Fujifilm Kyowa Kirin Biologics (development bevacizumab biosimilar) ◦ MSD (Manufacturing capacity sharing) ◦ Celgene (durvalumab development) ◦ Eli Lilly (immuno-oncology drugs) ◦ Moderna Therapeutics (immuno-oncology mRNA therapeutics) ◦ Regeneron (antibody-drug conjugates) ◦ Inovio (cancer vaccines)
10	AbbVie	◦ Humira®-adalimumab ◦ Synagis®-palivizumab	◦ New manufacturing facility Tuas (Singapore)	◦ Stemcentrx (2016) ◦ Pharmacyclics (2015)	–	–	◦ AbbVie will focus on expanding presence in emerging markets ◦ Via manufacturing plant Singapore	◦ Boehringer Ingelheim (immunology drugs) ◦ Bristol-Myers Squibb (oncology)
11	Amgen	◦ Blincyto®-blinatumomab ◦ Enbrel®-etanercept ◦ Epogen®-epoetin alfa ◦ Neupogen®-filgrastim ◦ Prolia®/Xgeva®-denosumab ◦ Repatha®-evolocumab ◦ Vectibix®-panitumumab	◦ Several production facilities focused on biologics ◦ New manufacturing facility Tuas (Singapore) ◦ Several biopharmaceutical medicines in pipeline (e.g., monoclonal/bispecific antibodies, fusion proteins)	◦ Micromet (2012) ◦ BioVex Group (2011)	◦ Darbepoetin alfa (Aranesp®) ◦ pegfilgrastim (Neulasta®)	◦ Adalimumab (Amjevita®) ◦ Pipeline: trastuzumab, bevacizumab, infliximab, rituximab, cetuximab	◦ Plans for increased presence in key new and emerging markets (e.g., China, Latin America, Middel East; via collaborations) ◦ Via Dr Reddy's (India)	◦ Allergan/Actavis (biosimilar monoclonal antibodies for oncology) ◦ Daiichi Sankyo (biosimilars) ◦ Dr Reddy's (commercialization Xgeva®, Vectibix® and Prolia® in India) ◦ UCB (romosozumab) ◦ Advaxis (cancer immunotherapy) ◦ Xencor (cancer immunotherapy and inflammation)
12	Allergan	◦ Botox®-onabotulinumtoxinA	◦ Biosimilar development center Liverpool (UK)	◦ RetroSense Therapeutics (2016) ◦ Motus Therapeutics (2016)	–	◦ Pipeline: Biosimilar program for oncology (Amgen)	◦ Presence in all continents of the world ◦ Actively investing in South Korea, China, Poland, Turkey, Philippines, South Africa, Russia, Indonesia and Vietnam	◦ Amgen (biosimilar monoclonal antibodies for oncology) ◦ Molecular Partners (DARPin-based products)

(Continued)

TABLE 1 | Continued

Rank (6, 7)	Company	Strategy biopharmaceutical market						
		(a) Development of originator biopharmaceuticals	(b) Investment in biotechnology		(c) Development of next-generation biopharmaceuticals	(d) Development of biosimilars	(e) Investment in emerging countries	(f) Collaboration and co-marketing
			Own development program	Acquisition				
13	Teva Pharmaceutical Industries	◦ Cinqair®-reslizumab ◦ Granix®- tbo-filgrastim	◦ Investment biotechnological production site Ulm (Germany)	◦ Labrys biologics (2014) ◦ CoGenesys (2008)	◦ Lipegfilgrastim (Lonquex®) ◦ Development of next-generation human growth hormone	◦ Filgrastim (Tevagrastim®) ◦ follitropin alfa (Ovaleap®) ◦ filgrastim (Ratiograstim®) via acquisition Ratiopharm	◦ Via Teva Growth Markets	◦ Celltrion (biosimilars, e.g., trastuzumab, rituximab commercialization in US and Canada) ◦ Regeneron (fasinumab)
14	Novo Nordisk	◦ Several insulins ◦ Norditropin®-somatropin ◦ Novoseven®-recombinant factor VIIa ◦ NovoEight®-recombinant factor VIII ◦ Novo Thirteen®-recombinant factor XIII	◦ Expansion production facilities US and Denmark for diabetes portfolio and hemophilia treatments	◦ Calibrium (2015) ◦ MB2 (2015)	◦ Liraglutide (Saxenda®/Victoza®) ◦ Insulin detemir (Levemir®) ◦ Insulin degludec (Tresiba®) ◦ Development of semaglutide (GLP-1 analog) ◦ Development of next-generation human growth hormone	–	◦ Core capability: building and maintaining a leading position in emerging markets ◦ Investments in China and Russia for R&D, production and sales ◦ Changing Diabetes for Children program, training HCP in poorest countries in the world	◦ Ablynx (nanobodies) ◦ Xencor (bispecific antibodies)
15	Eli Lilly	◦ Forteo®-teriparatide ◦ Glucagon®-glucagon ◦ Humulin®-insulin ◦ Humatrope®-somatropin ◦ Taltz®-ixekizumab ◦ Cyramza®-ramucirumab ◦ Lartruvo®-olaratumab ◦ Portrazza®-necitumumab	◦ Construction of commercial scale biologics facility Cork (Ireland) ◦ Expansion Lilly Biotechnology Center San Diego (US) ◦ Continuous investment in insulin producing sites	◦ SGX Pharmaceuticals (2008) ◦ ImClone Systems (2008) ◦ Icos Corporation (2007)	◦ Insulin lispro (Humalog®) ◦ Dulaglutide (Trulicity®)	◦ Insulin glargine (Abasaglar®/Basaglar®)	◦ Emerging markets business area ◦ China via Yabao Pharmaceuticals for diabetes ◦ China via Innovent Biologics	◦ Boehringer Ingelheim (Abasaglar®) ◦ AstraZeneca (MedImmune; immune-oncology drugs) ◦ Pfizer (tanezumab, chronic pain) ◦ Merck KGaA (manufacturing and commercialization cetuximab US and Canada)
16	Bayer	◦ Eylea®-aflibercept ◦ Betaferon®-interferon beta-1b ◦ Kogenate®-octocog alfa	◦ Expansion sites Germany and US for hemophilia-A products	◦ DIREVO Biotech (2008) ◦ Schering (2006)	◦ Development damoctocog alfa pegol (pegylated octocog alfa)	–	◦ Increasing sales in emerging markets	◦ Regeneron (aflibercept for eye diseases) ◦ OncoMed (development oncology drugs) ◦ Compugen (development and marketing antibody-based cancer therapeutics)
17	Bristol-Myers Squibb	◦ Orencia®-abatacept ◦ Opdivo®-nivolumab ◦ Yervoy®-ipilimumab ◦ Empliciti®-elotuzumab ◦ Nulojix®-belatacept	◦ Expansion biologics manufacturing facility Devens, Massachusetts (US) ◦ Construction of new large-scale manufacturing facility in Cruiserath (Ireland) ◦ Establishment of biomanufacturing process laboratory Dublin (Ireland)	◦ Padlock therapeutics (2016) ◦ Cormorant Pharmaceuticals (2016) ◦ iPierian (2014) ◦ ZymoGenetics (2010) ◦ Medarex (2009) ◦ Adnexus Therapeutics (2007)	◦ Development of pegylated fibroblast growth factor 21	–	◦ Expanding capacity in China ◦ Partnership agreements in China and Singapore, e.g., Simcere Pharmaceutical Group for abatacept ◦ R&D center in Bangalore (India)	◦ AbbVie (oncology) ◦ Samsung BioLogics (Production biopharmaceuticals at South-Korea plant) ◦ Janssen (immuno-oncology)

(Continued)

TABLE 1 | Continued

Rank (6, 7)	Company	Strategy biopharmaceutical market						
		(a) Development of originator biopharmaceuticals	(b) Investment in biotechnology		(c) Development of next-generation biopharmaceuticals	(d) Development of biosimilars	(e) Investment in emerging countries	(f) Collaboration and co-marketing
			Own development program	Acquisition				
18	Takeda	○ Entyvio®-vedolizumab ○ Adcetris®-brentuximab vedotin	○ Acquisition biologics manufacturing facility Minnesota (US) ○ Construction vaccine manufacturing plant Singen (Germany)	○ Inviragen (2013) ○ Multilab (2012) ○ LigoCyte (2012) ○ Millenium Pharmaceuticals (2008)	–	–	○ Enhancing position in Brazil via acquisition Multilab (2012) ○ Emerging markets business unit headquartered in Biopolis (Singapore)	○ Amgen (Marketing Japan e.g., panitumumab, etanercept) ○ Crescendo Biologics (Humabody®-based therapeutics) ○ MacroGenics (bispecific antibodies)
19	Boehringer Ingelheim	○ Praxbind®-idarucizumab	○ Contract manufacturing business via BioXcellence ○ Large scale facilities in Biberach (Germany, contract manufacturing) ○ Investments plant Vienna (Austria, contract manufacturing) ○ Acquisition biologics plant Fremont (US, contract manufacturing)	–	–	○ Insulin glargine (Abasaglar®/Basaglar®) ○ Pipeline: bevacizumab, adalimumab biosimilars	○ Biologics contract manufacturing site Shanghai (China)	○ Eli Lilly (Abasaglar®) ○ Xencor (monoclonal antibodies) ○ Zealand (therapeutic proteins diabetes/obesity)
20	Astellas Pharma	○ Eligard®-leuprolide acetate ○ Amevive®-alefacept	–	○ Ocata therapeutics (2016) ○ Ganymed Pharmaceuticals (2016)	–	–	○ Reinforce sales platform, focus on China and Russia	○ Vical (cytomegalovirus vaccin) ○ Amgen (joint venture Amgen Astellas Biopharma, development and co-marketing Japan) ○ Seatle genetics (Enfortumab Vedotin)
21	Mylan	–	–	–	–	○ Pipeline: Collaboration Biocon trastuzumab, adalimumab, bevacizumab, pegfilgrastim biosimilars, insulin analogs; collaboration Momenta abatacept biosimilar; collaboration Mabion rituximab biosimilar	○ Via Biocon for biosimilars	○ Biocon (biosimilars e.g., trastuzumab, pegfilgrastim, adalimumab, bevacizumab; insulin analogs) ○ Momenta (biosimilars e.g., abatacept) ○ Mabion (commercial rights rituximab biosimilar candidate)

(Continued)

TABLE 1 | Continued

Rank (6, 7)	Company	Strategy biopharmaceutical market						
		(a) Development of originator biopharmaceuticals	(b) Investment in biotechnology		(c) Development of next-generation biopharmaceuticals	(d) Development of biosimilars	(e) Investment in emerging countries	(f) Collaboration and co-marketing
			Own development program	Acquisition				
22	Biogen	◦ Avonex®-interferon beta-1a ◦ Tysabri®-natalizumab ◦ Zinbryta®-daclizumab	◦ New biologics manufacturing facility Luterbach (Switzerland)	◦ Stromedix (2012)	◦ Efmoroctocog alfa (Eloctate®/Elocta®) ◦ Eftrenonacog alfa (Alprolix®) ◦ Peginterferon beta-1a (Plegridy®)	◦ Via Samsung bioepis: ◦ etanercept (Benepali®) ◦ Infliximab (Flixabi®) ◦ Pipeline: Via Samsung Bioepis adalimumab, insulin glargine, trastuzumab, bevacizumab biosimilars	◦ Partnering with UCB for marketing products in emerging markets ◦ Via Samsung Bioepis for biosimilars	◦ Samsung BioLogics (via Samsung Bioepis, development biosimilars) ◦ Roche (co-development and marketing Rituxan® US, Gazyva® US) ◦ AbbVie (co-promotion Zinbryta® in US) ◦ Sobi (Alprolix®, Eloctate®) ◦ MSD (via Samsung Bioepis for commercialisation Benepali® and Flixabi®)
23	Celgene	–	◦ Looking to hire talented people for biologics development	◦ EngMab (2016) ◦ Abraxis BioScience (2010)	–	–	– ◦ Not for biopharmaceuticals	◦ OncoMed (development oncology drugs) ◦ AstraZeneca (MedImmune: durvalumab, oncology) ◦ Sutro Biopharma (multispecific antibodies, antibody-drug conjugates) ◦ Northern Biologics (antibodies cancer and fibrosis) ◦ Acceleron (protein therapeutics cancer and orphan diseases)
24	Merck KGaA	◦ Erbitux®-cetuximab ◦ Rebif®-interferon beta-1a ◦ GONAL-f® – follitropin alfa ◦ Pergoveris®-follitropin alfa/lutropin alfa ◦ Luveris®-lutropin alfa ◦ Ovitrelle®-choriogonadotropin alfa ◦ Cetrotide®-cetrorelix ◦ Saizen®-somatropin	◦ Merck Biotech Center Corsier-sur-Vevey (Switzerland) ◦ Investment in Biosimilars Unit	◦ BioReliance (2012) ◦ Molecular Medicine BioServices (2007) ◦ Serono (2006) ◦ Biochrom AG (2012) ◦ CellASIC (2012)	–	◦ Pipeline: E.g., bevacizumab, cetuximab, etanercept, infliximab, rituximab, adalimumab, and trastuzumab biosimilars	◦ R&D and manufacturing facilities in China to provide Chinese market ◦ Via partnership with Indian firm Lupin ◦ Plans to expand presence in Africa	◦ Dr. Reddy's (biosimilars oncology) ◦ Bionovis (biosimilars) ◦ Pfizer (avelumab) ◦ MorphoSys (antibodies) ◦ Sutro (antibody drug conjugates) ◦ Mersana (antibody drug conjugates)
25	Daiichi Sankyo	◦ Vaccines Japan	◦ Vaccine business unit	◦ U3 Pharma (2008)	–	◦ Pipeline: Collaboration Amgen e.g., adalimumab, bevacizumab, trastuzumab	– ◦ Not for biopharmaceuticals	◦ AstraZeneca (commercialization FluMist® Japan) ◦ Amgen (biosimilars Japan) ◦ CMC Biologics (antibodies)

Examples: non-exhaustive list

EEA, European Economic Area; EU, European Union; J&J, Johnson&Johnson; mAb, monoclonal antibody, R&D, Research and Development; US, United States of America

the company in emerging countries (focus on BRIC-countries: Brazil, Russia, India, and China). The last column provides information on collaborations between companies, this includes also co-marketing of products. Categories are not mutually exclusive, for example, next-generation biopharmaceuticals can also be classified as originator biopharmaceuticals. Furthermore, examples provided in **Table 1** are not exhaustive.

The first column of **Table 1** shows that 23 of the 25 companies listed (except for Mylan and Celgene) have originator biopharmaceuticals. However, Celgene has several originator biopharmaceuticals under development. The top 20 companies all have originator biopharmaceuticals on the market.

Twenty-three out of 25 companies invest in biotechnology by investing in their own development program and infrastructure. Also 23 companies invest in biotechnology via acquisition of biotechnological companies. Mylan did no acquisitions or investments in its own infrastructure, its presence on the biopharmaceutical market is limited to collaborations for biosimilar development. Mylan is the only company in the list that only engages in biosimilar development and is not focusing on originator biopharmaceuticals/innovation. The top 10 companies all have originator products and invest in biotechnology via investment in their own development program as well as via acquisitions.

Almost every company in the top 25 invests in originator biopharmaceuticals and in biotechnology in general, but only half of them develops next-generation biopharmaceuticals. Furthermore, only half of them invest in development and marketing of biosimilars. Six companies [6, 7, 10, 18, 20, 23] (numbers between square brackets indicate the position of the company in **Table 1**) only have originator biopharmaceuticals, and no next-generation biopharmaceuticals or biosimilars. Eight companies [1, 4, 5, 9, 11, 13, 15, 22] invest in next-generation biopharmaceuticals and also in biosimilars. Five companies [3, 8, 14, 16, 17] only invest in next-generation biopharmaceuticals and not in biosimilars, six companies [2, 12, 19, 21, 24, 25] invest in biosimilars, but not in next-generation biopharmaceuticals. These next-generation biopharmaceuticals are often a modified version of the companies' own originator biopharmaceuticals. A distinction can be made between biosimilars of less complex molecules (insulin, follitropin, epoetin, filgrastim, somatropin) and biosimilars of monoclonal antibodies (mAbs). Four companies [5, 13, 15, 19] only invest in biosimilars of less complex molecules, five companies [9, 11, 12, 24, 25] only in biosimilars of monoclonal antibodies, and five companies [1, 2, 4, 21, 22] invest in both. When looking at the pipeline of the companies, the focus of biosimilar development is mainly on biosimilar monoclonal antibodies and to some extent on biosimilar insulins. For example, Sanofi is making a biosimilar version of insulin lispro, a product of competitor Eli Lilly, whereas Eli Lilly has a biosimilar of Sanofi's insulin glargine.

Twenty-two out of 25 companies are actively expanding their presence in emerging markets. These are companies which already have biopharmaceutical products on the market and are focused on biopharmaceuticals. Gilead's focus is not on biopharmaceuticals. Celgene and Daiichi Sankyo do not market biopharmaceuticals yet.

Collaboration between companies is a common strategy for developing and marketing biopharmaceuticals. All but one company in the list, Gilead [6], are collaborating with other companies or are engaged in co-marketing. Seven companies use all six investment and development strategies [1, 4, 5, 11, 13, 15, 22].

DISCUSSION

As shown in the study by Calo-Fernández and Martínez-Hurtado (2012), in the 1990s big pharmaceutical companies and generics companies developed an interest in the market segment of biotechnology, and innovative biotechnological companies saw the potential of biosimilars. We again looked at the evolving industrial landscape, but now with biosimilars being an established option for all type of companies.

This article has identified the following investment and development strategies used by industrial players in the global biopharmaceutical market: (a) development of originator biopharmaceuticals, (b) investment in biotechnology, (c) development of next-generation biopharmaceuticals, (d) development of biosimilars, (e) investment in emerging countries, and (f) collaboration between companies. Each of these six investment and development strategies is discussed in the following paragraphs.

Development of Originator Biopharmaceuticals

Companies can look for new possibilities in diagnosis, prevention and treatment of chronic diseases, cancer,... and choose to develop originator biopharmaceuticals. Companies investing in originator biopharmaceuticals will, thanks to their investment in research and development (R&D) and new products, have a competitive advantage over companies mainly focusing on development of biosimilars, as they are able to charge a premium price for their originator molecules. However, the risk exists that the market share of the reference product declines due to competition with biosimilars and other non-originator products. If new originator molecules are not ready to follow up, revenue is lost. Big pharmaceutical companies that solely invest in innovation are companies like Roche, GSK, AbbVie, and J&J. AbbVie owns with Humira® one of the highest selling medicines in the world, with global sales in 2016 of US$ 16.1 billion (AbbVie, 2017). While facing loss of exclusivity rights in US in December 2016 and in Europe in 2018 (GaBI Online-Generics and Biosimilars Initiative, 2015), a key challenge will be to retain market share with new biopharmaceutical products. Until now, the answer is often a new formulation with a different concentration, which cannot be copied by biosimilar developers. Roche, which invested in several originator monoclonal antibodies (e.g., trastuzumab, rituximab, bevacizumab, pertuzumab), is just faced with competition from biosimilars with the first rituximab biosimilar being licensed in the EU, although patent and exclusivity rights of several molecules expired years ago (rituximab, 2013; trastuzumab, 2014) (GaBI Online-Generics

and Biosimilars Initiative, 2015; F. Hoffmann-La Roche Ltd., 2016). Roche, as a developer of complex molecules keeps focusing on innovation (Roche, 2014). The company developed subcutaneous forms of its intravenous medicines rituximab and trastuzumab in order to increase patients' convenience (Roche, 2016).

Investment in Biotechnology

When companies not established as biotechnological companies (e.g., traditional, big pharmaceutical companies) wish to enter the biopharmaceutical market, they would need the right infrastructure and knowledge. This can be achieved via acquisition of biotechnological companies. In this way, they can link their image and marketing to the experience and knowledge biotechnological companies have in developing biopharmaceutical medicines. For instance, the acquisition of Genentech by Roche, or MedImmune by AstraZeneca. When companies do not invest in their own development program or infrastructure, this can mean the company works via contract manufacturers. Boehringer Ingelheim, as a contract manufacturer, did no acquisitions of biotechnological companies, but is now collaborating with several companies on the development of biosimilars.

Development of Next-Generation Biopharmaceuticals

As a company focusing on innovation, the development of next-generation product Mircera®, a long-acting epoetin, fits in Roche's business strategy. These next-generation biopharmaceuticals are often characterized by higher bioavailability, increased half-life, lower immunogenicity... to create added value over existing products. Health care payers and hospitals will have to assess whether these products are cost-effective. Also Amgen, as one of the first manufacturers of biopharmaceutical medicines, remains an important player due to their investment in next-generation biopharmaceuticals. With Aranesp® (darbepoetin) and Neulasta® (pegfilgrastim), two products with an increased half-life relative to the originator, Amgen can keep market shares high in the G-CSF and epoetin market. By December 2016, four biosimilars to pegfilgrastim were under evaluation at the EMA (Amgen, 2016; EMA, 2016).

Development of Biosimilars

Companies can choose to focus on development of biosimilars, like Hospira (acquired by Pfizer in 2015) and Sandoz did. Sandoz, which was first to launch a biosimilar in a highly regulated market (Europe), has the highest market share of the biosimilar market (figures up to 2014) (Long, 2015), with biosimilars of somatropin, epoetin, filgrastim, and etanercept. **Table 1** shows that the focus of current biosimilar development is mainly on biosimilar monoclonal antibodies, and insulins. This market is not yet as developed as the biosimilar market with growth hormone, filgrastim and epoetin. Although many companies want a share of the biosimilar market, Merck KGaA is exploring to sell its biosimilar business (O'Donnell and Roumeliotis, 2016). Merck US has attempted to enter the biologics market via a biosimilar pathway, and recently entered into licensing agreements with e.g., Samsung Bioepis (**Table 1**). Similarly, Biogen, one of the first originator biotechnology companies, is now combining their expertise with biosimilars via a joint venture with Samsung BioLogics, Samsung Bioepis. Pfizer was one of the first innovator companies to set up a broad biosimilar development program (Nguyen, 2012). In addition to this, Pfizer took over Hospira for, amongst other things, its biosimilar portfolio.

Investment in Emerging Countries

Emerging countries can be attractive for companies to invest in, a large market is available to supply and economic growth is expected to rise rapidly. Companies can enter emerging countries via collaborations with local manufacturers. Mylan, for example, is working with Biocon, an Indian biotechnology company, to develop biosimilar monoclonal antibodies. Companies can also enter emerging countries by opening their own facilities or by starting initiatives to provide access to treatment in these markets (e.g., Roche's patient support initiative, the "Blue Tree," for cancer care in India). Overall, all companies in the top 25 invest in emerging countries. Some just not yet for biopharmaceutical medicines.

Collaboration between Companies

Collaboration between companies has been a common strategy for marketing pharmaceuticals for decennia, and is also used for biopharmaceuticals. In this way, the combined experience of companies can be used in synergy to compete on the market. Companies can work together with biotechnological companies from emerging countries in order to obtain a place on the local market. For smaller biotechnological companies, collaboration with a large, reputable pharmaceutical company can help to increase trust in their product by physicians and patients. The knowhow delivered by biotechnological companies may, in combination with a well-defined market strategy of big pharmaceutical companies, aid in enhancing the uptake of a new product. New entrants and companies from emerging countries may increase trust by collaborations with established companies in the biopharmaceutical market. Another factor that may play a role in entering into an agreement between companies is risk sharing, where profits and losses are shared between companies. The development cost of a biopharmaceutical medicine is traditionally higher than that of a chemically developed medicine, consequently failure to develop and market a biopharmaceutical medicine may have serious financial implications. Examples of this strategy with respect to biosimilars are the arrangements made by new market entrants, such as Celltrion and Samsung Bioepis, with more established companies. Celltrion is collaborating with Hospira (Pfizer) in different regions in the world, and with Mundipharma and Orion in Europe. Likewise, Samsung Bioepis has a co-investment strategy with US biotech originator company Biogen, and with Merck US.

General Aspects

It is interesting to note that in the top 10 five companies (50%) and in the top 25 eleven companies (44%)

currently have not entered in the development or marketing of biosimilars. It suggests that companies deliberately choose whether or not to enter the biosimilar market.

This study is subject to a number of limitations. The analysis is limited to the top 25 pharmaceutical companies, and new entrants like Samsung BioLogics are not (yet?) in the top 25, although it can be argued that mostly big companies have the resources, capacity and expertise needed to invest in biopharmaceutical medicines. This article only gives a static snapshot anno 2016 of a dynamic industrial landscape and follow-up is needed to investigate changes in the global biopharmaceutical market. In this respect, it should be noted that now that patents of new classes of biopharmaceutical products (e.g., mAbs in oncology) expire, many companies revise their strategy. For instance, Amgen will, as an innovator with originator medicines and next-generation products, focus on the development of biosimilars of monoclonal antibodies. Amgen will use its experience as an innovator to compete with other biosimilar developers. **Table 1** only provides a qualitative overview of the investment and development strategies used by different players in the biopharmaceutical market and does not give quantitative information like sales figures and amounts invested. Furthermore, only publicly available information was consulted, as access to inside business information, often confidential, was missing. It can be noted that there is a lack of peer-reviewed scientific articles providing data on investment and development strategies, and therefore extensive use has been made of gray literature. The classification system is not specific to the biopharmaceutical market. However, its broad application can be valuable in further research and analysis of the market of other types of medicines. To the best of the authors' knowledge, this is the first study to provide a systematic overview of investment and development strategies adopted by industrial players in the global biopharmaceutical market.

CONCLUSION

This article presented a snapshot of investment and development strategies used by industrial players in the global biopharmaceutical market. This snapshot shows that all top 25 pharmaceutical companies are engaged in the biopharmaceutical market and that this industrial landscape is diverse. Companies can develop biosimilars or can decide to solely focus on innovation, can seek support from biotechnological companies, or target emerging countries. Companies do not focus on a single strategy, but are involved in multiple investment and development strategies. A common strategy to market biopharmaceutical medicines is collaboration between companies, whether or not from different regions in the world. These collaborations can as well be used to gain access in regions the company has less experience with. With patents expiring for some of the highest selling monoclonal antibodies, this snapshot highlights the interest of companies to invest in the development of these molecules and/or enter into collaborations to create access to these molecules.

AUTHOR CONTRIBUTIONS

SS, IH, AV, EM, and NM developed the idea for and were involved in the design of this study. EM and NM reviewed available data sources and drafted the initial version of the manuscript. IH, AV, PD, and SS critically revised the manuscript. All authors read and approved the final manuscript.

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GENERAL COMMENTARY
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Commentary: Comparison of historical medical spending patterns among the BRICS and G7

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Jakovljevic's comparison of historical medical spending patterns between BRICS and G7 groups of countries provides a highly valid contribution both from a group, as well as from an individual nation perspective (Jakovljevic, 2015). The author considers two very diverse groups of countries in terms of their wealth, population demographic profiles, as well as population health, health system needs and medical spending patterns.

The first perspective is of an ethical nature and argued through the lens of the principles of distributive justice intended for prioritizing populations on the basis of context, and in relation to allocation of scarce healthcare resources. Two principles, often used interchangeably, are the egalitarian and the equity principles. The former dictates serving those in need equally, whereas the latter consents for contextual differences so that resources are allocated fairly and justly (Persad et al., 2009; Hankins et al., 2015). In particular, equity justifies access to healthcare in that utilization should echo the populations' real needs and aims to eliminate socio-economic and other obstacles. The comparison of the two groups provides a picture of global wealth inequality that is likewise reflected in medical spending. It is therefore worth looking at additional demographic and economic indicators as shown in **Table 1** to gain a more holistic understanding of the inequalities.

The information in **Table 1** clearly shows that the egalitarian principle is not supported in view of the gross global wealth inequality in relation to the populations served; a situation that spills over to healthcare. More challenging is upholding the equity principle in that one assumes that the BRICS populations' real needs far outweigh those of G7 countries, yet their share of Total Health Expenditure (THE) as % of GDP is far less. Furthermore, the BRICS upward trend is mainly dominated by China's foremost contribution to medical spending trends worldwide. The increasing ratio of THE as a % of GDP is an indication that the BRICS countries' health expenditure is growing at a fast rate. Furthermore, one might question the meaning of real need. Population aging and chronic non-communicable diseases, referred to as "prosperity" diseases, appear to be key expensive drivers for G7 countries. However, Jakovljevic also records a historical delay of these drivers on THE in BRICS countries, which may justify the higher spending in G7 countries.

From a public health perspective, it is also wise to apply the widely used utilitarian principle of distributive justice when allocating scarce medical resources, namely to achieve maximum benefit to the maximum percentage of the world population. Conducting cost-effectiveness analysis is

TABLE 1 | Demographic and economic indicators in BRICS and G7 groups of countries.

Demographic and economic indicators	Groups of Countries	
	BRICS	**G7**
Description of economy	Five major emerging yet large and fast-growing national economies (Sui and Sun, 2016)	Seven major advanced economies as acknowledged by IMF (World Economic Outlook, 2016)
Population size	3 billion people or 42% of the world population (World Economic Outlook, 2016)	750.47 million people or 10% of the world population (Group of 7 countries (G7): Statistical Profile, 2016)
Combined nominal GDP	Approximately 20% of the gross world GDP (World Economic Outlook, 2016)	Approximately 39% of the gross world GDP (Group of 7 countries (G7): Statistical Profile, 2016)
Average total per capita health spending	$1004 Purchase Power Parity (PPP) in 2013 (Jakovljevic, 2015)	$4747 PPP in 2013 (Jakovljevic, 2015)

important to choose the most effective health policy, albeit potentially conflicting with ethical principles that do not rely on the monetary value. This principle is however difficult to assess in the report without delving deeper into the countries' disease burden and characteristics. Moreover, the report challenges the readership to question the attainability of WHO's "Health for all-all for health!" (Hong, 2014) by emphasizing the importance of long-term macro-economic analysis and its influence on medical spending. Indeed, the appreciation of the economic viewpoint enables international health organizations and health policy makers to jointly reach more meaningful explanations of the differences worldwide when formulating policies on the provision and utilization of healthcare resources and on overcoming health inequalities worldwide.

The second perspective focuses on the downward trend in all G7 countries' share of THE to global THE in 1995-2013, in contrast to the upward trend of the BRICS (with the exception of South Africa). This raises hope that the gap in THE between the two groups is diminishing. However, the stark differences in % points for individual countries' THE to global THE spells out the reality that the gap is expected to remain wide for the foreseeable future. Nevertheless, this report provides a rather enlightening picture that "successful health reforms in leading markets such as BRICS reveal a reshaping of their medical care-related expenditures" (p. 70). Despite the "bold increase in national health spending across the globe" (p. 70), the report highlights medical innovation, rising public expectations and extended longevity to explain the accelerated growth in health care spending over time. Additionally, the author discusses the two groups' population demographic differences (aging vs. younger nations) within the context of access to medical care and population needs for healthcare. However, as the author's discussion indicates, these statistics alone do not reveal sufficient information about whether spending is allocated appropriately and efficiently. Therefore, further studies are needed to determine and quantify the effect of these behavioral drivers in particular to help curb wastage and misuse/abuse of scarce resources. Additionally, barriers to global dissemination, adoption and implementation of medical innovation, from G7 (often considered as world leaders in this sector) (Kesselheim et al., 2013; Ma et al., 2014) to BRICS countries must be researched. Furthermore, even after accounting for demographic differences, public expectations in different nations/regions, e.g., North America rather than in groups of countries may help to explain higher levels of medical spending. This calls for a better understanding and quantifying of the value of needs vs. demands and their drivers.

Finally, the report uses single source data to facilitate comparisons. Additionally, the author considers 19 years of observations as insufficient to uncover long-term THE trends. A number of factors, which are usually expected to affect THE of a country tend to vary over a long period rather than a short period of time (e.g., changing population structures). The effect of such factors might not be fully captured if the data set being used is of a relatively short time frame. However, the counter-argument is that longer periods may distort findings because of larger variations over time particularly in medical and information technology innovations that distinguished this period from the previous decades.

AUTHOR CONTRIBUTIONS

All three authors contributed actively in the development and finalization of this general commentary. The corresponding author provided the first draft after a group discussion with the two co-authors providing comments and edits until we reached consensus on the final version for submission.

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DATA REPORT
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Length of Hospital Stay and Bed Occupancy Rates in Former Yugoslav Republics 1989–2015

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Keywords: hospital care, healthcare globalization, transition, economic burden, healthcare cost

HOSPITAL SERVICES PROVISION AND FINANCING LEGACY OF FORMER YUGOSLAVIA

Recent decades have been witnesses that developing world economies preceded global economic growth with all the consequences on healthcare systems of their countries. Complex and dynamic socioeconomic and technological evolution, primarily in free market of capitalist economies as well as in former socialist countries/economies with some postponement, provided significant advances and improvements in health outcomes (Jakovljevic and Ogura, 2016). Large differences in the quality of health systems are evident. Globalization among many changes led to the creation of so called emerging markets. The one with the most intensive development were marked by Goldman Sachs as BRICS (Brazil, Russia, India, China, and South Africa; Jakovljevic, 2015).

European region offers great opportunities for studying variations in the magnitude of inequalities in health system quality because of the numerous intercountry varieties of political, cultural, economic, and epidemiologic nature (Arcaya et al., 2015). Eastern Europe and Balkans allow very good insight whether states with history of recent period of war, political instability, economic crisis, and different types of health care reforms have larger inequalities in health than countries elsewhere in Europe and worldwide (Mackenbach et al., 2008).

We conducted a study within former Yugoslav republics, today independent countries and tried to identify some of the indicators determining these variations. A shortage of published data related to the consequences of South-Eastern European transition on healthcare is evident, especially regarding former Yugoslavia. The civil war events between 1989 and 1995 initiated a huge wave of socioeconomic changes in the whole region of the Balkans that inevitably influenced national health systems quality referring to health care provision, planning and financing. These reforms were significantly more prosperous in some states of former Yugoslavia compared to the others (Jakovljevic et al., 2015a). National health system of former Yugoslavia was actually something in between Western European and Eastern Soviet bloc financing pattern. Serbia is the largest Western Balkans medical equipment and pharmaceutical market in terms of population size as well as the value of sales among neighboring non-EU countries. Global recession caused serious problems in provision of sustainable financing and increased shortages of pharmaceuticals and medical equipment across the region of former Yugoslavia (Jakovljevic et al., 2015b).

Health insurance systems are similar in all former Yugoslav republics. All employed citizens are insured and they use health care services in public health care institutions as well as in private institutions which have a signed contract with the Health Insurance Fund, a legal entity established by the Republic Ministry of Health. Unemployed citizens are insured by the employed family member premiums. One of the main functions of the Health Insurance Fund is collection

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of contributions for health insurance and contracting of health services. Health Insurance Fund cooperates closely with Pension and Disability Insurance Fund (Petrusic and Jakovljevic, 2015).

World-widely, out-of-pocket (OOP) payment for health care is the predominant form of health financing. The catastrophic expenditure is defined as an expenditure of over 40% of non-food household expenditure or 10% of overall household expenditure. Little is known about global distribution of catastrophic expenditure especially in developing countries (Shrime et al., 2015).

THE DATA REPORT METHODS

Public Data Set Description—European Health for all—HFA-DB

Public data sources used in this Data Report was the European Health for all Database (WHO, 2015) relying on: http://data.euro.who.int/hfadb/. HFA-DB provides health statistics data related to basic demographics, health status, risk factors, health-care resources, utilization, and expenditure in the 53 countries in the WHO European Region. The indicators are organized into following groups: demographic and socioeconomic statistics, mortality-based indicators, morbidity, disability, and hospital discharges, lifestyles, environment, health care resources health care utilization, and costs, maternal, and child health. It allows queries for country, intercountry, and regional analyses, and displays the results in tables, graphs, or maps, which can be exported for further use. The data are compiled from various sources, including a network of country experts, WHO/Europe's technical programs, and partner organizations, such as agencies of the United Nations system, the statistical office of the European Union (EUROSTAT) and the Organization for Economic Cooperation and Development.

Filters that we applied to these extensive data sources were: inpatient surgical procedures per year per 100 000, total number of inpatient surgical procedures per year, average length of stay for all hospitals, average length of stay for acute care hospitals only, bed occupancy rate (%) for acute care hospitals only and outpatient contacts per person per year. Although HFA-DB is updated twice a year, data availability can vary between countries, and indicators. We used the database for comparison and assessing the health care quality and trends in former Yugoslav republics (Slovenia, Croatia, Bosnia, and Herzegovina, Serbia, Montenegro, and FJR Macedonia) in an international context from 1989 to 2015. Data were acquired based on reported values to the WHO by the national officially released in respective years. Readers are free to access and reuse these publicly available data at the link provided (WHO, 2015).

IMPACT OF TRANSITIONAL HEALTH REFORMS TO THE REGIONAL HOSPITAL SECTOR

Obviously, there are numerous differences in the quality of health services among the countries of the former Yugoslavia. Quality of health services can be expressed by parameters such as: inpatient surgical procedures per year per 100 000, total number of inpatient surgical procedures per year, average length of stay, average length of stay (acute care hospitals only), bed occupancy rate (%), (acute care hospitals only), and outpatient contacts per person per year, which all are the indicators studied in this paper. Today many interventional medical procedures are being performed in a modern way, with modern diagnostic and therapeutic equipment. It certainly contributes to faster and more efficient treatment, as well as the rapid return of patients in the living and working environment with all its economic implications (Caruso et al., 2016).

The significance of surgical disease worldwide has only recently been estimated. Although original estimations suggested that up to 11% of global morbidity and mortality is in correlation with surgical disease, more recent reports suggested that this number is much greater and that even up to 1/3 of the global burden of disease is surgical in nature (Shrime et al., 2016). Although improvements in regular open surgery are evident, laparoscopic surgery represents one of the most important breakthroughs in surgical treatment during recent years. It has many advantages such as shorter hospital stay, reduced pharmaceutics application, rare wound infections, etc., Thanks to modern advances today there is the concept of 1-day surgery (Zhou et al., 2016). However, minimally invasive approach also has a few disadvantages and one of the most important is limited range of motion. It has been eliminated by development of robotic surgery, which will further improve outcome, and reduce the length of hospital stay. Advantages of robotic surgery are evident, despite the high cost of use of such sophisticated equipment (Brunaud et al., 2011).

A short stay in hospital has its many advantages. First of all, the patient spends less time in an environment where they can become a victim of hospital infections that are very difficult to treat. This is particularly important for patients who require treatment in intensive care units. Resistance can occur in all types of pathogen agents (Kramer and Zimmerman, 2010; Barnett et al., 2013; Sganga et al., 2016).

This trend of reducing the average length of hospital stay is present in all countries of the former Yugoslav states. In the reporting period, chart of the average length of stay in hospitals has the linear flow and displays a constant reduction. This is an expected result considering the penetration and adoption of new technical developments in the region, albeit with a slight delay compared to the developed parts of the world. This trend is most distinct in Slovenia. The explanation is probably in the fastest economic development of this country, which resulted in the use of modern means of treatment and medical equipment. For example, Slovenia is the first among former Yugoslav republics that included robotic surgery in routine practice using the da Vinci surgical system. Furthermore, Slovenia is the first of all the member states of the former Yugoslavia that entered the EU. Bosnia and Herzegovina has made great efforts to introduce the guides of good clinical practice, which involves reducing the misuse of antibiotics. That reduced the number of nosocomial infections and consequently length of hospital stay (Petrusic and Jakovljevic, 2015). Although the same trends can also be observed in Serbia, FJRM, Montenegro, and Croatia, their progress was

not as impressive as in Slovenia. A fluctuation in the trend of shortening the average hospital stay, as the consequence of the civil war, is present in the period from 1990 to 1995. This trend is most prominent in Bosnia and Herzegovina and FJRM with a significant increase in the average hospital stay within the specified period. Slovenia had the shortest average length of stay for all hospitals, in regard to Croatia and Former Yugoslav Republic of Macedonia (**Figure 1**).

The economic aspect of the length of hospital stay should not be neglected, because the shortening of hospital stay leads to less consumption of often very expensive drugs, less engagement and fatigue of staff as well as to a faster return of patient to work place (Yin et al., 2013). The development of medicine leads to shortening of hospital stay, but nowadays, there are patients in very serious medical condition carried in intensive care units that previously would not have survived without new medical advances. It leads to an increase in the number of patients and duration of treatment (Karam et al., 2016). This case is especially obvious in intensive care units, where hospital infections are common problem. Failure to follow the rule of fast and well-timed discharge from clinic and misuse of pharmaceuticals lead to longer application of antibiotics, which can cause the development of multiresistance on antibiotics with well-known consequences. Frequent consequence of such manners in the administration of the antibiotics, especially in combination with proton pump inhibitors, is the emergence of Clostridium difficile colitis (Burnham and Carroll, 2013; Mathur et al., 2014; Kandel et al., 2016).

There are many medical breakthroughs that were previously available to a small number of patients or major medical centers. Also, human population constantly rises so that the number of newly diagnosed patients each year increases. The aging of population is also constant, with its entire spectrum of geriatric diagnosis burden. According to the generally accepted forecasts scenario, population aging will even accelerate its trend. Deep demographic transformation of modern societies started a century and a half ago in most of the developed states, but now, this phenomenon is moving from rich north hemisphere to the emerging markets of the south. Developing nations age even faster than developed part of the world. For example, increasing of the number of people over 60 years from 7 to 14% in France occurred over 115 years, while in China during only 26 years. So far, most of the global aging has occurred in the most developed regions of the world (UN, World Population Ageing, 2013).

The development of diagnostics led to better detection of conditions and diseases; therefore today we have "incidentalomas" as incidentally discovered disease, which also requires time and money for medical treatment as well as the engagement of professional staff (Ye et al., 2016). Technical development with better diagnostics ant treatment caused extended longevity and together contributed to increasing in outpatient contacts per person per year in every former Yugoslav republic. The elderly citizens have higher medical needs (Getzen, 1992). Often last years of someone's life in an severe illness require expensive intensive care treatment or involvement of personnel home care service, with costs greater than over the entire lifespan (Kovacević et al., 2015). This trend is especially conspicuous in Croatia. Again, decrease of this trend observed in almost all studied countries from 1990 to 1995 can be attributed to civil war activities. Also, the same factors together with severe hospital infections led to increasing of bed occupancy rate in intensive care hospital units (Udy et al., 2013; Denny et al., 2016; Vincent et al., 2016). The same trend can be observed in all former Yugoslav republics. There is no decreasing in bed occupancy rate in acute care units during observed period from 1989 to 2015, despite the global shortening of average hospital stay (**Figure 2**).

Despite a great reduction of bed number due to cost saving measure, bed occupancy rate remained constant (Forster et al., 2003). Percentage of bed occupancy rate for acute care hospitals only has the highest level in Croatia and the lowest in Former Yugoslav Republic of Macedonia. Data for Montenegro until 2001 are missing.

The global health system changes in the former Yugoslavia must be viewed from the aspect of the relatively recent war events as well as the late Serbian economic opening to the world after 2000. During the war events there was an evident increase in the number of hospitalized patients in the field of trauma, with the consequences of treatment that are correlated with the degree of availability and quality of medical services in such circumstances. Slovenia and Croatia accomplished faster progress in the development of the health system services which is a trend that existed even before the war. The impacts of world macroeconomic crisis that started in 2008 should not be neglected. It pushed all of the Western Balkan countries into numerous difficulties in providing healthcare financing with all consequences in healthcare quality (Jakovljevic et al., 2016).

LIMITATION OF STUDY

HFA-DB is updated twice a year, but data for some countries and some periods are missing. The data are collected from various local sources, which were insufficient in the former Yugoslav republics. It can be attributed to unfavorable socio-economic and political situation during recent years. The authors considered that this lack of data would not change the general trends landscape.

UPCOMING CHALLENGES FOR THE HOSPITAL CARE IN WESTERN BALKANS

The South Eastern Europe and Balkan represent numerous and very diverse ethnic, religious, and traditional patterns, lifestyle models, and social-economic strength levels (Jakovljevic, 2013). It is very important to provide a comprehensive insight into the population aging in this part of Europe, with all social and economic consequences on regional health systems development. However, there is a significant absence of population aging data and its consequences in the Eastern Europe and the Balkan (Jakovljevic and Laaser, 2015). Health policy makers in many developing countries are conscious that their national financial capabilities to invest in the most effective and also expensive medical procedures and

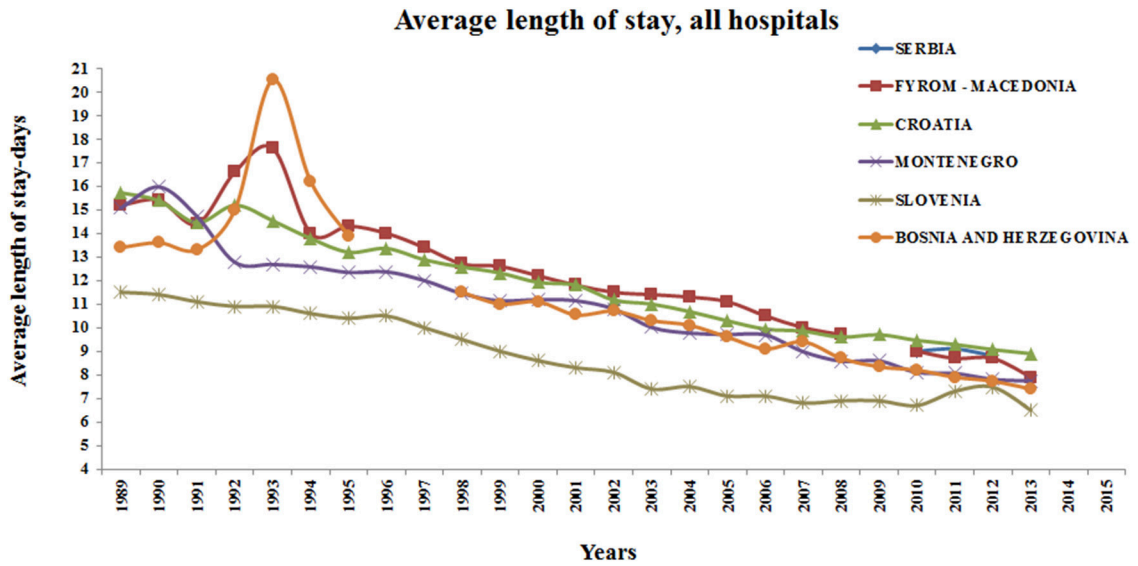

FIGURE 1 | Average length of stay, all hospitals, former Yugoslav republics.

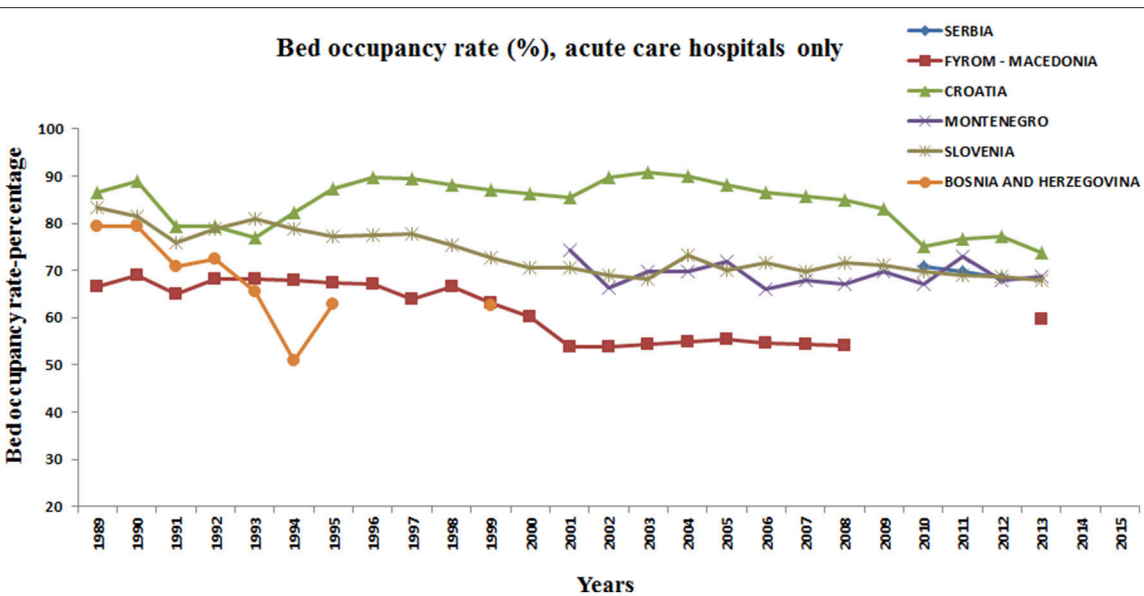

FIGURE 2 | Bed occupancy rate (%), acute care hospitals only, former Yugoslav republics.

drugs remain very limited. Resource distribution based on knowledge must be main determinant in health policy of developed and especially developing economies (Jakovljevic, 2013).

Final judgment on health care system quality is of course in the hands of patients, with easily identifiable parameters such as extended lifespan, fall in neonatal and maternal mortality, and decreasing rates of communicable diseases. Life expectancy at birth and good health at an advanced age are much higher in high-income countries with leading of Japan (Ogura and Jakovljevic, 2014). Accelerated population aging will affect nations in demographic transition much more compared to developed economies (Jakovljevic, 2015). Financial performance of each of the local health care system must be based on local particularities. Health insurance systems in countries of South Eastern Europe must be reformed based on the insurance models of the leading countries but certainly in the light of the peculiarities of each domestic economy. Unfortunately, simple copying of health system from developed countries is not applicable for developing economies due to

their substantially different legacy, traditional value systems and socioeconomic status (Jakovljević et al., 2011). One way to concretize the impact of disease, global or local, is to estimate the economic consequences it causes. Although there is a debate in published data regarding how health and economic status are connected, it is evident that good global population health contributes to economic prosperity (Alkire et al., 2015).

Certainly, one part of the increased health needs is caused by increased availability of health care and protection as well as the aging population and the increasing number of patients in the advanced stages of the disease. Hospitalization rate increased in the level of tertiary-care, which is probably the consequence of poor reorganization at lower levels of health care. Primary health care remained robust and bureaucratic. It relies on general practitioners who work in the primary health care institutions and are not the type of family doctors as it is common in most of Western countries. It seems that health authorities in most of former Yugoslav republics lost their chance to implement major reforms of the health systems in their countries. Stronger insistence on outpatient prescription and dispensing of medicines should be the long-term aim in developing countries as former Yugoslav republics, since this approach is widely considered as one of the main guardians of the whole healthcare system (Jakovljevic et al., 2015b).

ETHICS STATEMENT

Ethics Committee consideration and approval are not necessary in accordance with Good Research Practice guidelines, in retrospective studies observing national level data.

AUTHOR CONTRIBUTIONS

All authors listed, have made substantial, direct and intellectual contribution to the work, and approved it for publication. AC and NZ developed research questions, designed the study, and prepared manuscript for this Data Report. DC and VS participated in the presentation and interpretation of the results.

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Health Promotion Development in the Spa Treatment. Perspectives for the European Countries Learned from Poland's Experiences

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The main aim of the paper is to outline the perspective for future developments of the spa treatment in light of demographic transitions characterized by the increasing number of seniors, as well as changing expectations and health needs of younger population. We made a systematic review of literature referring to the experience of Poland, and similar experiences of other countries in Central Europe. Based on the existing knowledge we conclude that spa treatment should become one of the preferred directions of development of health systems in European countries. Moreover, we state that a desirable direction to modify the therapeutic paradigm used in spa treatment is to put a far-reaching greater emphasis on the provision of innovative health promotion, which is justified by both its effectiveness, and strongly good foundation for its provision in spas. For this purpose it is necessary to extend the specialized health sector personnel with qualified health educators, which will enable an effective implementation of health promotion actions and their proper alignment to the specific target groups. Developing this category of specialists will also enable other professionals to concentrate on therapeutic activity fitting their competence.

Keywords: health promotion, spa and wellness, spa services, health educators, health system and staff attributes

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Spa treatment is perceived as an integral part of health care system in Poland and in other countries in Central and Eastern Europe. This is a result of historical conditions, that shaped the role of this form of therapy. Currently in Poland spa services annually are being used by more than 300,000 patients who receive treatment financed by public payers—most frequently the National Health Fund, but also the Social Insurance Institution or Agricultural Social Insurance Fund (patients undergoing treatment on the basis of a referral and the time delimitation). Additionally, there are about 100,000 commercial patients, including foreign ones, who pay out-of-pocket for the treatment, and do not require referral. Due to the increasing needs of the population arising of demographic phenomena the role of spa sector tends to even increase, and will probably demonstrate further increase of its potential as a response to the projected demographic and epidemiological changes in Poland and Europe (Holecki and Woźniak-Holecka, 2012).

The essence of the spa treatment is a 2- or 3-weeks long therapeutic, rehabilitative, and preventive procedure delivered in sanatoriums, spa hospitals, and spa outpatient clinics. It is offered primarily to patients suffering from chronic cardiovascular, orthopedic, rheumatological, and neurological diseases (Narodowy Fundusz Zdrowia, 2011). Regardless of the type of provider, every form of spa treatment includes provision of health promotion (health education, nutritional education, prevention of all levels, including rehabilitation; Ustawa z dnia 28 lipca, 2005; Rozporządzenie Ministra Zdrowia, 2015). Unfortunately, despite the fact, that health education is one of the basic services included in spa treatment, and as such, it should be a mandatory component of any treatment, it is considered now only as a supplement to the basic services. Meanwhile, the spa treatment based on practical tools of promoting health might, and should be, a crucial component of the continuum of medical therapy (Kalmus, 1998; Gutenbrunner et al., 2010).

ANTICIPATED TRENDS IN THE DEVELOPMENT OF SPA SERVICES

The reason for the increase of needs regarding spa treatment are changes in the social structure, especially the increasing life expectancy contributing to the problem of aging populations in European countries (Jakovljevic and Laaser, 2015). In 2009, European Commission predicted increase in the proportion of people in retirement age in Europe to on average 30% in 2060, while in some countries the growth rate will be even higher—in Poland the share of the population above 65 years may be as high as 36% (European Commission, 2008). Undoubtedly, the Polish society is one of the fastest aging throughout the European Union (European Commission, 2015). While there has been a systematic increase in the average life expectancy of Poles by 6.1 years in women and 7.2 in men since 1990 (Główny Urząd Statystyczny, 2014; www.pwc.pl; 10 Trendów w Polskiej Ochronie Zdrowia, 2016), the 65+ population at the end of 2014 in nominal terms was nearly 5.9 million (Główny Urząd Statystyczny, 2014), and in the next 20 years, according to estimations, this number will increase to 8.5 million (www.pwc.pl; 10 Trendów w Polskiej Ochronie Zdrowia, 2016).

This obviously translates on morbidity and disability occurring in this population. Currently the number of older people suffering from chronic diseases in the age group 60–69 years is 60%, and in the group above 79 years—over 80% (Główny Urząd Statystyczny, 2015a,b). It is estimated that in the next 20 years the incidence of chronic diseases will increase by 2–8% (www.pwc.pl; 10 Trendów w Polskiej Ochronie Zdrowia, 2016). Regardless of the reason for this increase, whether it is a growing prevalence in this age group, or the greater share of seniors in the general population, it translates into a substantial increase in the number of patients requiring access to adequate health services. Polish seniors frequently suffer from cardiovascular diseases (hypertension and ischemic heart disease), lung diseases, osteoporosis, diabetes, visual impairment and hearing loss, arthritis, and cognitive disorders (Polsenior, 2012). Often there are several coexisting chronic diseases in one patient, which significantly increases the likelihood of organ damage limiting psychomotor performance.

In response to the upcoming demographic and epidemiological changes, as well as based on the latest concepts developed in health promotion, proactive measures should be intensified in these patient groups, who generate the highest health needs due to age or sex. Additionally, it is a fact that in spite of severe aging, modern Europeans tend to be more willing to keep active, while having more free time and often satisfactory income. Consequently, this leads to greater mobility manifested in higher propensity to travel abroad, including to the spas. This produces additional advantage and opportunity for applying intensified promotional activities for the elderly and chronically ill patients through the system of spa treatment (Braczkowski, 2014), where the highest rates of representativeness is present.

At the same time, as the experience of highly developed countries show, there is a second group of stakeholders consisting of young people, who pay high attention to a healthy lifestyle and physical fitness (Słomka and Kicińska, 2009). They are also potential consumers of spa-related health services, but require system of communication adequate to their profile and expectations, as well as structure and content of the offered service. This group expects possibilities of active leisure, nature touring, combined with a range of spa and wellness treatment, healthy diet, and physical activity (Górna, 2013). Finally, spa facilities located in attractive regions, but also possessing the infrastructure offering a rich set of procedures to improve the beauty and well-being, have favorable conditions to the implementation of professional trainings in nutritional education, health risk factors, or the general development of well-being through selected forms of physical activity.

Apart from clearly outlined two basic target group for spa services, there are also other target groups potentially interesting for the spa centers. These are groups which do not demonstrate clear symptom of illness, but reveal health needs which are often the consequence of negative effects of the civilizational development. There are also cases of occupation-related burden, such as stress, overstrain, burnout, or post-traumatic stress disorder (PTSD). Multistage spa therapy which is a combination of relaxation treatments with psychotherapy, health education, and prevention of somatic disorders may become an innovative health product and a good response for emerging new health needs of different population groups. The innovative nature of the proposed perspective fits both the specifics of the services to be provided in spas, in particular by strengthening the emphasis on promoting health and building a sustainable health potential of spa services beneficiaries, as well as in the increase of the scope and role of spa treatment in health care system. On the one hand, by expanding the target groups who are recipients of their offer, on the other one—by expansion of the spa sector potential in countries where historical tradition of its use cannot be matched to countries such as Poland and other countries of central Europe.

PROFESSIONAL HEALTH EDUCATOR AS A COMPONENT OF SPA SERVICES

Following the path of innovation coming from outside Europe, among the activities that should be adapted are modern tools of training a new categories of health professionals, since the expected state of things is that every spa facility employ a qualified health educators, e.g., as is the case of the American health care system (Lee et al., 2004). As shows the example of Poland, the role of health education is still underestimated in relation to the dominating paradigm of curative medicine, while application of education for patients is the responsibility of doctors and mid-level personnel, who in the face of an overload with other duties are not able to conduct it in a comprehensive and effective way.

These ideas fit into general challenges health care systems in the world are currently facing, like a sharp increase in spendings on health services, dynamic progress in medical technologies but also the growing social expectations regarding expensive ways of care for elderly (Borek-Wojciechowska and Kłokow, 2007). The wider competence of health providers in providing health promotion is a manifestation of these changes and an effort to address them. So should be also the shift in spa treatment. While in the past the responsibilities of spa sector were related only to a narrow area of rehabilitation and treatment of chronic diseases, now, in face of the new expectations and needs, it should demonstrate more focus on disease prevention, health education, and dietetics, aiming at expansion of patients' conscious learning capabilities, which should in turn result with health-related behavioral change.

A look at the case of spa sector in Poland gives an impression that there is a wide range of educational services related to disease risk factors, pharmacotherapy, and nutrition. Nonetheless, in reality the health education of patients in sanatoriums is highly imperfect and needs a strong systemic correction.

Due to its interdisciplinarity and clear links with such sciences as pedagogics or social psychology, health education presents itself as a useful tool not only in promoting health, but also in other areas of the health system, like prevention, rehabilitation or medical, and social care. To develop the profession of health educator should be therefore regarded as a contribution to the increase of quality and share of health promotion in system of health services, but also general raise of the efficiency of health system in producing better health outcomes. It is important, however, to design his role in a way, which should not be limited only to the transfer of knowledge about health determinants. In light of the latest research, such knowledge is not sufficient to change behavior and establish desired attitudes to health. This category of professionals should primarily get competence in building patient's health capacity and competence, which are the foundation for conscious behaviors (Woynarowska, 2016).

The transfer of service provision toward health education professionals will bring a range of tangible benefits. It will improve the quality of health education in spas, relieve doctors and nurses from carrying out time-consuming procedures related to health promotion and prevention, as well as will allow to better understand and meet patients' needs. In addition, lower cost of professionals' labor will bring savings in the health system and increase the availability of other services, as physicians released from a part of their current duties will be able to concentrate on treatment. The control of the quality and efficiency of health education services should include application of a separate pricing and financing procedures for these services (Rezner et al., 2013).

Innovative solutions in the field of health education may also contribute to building a competitive advantage, which is especially important in case of spa facilities located close to other institutions offering access to a similar scope of natural resources. To create innovative touristic products including effective health promotion, it is necessary to observe the changing trends in tourism, including health tourism. In this particular case, it is important to collect information about the quality, usability, and attractiveness of tourism products, as well as the specific needs of potential service receivers, in conjunction with the use of appropriate promotional channels (Dryglas, 2009).

Proposed trends in the development of spa services and related issue of health promotion can be cataloged using financial, managerial, and organizational factors. Unfortunately, one of the obstacles hardest to break are financial constraints (www.pwc.pl; 10 Trendów w Polskiej Ochronie Zdrowia, 2016) occurring in the form of public payer's limited budget, in conjunction with a diverse pricing of medical procedures and long waiting times for non-commercial spa treatment. These factors result in poor financial condition of companies providing spa services. Additionally, uncertainty associated with changes in legislation is also destructive for the development of the market. A potentially positive factor in turn, might be a clear increase in the phenomenon integrated into the concept of medical tourism, along with the high growth rate in demand for this category of services, estimated at 12–15%, in conjunction with international flows of patients: only in Poland there is almost 100,000 foreign patients every year. Moreover, the mere increase in the number of long-term services is ∼6% per year (www.pwc.pl; 10 Trendów w Polskiej Ochronie Zdrowia, 2016). This expected change to occur in across the European Community should be used as an opportunity to take advantage of spa sector in the health care market.

CONCLUSIONS

Application in the health system exclusively procedures of curative medicine is certainly insufficient. To meet the growing public expectations and health needs, the systems should move toward making the full use of all segments of the health care market, including a comprehensive spa treatment. This is all the more justified in light of the aging of population. As this is in part result of lengthening average life expectancy, to improve life quality of seniors becomes one of key priorities, along with limiting the effects of disability and preserving good mental health. For that reasons strengthening spa sector and applying wide range of health promotion activities on this basis appears to be an important element of the national health policy to limit the risk of disease. The aim should be to broaden the scope of holistically perceived services provided in spas, which should manifest itself in a continuity and complexity of the implemented

actions aimed at strengthening the health potential of young people, and effectively supporting the elderly in the preventing social exclusion.

Although primarily addressed to seniors, spa health care in European countries should be opened also to the needs of young population struggling with health problems, or willing to increase its health potential, often in conjunction with health tourism. Activities aimed at this group of stakeholders should be treated as long-term socio-economic investment.

Moreover, because health promotion can be provided in spas in a most precise and comprehensive way, we should expect that in the near future it will change the nature of both spa services and spa tourism. Thus, it becomes a crucial link between tourism and spa treatment (Madeyski, 1998). The existing experiences may be quite a good foundation for coordination of tasks arising from the relationship of patients with physician, nurse, physiotherapist, and dietitian (Woźniak-Holecka, 2012). The fully effective coordinated system of spa service however should be based on professional health educators, whose additional advantage should be high efficiency provided at a relatively low cost.

AUTHOR CONTRIBUTIONS

JW conceived the study, defined basic theses, and prepared draft of the paper; PR contributed to study design and final version of the paper; TH contributed to study design and final version of the paper; AF contributed to study design and final version of the paper; SJ did the literature review, prepared material for the paper, and contributed to paper draft.

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Modeling Determinants of Health Expenditures in Malaysia: Evidence from Time Series Analysis

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INTRODUCTION

The purpose of this paper is to model the determinants of health care expenditures (HCE) and investigate the short-run, long-run equilibrium dynamic causal relationship between health care and income per capita within the time series framework from 1981 to 2014 in Malaysia. For appropriate model specification and forecasting accuracy, different econometric diagnostic tests were applied. Ordinary least square (OLS) method was used to estimate the long run parameters. Long run co-integration was investigated by Auto-Regressive Distributed *Lag* Model (ARDL) Bound approach, whereas, for causality analysis the Engle-Granger method was used. Income, population structure, and population growth was identified as the significant contributing factors to explain variations in HCE. The estimated income elasticity for HCE was found $0.99 < 1$ showing health care was a necessity. The results confirmed a feed-back hypothesis between health expenditure and income per capita.

Money spending and health care expenditure relationship has long been established (Getzen, 2014). Better health has been identified as an important factor to raise economic growth and increased productivity. A healthy population of any country is of important importance and has positive connections to economic growth (Sachs, 2002; Khan et al., 2015). However, rapidly growing HCE is a matter of grave concern for policy and decision makers across countries in the world. The fast growth rate of health care spending exerts pressure on various sectors of the economy, which might slow down the economic growth sustainability (Jakovljevic and Milovanovic, 2015; Jakovljevic, 2016) create poverty trap, as more out-of-pocket health expenditure hugely affects household income (Khan et al., 2015).

Health Care Expenditure and the Malaysia Case

Malaysia with a total land area of 329,758 square kilometers is one of the leading and fast growing high middle-income economies in the Southeast Asian countries. The total population of the country is approximately 29,717 million which is distributed within 14 states, with a per capita gross national income of US $22 (international PPP); and life expectancy rate ranging from 72 to 76 years at birth of male and female respectively. It spends US$ 938 billion total on health with a growth rate of more than 4.49% on HCE (WHO, 2013). Malaysia, a rapidly fast growing developing economy in the Southeast Asian countries, spent 2.94, and 4.49% of GDP on its total health expenditure, in 1997 and 2012, respectively. The overall per capita spending over the same period was US $223 and US$463, respectively. In 2012, the sector-wise share of health care financing expenditure was: Ministry of health 44%; out-of-pocket 37%; private insurance 7%; other federal agencies 4% (MOH, 2014). The health expenditure growth rate of 4.49%, when compared to the annual GDP growth rate of 6%, shows the persistent rise in growth of health expenditure which might

cause slowing down growth process of economy to a snail's pace. This might exert burden on country's GDP in the form of deficit budget, provision of health care services, and patients out of pocket finances. Thus, it is needed to model and forecast determinants of health care expenditure and future trends in the health care spending, in order to devise appropriate policies to control the rapidly growing HCE growth, equitable health care services provision, and affordable treatments to the people of Malaysia.

This paper aims at, modeling the determinants of health care expenditure (HCE) and the effects of contributing factors of increased health care spending on economic growth by using annual data ranging from 1981 to 2014 in Malaysia.

Motivation of the Study

Based on the current literature survey, this study is first of its kind which attempts to model and investigate factors influencing HCE over an extended time period in Malaysia economy using, ordinary least square (OLS), Autoregressive Distributed Lag Model (ARDL) using annual time series data ranging from 1981 to 2014. We investigate time series properties such as unit root and co-integration between health care and income per capita. Besides, the causality is also examined through Engle Granger (1969) test to find out the direction of causation and for policy implications. The remainder paper is structured as follows:

Section 2 is devoted to an overview of the existing literature on the topic. In section 3, data and sources of data; variables and their measurements are discussed. Moreover, model specification and methodology is also included in this section. Section 4 discusses estimated results and section 5 concludes with some policy implications and suggestions.

LITERATURE REVIEW

Introduction

Rapid population growth has raised serious concerns about the improvements in health status of the general public, health care systems' financial sustainability, both in developed and developing countries as well. Over the last couple of decades, it has been a point of debate, both for applied econometricians and health economists to analyze HCE and its determinants. In addition to that, it has also been very tempting to growth economists and to theoretical and applied econometricians to study economic growth and factors affecting economic growth. The applied econometricians and economists made attempts to model and analyze the relationship between HCE, determinants of HCE, and GDP per capita, including their factors by modeling and analyzing the association between HCE and other non-economic, social and demographic variables at individual country levels and in a panel of countries. Further, accumulated review of the literature on the subject is overviewed in the sections discussed below.

Major Factors of Health Care Expenditure

Income as a Driver of Health Care Expenditure

Numerous studies investigated the HCE and income relationship in a cross-sectional framework with principal findings (1) Income as a potential factor responsible for explaining variations in level and growth of HCE across countries; (2) health expenditure a luxury good with an income elasticity above one (Kleiman, 1974; Newhouse, 1977; Parkin et al., 1987; Gbesemete and Gerdtham, 1992; Gerdtham et al., 1992a,b). This strand of literature emphasized on measuring the size of income elasticity of health care (HC), and the policy effects for the investing and delivery of HC resources. On one hand, supporters of health spending being a luxury commodity claim that it is a good same as other goods and should be put up for market forces. Whereas, advocates of HCE being a necessity, stress the role of government control and intervention in the delivery of health care (Culyer, 1989; Di Matteo, 2003). Many of the past studies either have the issue of variables omission and conversion factor procedures or some methodological problems (Kleiman, 1974; Newhouse, 1977). These studies considered income as a main contributing factor in explaining variations in HCE. However, many researchers in the aftermath incorporated non-income variables as determinants of HCE and investigated the effects of these variables on HCE. Age structure of population was identified as a key indicator to explain changes in HCE across nations (Leu, 1987; Cuyler, 1988). The share of population lees than 15 years of age and elderly population such as 65 years and over or up to 75 years of age was estimated in the model while explaining changes in the HCE per capita. It was noted that, these variables showed marginal influence on HCE (Grossman, 1972; Leu, 1986; Di Matteo and Di Matteo, 1998).

Technology' Role in Health Care Expenditure

Technological progress is one of the key factors to explain variations of HCE (Newhouse, 1992). However, little attention has been paid to the research in order to study the effects of technological progress on HCE, due to the non-availability of an appropriate proxy to capture variations in the medical care technologies. Various proxies have been used in the past studies, such as surgical methods and specific equipment (Baker and Wheeler, 1998; Weil, 2007), health care specific research and development expenditure (Okunad and Murthy, 2002); infant mortality and life expectancy at birth (Dreger, 2005); time index as a proxy for the impact of technology change (Gerdtham and Löthgren, 2000); time-specific intercepts (Di Matteo, 2004). Innovations in technology along with weak cost containment policy were identified as a main contributing factor in increasing health care cost. Major improvements in the health-related technologies, in general, increase health care (Bodenheimer, 2005). The addition of new low cost per patient per year technology to the health care system increases spending on health and health care, because more people are being treated (Lubitz, 2005). Advances and diffusions in medical care technology into the health care systems were the major responsible factors for growing expenditure in health care (Newhouse, 1992). However, there was a conflicting and complex relationship between medical technology and HCE (Sorenson et al., 2013). Health care technology increased survival rates on one hand, but on the other hand it has rapidly increased the cost pertaining to health care as a ratio to GDP (Chandra and Skinner, 2012). Properly managed use of technology, especially mobile technology could

be a major driver to cut cost, improve safety, and as a source of improved decision making for health care professionals (Junglas et al., 2009). Medium and long term forecast models try to elucidate the responsible and driving factors of heath care spending for more clear policy choices available. Expenditure growth is more related to budget decisions. Varying innovative technologies contributed more to growth in the medium term as was the case with targeted biologicals (Jakovljevic, 2015), diagnostic radiology (Ranković et al., 2013) and radiation therapy of cancer (Jakovljevic et al., 2014). Various risk factors such as obesity, and variations in the chronic diseases prevalence turned out to be important in the long term forecasting (Thorpe et al., 2004).

Aging Population and Health Care Expenditure

It is generally anticipated that aging population would be a key factor in health care system and HCE in the near future (United States Congressional Budget Office, 2007). It is also likely that future trends in the health care and long run care would be different (Spillman and Lubitz, 2000). The impact of aging population in the health care spending growth has been extensively investigated in the past studies (Zweifel et al., 1999; Hogan et al., 2001). The Non-significant impact of aging population was found on total per capita HCE (Hoover et al., 2002; Tchoe and Nam, 2010). However, Breyer and Felder (2006), Schulz et al. (2004), (Ogura and Jakovljevic (2014) and Khan et al. (2015) identified aging population as a contributing factor of accruing health care costs; a positive relationship between aging and HCE in short run (Bech et al., 2011). As population ages, total health care spending and expenditure on care of elderly growing (Häkkinen et al., 2008; Mao and Xu, 2014). Aging population was found as a major driver for the health care demand, and thus, an increasing source of health care spending (Reinhardt, 2003). Aging population and aggregate HCE were found to be negatively correlated (Palangkaraya and Yong, 2009). In contrast, the micro-simulation method study showed that there is no sizable impact of aging on health care spending, but the upward movements in the variations were because of prevailing practices (Dormont et al., 2006). However, some studies found that the costs associated with age profile have a tendency to increase to reach a certain level but decline after that level (Martins et al., 2006; Przywara, 2010). Other micro-level studies, (Lubitz et al., 1995; Seshamani and Gray, 2004; Breyer and Felder, 2006) focused on testing whether age or time to death (hereafter, TTD) is responsible for explaining increasing trends of variations in health care spending. Several individual-level studies has suggested that acute health care cost increased as TTD reached nearer and nearer, (Zweifel et al., 1999; Hoover et al., 2002; Breyer and Felder, 2006). However, no significant association found between general practitioners and TTD (Madsen et al., 2002).

A little attention has been paid to find the relationship between the costs of age profile of dying and health care expenditure (Lubitz et al., 1995; Kovacević et al., 2015). Seshamani and Gray (2004) investigated the relationship and found that cost of dying due to acute health care declined beyond a particular age. They found that the reduced acute health care expenditure reflected the possibility of aged populace hospitalization and /or minimizing the chances of introducing intensive treatment.

In many earlier studies, population forecasts and various assumptions were the building blocks for forecasting healthcare or long-term health care cost, particularly, with respect to time spent in good health (Spillman and Lubitz, 2000; Madsen et al., 2002; Breyer and Felder, 2006; Martins et al., 2006). The results of these studies based on time series data were dependent upon the variations in demand as well as on supply sides. Therefore, the estimated HCE be interpreted with respect to utilization of health care instead of demand for health care. On the other hand, projection results were based on certain assumptions made to future age-specific health issues, which were supply side changes. In most of the projections, the utilization rate of age-specific and health care allocation was considered to be constant, and so, could be interpreted from demand side projections. A large portion of this ever increasing demand for medical services appears to be driven by non-communicable prosperity diseases even in top performing BRICS markets (Jakovljevic, 2016).

DATA, MODEL SPECIFICATION, AND METHODS

Data Sources, Variables, and their Description

This study used annual time series data ranging from 1981 to 2014. Data on relevant variables was collected from various data sources such as Statistics Division Malaysia, World Development Indicators (World Bank Group, 2014), Statistical, Economic and Social Research and Training Centre for Islamic Countries (SESRIC), and Asian Development Bank (ADB) and other published reports. The variables and their description are given in **Table 1**.

This study included aging population, as a key driver of HCE because when population ages, public spending as a percentage of GDP is likely to increase, and increased life expectancy is

TABLE 1 | Variable names and descriptions.

Variables	Description	Sources
gdp, gdp_{t-1}	Gross domestic product/capita and its lag value in real term	WDI[a]/WHO[b]/ADB[c]
he, he_{t-1}	Healthcare expenditure /capita and its lagged values in real term	WDI/SESRIC[d]/ADB
pop_{65+}	Share of population age 65 years and above	WDI/SESRIC/ADB
pop_{15}	Share of the population under 15 years	WDI/SESRIC/ADB
Le	Life expectancy	WDI/SESRIC/ADB
Popgw	Population growth rate	WDI/SESRIC/ADB

[a] *WDI, World Development Indicators (World Development Indicators (WDI), December 2015).*
[b] *WHO, World Health Organization (http://www.who.int/GHO/).*
[c] *ADB, Asian Development Bank (http://www.adb.org/data/statistics).*
[d] *SESRIC, Statistical, Economic and Social Research and Training Centre for Islamic Countries (http://www.sesric.org).*

expected to be linked to a decreasing population health status and output (Cuyler, 1988). Life expectancy[1], real per capita HCEs, real GDP per capita, GDP growth rate[2], and share of population under age 15 years and 65 years[3] and above are other variables used in the study. The brief description and data sources are given in the following table.

Model Specification for Health Care Expenditures

The general HCE model can be specified as:

$$hce_t = \beta_0 + \beta_1 hce_{t-1} + \beta_2 gdp_t + \beta_3 gdp_{t-1} + \beta_4 le_t + \beta_5 pop_{t65} + \\ + \beta_6 pop_{t15^-} + \beta_7 popgw_t + \varepsilon_{1t} \quad (1)$$

$$gdp_t = \alpha_0 + \alpha_1 gdp_{t-1} + \alpha_2 hce_t + \alpha_3 hce_{t-1} + \alpha_4 le_t \\ + \alpha_5 pop_{56^+ t} + \varepsilon_{2t}{}^4, \quad (2)$$

where

hce_t, hce_{t-1} = real per capita health care expenditure[5] at time t and t-1

gdp_t, gdp_{t-1} = is GDP per capita in real term at current time and one period lag

le_t = is life expectancy at birth

pop^+_{t65}, pop^-_{t15} = Population age 65 years and above, and age less than 15 years *and*

$popgw_t$ = population growth at time t

ε_{it} = are independent and identical distributed (*iid)* error terms.

In Equation (1), HCE acts as an endogenous variable (hec_t), a function of GDP per capita and other exogenous variables explained as above. In the Equation (2), real GDP per capita (gdp_t) acts as endogenous and HCE as exogenous variable with other explanatory variables.

The β_1 and β_3 are adjustment parameters that could be converged to the equilibrium level if there is any shock to the system, and its value lies between 0 and 1. According to economic theory as the real per capita income increases, the expenditure on healthcare is expected to rise, hence $\beta_2 > 0$. Increasing life expectancy indicates increased overall health conditions of the general public of an economy that could be due to the provision of advanced technologies in the healthcare sector, which have a positive influence on health care spending, so $\beta_4 > 0$. The β_5 and β_6 represent the cohort of the population under the age group of 65 years and above and ages less than 15 years; and as the shares of these two cohorts increase the expenditure on health and health care is likely to increase due to more demand for health care services. $0\langle\alpha_1\langle 1$ and $0\langle\alpha_3\langle 1$ are the adjustment coefficients; $\alpha_1\rangle 0$ because increased health spending enhances good health which as a result increases economic growth; $\alpha_4\rangle 0$ because increased life expectancy is a measure of technological changes, which enhances labor force skills and efficiency. The more the skilled and technologically well-versed labor forces the more the efficiency which ultimately spurs GDP per capita. The effect of Population structure on GDP per capita somewhat acts differently and may have negative effect on GDP per capita as more the population ages the dependency ratio increases which affects the income per capita at household levels as well as at country aggregate level. However, if the share of aging population is healthy and participate actively in the economy, then economic growth increase.

Methods

Based on the objectives of the paper, in the first step, we check the variables for the existence of possible unit root problem in order to get rid of spurious results and for appropriate policy relevance. To this end, we applied ADF and PP individual unit root tests. In the second step, we applied ARDL Bound test to find the short and the long-run relationship between the variables. The variables were checked through various diagnostic tests in order to get reliable, unbiased and consistent estimates of the parameters. Thus, at the final stage to estimate long and short run dynamics equilibrium relation among the series, we used the Unrestricted Vector Error Correction Model (UVECM), and the short and the long run causality were investigated by Granger (1969). During Causality test finally, we employed Granger causality test to investigate the causal link between the variables.

RESULTS AND DISCUSSION

Graphical Investigations

Figure 1A showed an upward trend over time with drift. So, the series, HCE a non-stationary series. **Figure 1B** showed that GDP per capita is upward trending with non-stationarity behavior without drift. **Figure 1C** of aging population exhibits steady increase from 1981 to 2000, but afterward drifting with a trending pattern, which clearly shows time-variance. Looking at the above **Figure 1D** of population growth since 1981, no prominent pattern exists in the data, so the data generating process showing random walk with drift and some irregularities during 1985 to 1995 and low growth rate in 1998, 2001 and 2008-2009.

Unit Root Test

The ADF and PP unit root test results show that the variables are mixtures of I(0) and I(1) and no variable is found to be I(2), however, the results are not reported here in order to save the space and can be obtained on request.

ARDL Co-integration Results

Since the unit root tests show a mixture of I(0) and I(1) variables and none of the variables is I(2), which is the pre-assumption for application an ARDL bound test. The bound test results confirm a long co-integration relationship between HCE and income per

[1]Life expectancy is used as a proxy to capture the effect of technology change on health care expenditure. A change in the levels of life expectancy has influence human behavior at individual and aggregate level. It also impacts fertility, human capital, growth process (Coile et al., 2002).

[2]Lagged values of the health care and gdp are included as previous year values effect current expenditures.

[3]Share of population under age 15 and 65^+ years is used to investigate the influence of changing population.

[4]Gross domestic product (GDP) is modelled in Equation (2) to find the causal effect if any between health care expenditure and GDP.

[5]All the variables are transformed into natural log and model the data in the linear log form for interpreting the estimated results in elasticities and for allowing diminishing marginal returns to other explanatory variables.

capita and the data series pass all the relevant diagnostic tests. These results can be provided on request as has not been shown due to space limitations.

Regression Results

Table 2 summarized the estimated results of the regression taking HCE as a dependent variable, regressed on other explanatory variables as shown in the Equation (1). All the variables significantly affecting health expenditure, however, the impact of GDP growth was non-significant. The estimated signs of the variables were consistent as reported in the past literature. Income per capita has a positive and significant influence on HCE and the estimated elasticity value for HCE was 0.995502 < 1. The value of income elasticity value less than one indicated that HCE was still treated as a necessity good (Khan et al., 2015). The highest t-ratio of income per capita showed that it was a major contributing factor responsible for explaining variations in HCE. Therefore, as the real per capita income of the general public increases, people spend more on their health in order to keep themselves healthier, active, and live longer lives. This result is consistent with previous studies, conducted either at the individual country level or as a panel of countries, for example, (Newhouse, 1977; Parkin et al., 1987; Gbesemete and Gerdtham, 1992; Gerdtham et al., 1998; Dreger, 2005; Khan et al., 2015). The impact of population growth and population structure was also significant. Negative signs of the population with the age group under 15 years and age group of 65 years and above were according to the expectations and are consistent with the earlier research (Khan et al., 2015). The negative influence of the population structure showed increase dependancny ratio on the working age group, which might put pressure on the overall GDP of the country and on allocation of resouces to other sectors of the economy. The possible reason could be that people in this two cohort, spend more on their health either from their past savings or household expenditure. The 15 years and below age group contributes lesser to the development of the economy as they are not actively engaged in economic activities. This age group spends more on health and earns less. Similarly, the elderly population in the declining periods of life are more susceptible to illness, thus, they need health care to keep themselves healthy (Ogura and Jakovljevic, 2014; Khan et al., 2015). This result implies that for people over age 65 proximity of death may increase, which eventually reduces short run HCE in Malaysia. This result is consistent with (Erdil and Yetkiner, 2009; Ogura and Jakovljevic, 2014; Khan et al., 2015). The negative relationship between health care and population growth could be due to the non-random pattern of the population growth. As was obvious from the **Figure 1D** where the growth rate significantly drops down over certain time periods, which outpaces the positive effects.

TABLE 2 | Model: OLS results [1981-2014 ($T = 34$)] Dependent variable: lnhce.

Var	Coeff	*SE*	T-ratios	*P*-value
Constt	0.960535	0.245831	3.9073	0.00054*
Lngdpp	0.995502	0.044104	22.5713	< 0.00001*
Popgr	−0.31141	0.038114	−8.1702	< 0.00001*
Pop15	−0.10281	0.018512	−5.552	0.00264*
Pop65	−0.10827	0.028645	−3.7798	0.00076*
Gdpgr	0.000317	0.001738	0.1826	0.85640
Le	0.567102	0.073540	7.71148	0.00016*

R-squared: 0.994967 and Adjusted R-squared: 0.994068.
**Shows significant at 5 percent and 1 percent significant level.*

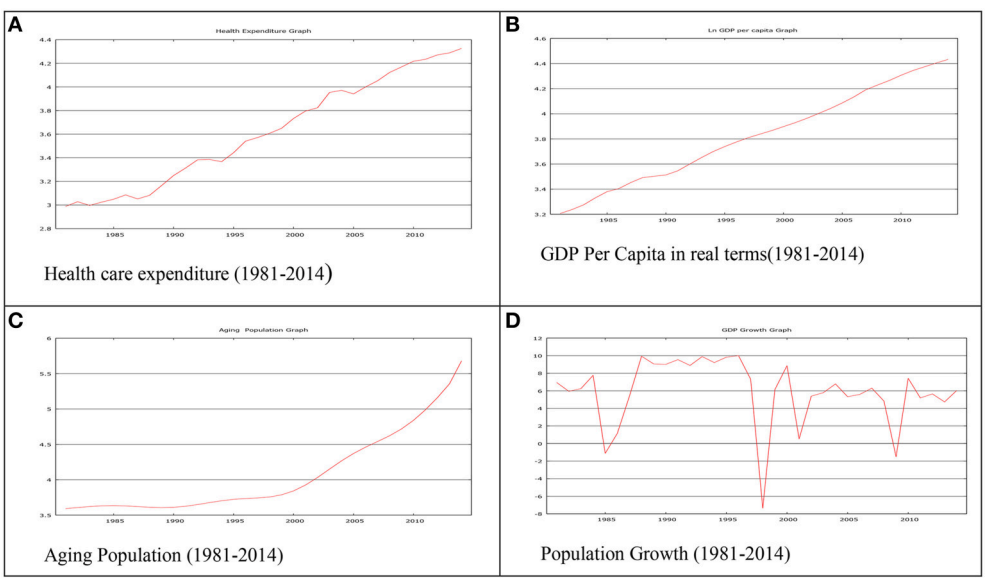

FIGURE 1 | Graphical investigation. (A) Health care expenditure (1981-2014). **(B)** GDP Per Capita in real terms(1981-2014). **(C)** Aging Population (1981-2014). **(D)** Population Growth (1981-2014).

CONCLUSION

The rapid increasing pattern of HCE in Malaysia is a serious concern for the policy makers as well as the decision makers. The purpose of this paper is to model the determinants of HCE and find the effects of these determinants on HCE in the time series framewok from 1981 to 2014 in Malaysia. For the empirical investigation, the paper used ADF, PP tests to check for unit root issue and the ARDL approach for co-integration. For causality between HCE and GDP per capita Ganger VECM is applied. For long run parameters estimation an Ordinary Least Square (OLS) regression is used. The unit root tests confirm mixture of integrating order of the variables, i.e., I(0) and I(1). The ARDL Bound test shows the presence of a long run co-integration between HCE and GDP per capita. The rgeression results confirm that income per capita has a positive and significant effect on HCE with income elasticity for HCE $0.999 < 1$. The income elasticty value shows that HCE is a necessity. The closest value of income elasticity for HCE to one is the most important and intersting result of the study in the case of Malaysia for the sampled period. This indicates that Malaysia is the most rapidly growing economy in the Association of southest nations (ASEAN) and in the near future would be in the list of developed countries. Moreover, population growth and population structure have significant negative impact on HCE. The effect of technological changes, proxy by life expectancy also has a positive and significant influence on HCE. Thus, GDP per capita in real term, population growth, population strucutre and technology is the major contribtor to explain variations in HCE in Malaysia. The Ganger VECM results also comfirm a bidirectional causality between HCE and real GDP per capita.

The findings of the paper provide an insight to the policy makers that health expenditure play a significant role in the economic development of Malaysia. Therefore, to create healthy, efficient, technologically skilled and productive labor force it is suggested that encouraging HCE policies be adopted in Malaysia. The Ministry of Health Malaysia (MOH) should provide basis health facilities as well as promote health education to the common people of the country with a special emphasis on rural health.

AUTHOR CONTRIBUTIONS

All authors listed, have made substantial, direct and intellectual contribution to the work, and approved it for publication.

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Perspectives for the Use of Social Media in e-Pharmamarketing

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The Internet has become a common and global medium. It contains vast information resources and a wide range of communication instruments. One of the communication channels are social media, which increasingly are also used in the business field. Social media combined with mobile technology introduced new challenges to marketing activity. This trend is also observed on specific and highly regulated drug market. The aim of this article is to describe the perspectives for the use of social media in e-pharmamarketing. We find that this require personalized communication, the use of online promotion tools, in order to perform advertising in contact with a demanding client. Currently pharmaceutical companies use social media to communicate basic information on their life, but they still do not appreciate it sufficiently as a tool to build the image of company or products. It is therefore considered that these companies should attach greater importance to the presence in this type of media, especially in the light of dynamic changes in the way people communicate.

Keywords: social media marketing, social media, pharmamarketing, health management, public health

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INTRODUCTION

The Internet has revolutionized the world and is growing rapidly, the same as possibilities of using it in the functioning of society and business. Better access to the global network increases the number of users [46% of world population – 3,42 billion people (Blog smmeasure. Liczby Polskiego Internetu, 2016)]. The traditional media are being replaced by the Internet to some extent, because of its accessibility: convenient time of information releases and the possibility of selecting interesting news by the recipient. One of the online media is social media, which is currently used by 2.31 billion people in the world (Mobirank, 2016), including 1.97 billion (27% of the world's population) using mobile devices. (Mobirank, 2016). Their main advantage is the interactivity and two-way flow of information (Syrkiewicz-Świtała and Świtała, 2012).

Since the introduction of e-mail, new media (e.g., YouTube) and social networking (e.g., Facebook, and Twitter) the ways of human communication have changed noticeable. These changes are observed regardless of the age of Internet users. This is obviously more popular among the younger generation but it is used increasingly among the elderly as well (Syrkiewicz-Świtała, 2015b). Popular nowadays social media, which were meant only to maintain ties and relationships, has also become a place to promote and strengthen the image of companies (Chaudhry, 2011; Gibson, 2012; Królewski and Sala, 2014). They have created a new paradigm of communication, which is based on web surfers' activity. Internet users make and distribute Internet transmission, they become even prosumers (Pikuła-Małachowska, 2010; Syrkiewicz-Świtała, 2014). These new media outdated existing action scheme in marketing. In last 5 years, the importance of social

media has increased significantly, and market activities in this area are the fastest growing sector of Internet marketing. Social media become finally also a source of health information (Evans, 2006; Bernhardt et al., 2014; Syrkiewicz-Świtała and Świtała, 2015). In recent years, Facebook has become one of the most popular sources of information on health in the UK (Collier, 2014; Syrkiewicz-Świtała, 2015a).

The use of modern technology in the pharmaceutical market is not only the implementation of modern production techniques and supply of consumers with innovative medicinal products. The dynamic development of interactive electronic media of a social network gives also a huge field of possibilities for the use of innovative methods of selling and building market position of companies operating in the pharmaceutical industry. Thus is created e-pharmamarketing. It is an activity of a pharmaceutical company aimed to promote and sell its products and build a relationship with the customer or selected groups of recipients, conducted via the Internet (Armstrong and Kotler, 2012). The purpose of this article is to describe the prospects for the use of e-pharmamarketing via social media.

THE EXPERIENCE OF PHARMACEUTICAL COMPANIES IN SOCIAL MEDIA MARKETING

Marketing of pharmaceutical companies in social media can rely on generating Internet traffic by the use of social networking sites. It enables direct contact with a target group, also reducing marketing costs. It aims at formation of relationship between a pharmaceutical company and doctors or patients. This is not a method to achieve rapid sales growth, but it is to become a partner for dialog. The goal is to influence positive image of a company and, at the same time, to encourage customers to share information with friends. Social media marketing relies on effective fanpage management of a brand or a company. This is public relations and marketing operation. Pharmaceutical companies may place counseling articles on social networking sites. The topics may cover health, medicine, lifestyle, nutrition, etc. Photos, videos, commercials, and short text messages can be also published.

The authors of this article conducted a survey on 50 biggest pharmaceutical companies operating in Poland (Pharmaceutical Representative luty-marzec 2014/nr1(31) TOP 50, 2016). The obtained results showed that the vast majority of pharmaceutical companies (86% of companies surveyed) has an account on a social networking site. The most popular services were: Facebook (76% of responses), Twitter (34%), LinkedIn (32%) and Google+ (12%). These are also the most popular portals globally. Facebook unites 1.59 billion users worldwide (Blog smmeasure. Liczby Polskiego Internetu, 2016), Twitter 320 million users (Blog smmeasure. Liczby Polskiego Internetu, 2016), LinkedIn has a base of 100 million people (Blog smmeasure. Liczby Polskiego Internetu, 2016), and Google+ although is the youngest (opened in 2011) was able to convince already 1 billion Internet users (Grabiec, 2016).

A vast majority of pharmaceutical companies benefit from the YouTube platform as well. YT has already over 1 billion users in the world (YouTube Statystyki, 2016). 70% of surveyed companies provide audiovisual messages in this way, but only 32% of them declare the use of YT for advertising purposes. This may be due to legal restrictions on advertising of medicines in different countries. The companies use YT to present their functioning (company events, charitable activities, drug manufacturing process and other information that can positively affect the company's image). Thanks the dynamic ability to distribute similar types of materials in social networks, companies gain maximum reach and brand visibility. It is done with a relatively small outlay of work by PR and marketing professionals.

Video marketing and discussion forums are much less used. Blogging is not popular. None of companies used chat. While social networking, the companies: provide information reference (56%), try to build the company image (54%), communicate professional staff and consumer (28%). 26% of surveyed companies want to increase sales of their products. Only few of them (8%) use social media to strengthen brand awareness.

Unfortunately, microblogs are still less popular than social networking among pharmaceutical companies. Microblogs provide the opportunity for pharmaceutical companies to submit short entries, slogan, logo, links to other reference sites or articles. Microblog's entries are only to encouraged to click on a link and read full content on a website or enter into a discussion. The companies often indicate briefly on a received award, sponsored events, study on a new product, a new drug registration and others.

PERSPECTIVES FOR THE USE OF E-PHARMAMARKETING CARRIED OUT THROUGH SOCIAL MEDIA

E-pharmamarketing in social media is not without disadvantages. Among the most important are the lack of immediate results and difficult measurability. It is because similar types of activities are carried out in an integrated promotional activities of pharmaceutical companies (Düssel, 2009; Heuristic, 2016). It is also a time-consuming form which requires regularity, driving continual dialog, permanent relationships maintaining and involvement (Heuristic, 2016). This form is insufficient in developing countries, where the problem of digital exclusion is widespread. Even among EU member states this is not completely abstract problems. In Romania less than 50% of the population use the Internet (Wykluczenie cyfrowe w Polsce. Raport grudzień, 2015).

Not without significance is the lack of full acceptance of social media. There is relatively low confidence in the network and the Internet users dislike impudence (spam; Hamala, 2014; Heuristic, 2016). The overabundance of information available on the Internet raises the noise effect in communication and searching for true and accurate content (Syrkiewicz-Świtała and Świtała, 2012). No full control over the flow of information

provides the risk of unauthorized content, as well as an unethical actions – information fraud, falsification of identity or privacy violation (Hamala, 2014; Heuristic, 2016).

A significant difficulty is in final subordination of distributed content to legal and ethical requirements in different countries and cultures, which reduces the possibility of full universalization of globally distributed content.

Nevertheless, there are a lot of potential benefits: high interactivity, knowing competition and customer expectations (Syrkiewicz-Świtała and Świtała, 2015), possibility of far-reaching personalization of media and communication (Nowy Marketing, 2015b; Raport IRCenter.com styczeñ, 2016), expanding the availability of online communication channels (Google Trends, 2016), high dynamic of communication spread (Nowy Marketing, 2015b) and possibility of building a positive company image (Szydłowska, 2013; RAPORT, 2016). In the light of the observable trends it is simply necessary to maintain a competitive position in the market.

The potential of social media, however, still seems to be overlooked by pharmaceutical companies (Ustawa, 2001; Niedzielska and Syrkiewicz-Świtała, 2011; Syrkiewicz-Świtała et al., 2015). Many companies neglect important aspects of the use of tools such as e.g., ability to know the expectations of customers, as well as free publicity ($n = 2$; 4%) and the ability to control competition. As burdensome is perceived the need to constantly monitor the content or possibility of losing the positive company image, as well as lack of control over the content being placed. As a result, companies operating in the pharmaceutical industry tend to remain at least one step behind the technological progress in the field of communication tools, losing the ability to generate available benefits. One example of this may be Polish pharmacies. According to conducted monitoring in social media by the Institute of Media Monitoring (IMM) in the first half of 2016 only 20% requests for pharmacy recommendation received answers within the first 36 h after publication. So 80% of pharmacies lost the possibility of contact with the client in the network (Marketing, 2016). Companies do not appreciate the potential of specialized portals such as GoldenLine, which is the local equivalent of LinkedIn, visited by almost 2 million Internet users in Poland (Wirtualnemedia.pl., 2016). Potentially, this is a very useful tool in the process of the recruitment of skilled workers (Kowalczyk, 2012; Profil firmy Adamed na portalu LinkedIn, 2016).

It is expected to boost the activity of companies in this field. It is inevitable for the substantial development of modern mobile technologies, which directly translates to the popularity of social media. However, one can expect the change of interest of Internet users in specific digital medium. Perhaps, instead of popular Facebook there will be some other medium more attractive for customers. Therefore, it is important to monitor constantly the activities of Internet users in social media and on specific portals. Technological progress creates new marketing opportunities for pharmaceutical companies. It also forces to follow new trends, or their creation. Companies need to take creative and innovative approach and to act beyond tamed schemes.

CONCLUSION

Skillfully lead social media pharmamarketing can help build a good relationship with the client on a specific and highly regulated pharmaceutical market. It can be helpful in communicating all necessary information about pharmaceutical products but also promote pro-health actions in the field of promotion and prevention (Akhtar et al., 2015). Social media marketing of pharmaceutical companies is therefore a growing area with great potential. This development is also supported by certain organizational measures on the drug market (Holecki et al., 2013). In November 2015, American Food and Drug Administration (FDA) has encouraged the use of social media to improve communication and information exchange in health promotion and public health (U.S. Food and Drug Administration Social Media Policy, 2015). Foreign studies show that one in four interactions with doctor, patient, and healthcare provider in the United States is a digital contact (Social media in the pharmaceutical sector. UK Synapse, 2013). Patient education through social media is therefore an opportunity for the pharmaceutical industry to gain confidence in the company and increase the awareness of consumer when choosing a product. In this way, customer acquires knowledge about health, diseases, and treatment. In various social media channels it is possible to find information on any drug. This information is available on: websites of a manufacturer, social network brand fanpages, portals for white staff specialists. According to a study, conducted by Comscore, patients who are familiar with drug brand website often followed the recommendations for its use (20% of patients). Internet advertising also influenced the use of a drug (13.5% of patients; ROI Media, 2016). E-pharmamarketing activities in social media and in the network tend to increase. It is estimated that in the year 2016 the US pharmaceutical companies allocate for this purpose 2.48 billion dollars (Berezowski, 2015). Media house Codemedia reported that spending on advertising in Poland on the Internet reaches 7%, i.e., more than 17 million PLN (year 2015) and it increased by 68%, as compared to the previous year (Nowy Marketing, 2015a).

Having a website is no longer a novelty by pharmaceutical companies, but actions in social media are innovative. It is still a very demanding area, obliging a good knowledge of the medical community and the needs of patients, as well as the compliance of pharmaceutical law in force in a country. All information on the websites of drug manufacturers is assessed by regulatory agencies in terms of their compliance with the pharmaceutical law. Therefore, besides the promotion of a brand itself, much of the information applies to illnesses, possible treatments, preventions, health information and healthy lifestyles (Bell et al., 2014). By placing the counseling health related topics, the public awareness increases. Thus positive recommendations among Internet users translate into sales (Akhtar et al., 2015). Every advertising or educational campaign carried out in social media must be very well thought out. It requires also constant monitoring of various social media. It should be also noted that the conduct of strategy in social media cannot be standardized, despite the fact that most companies have a global reach. It is to mention that widespread use of social media is very similar in all markets

but the reactions of people belonging to different cultures are very different. Therefore, companies in this marketing strategy in social media should use adaptive approach i.e., the content and form of communication must comply with the specifics culture of the community. Then that action in this field will be more effective. Involvement in social media will help to build a positive relationship oriented to the needs of a particular client.

Activities in social media may be helpful also in emergency situations. They may assist in all situations such as: pollution in batches of the drug or an incorrect description on the packaging. In such situation it is important to reach a wide audience quickly and effectively. Social media can supplement the instruments used in effective crisis management. They can be used as a source of transmission of reliable and proven information to prevent dissemination of adverse scheme: no information – guess – rumors. Conducting marketing strategies of pharmaceutical companies through social media has also a social significance. It is also possible to use social media in emergency situations i.e., natural disasters (floods, earthquakes, etc.). Most of the large pharmaceutical companies, operating on corporate principles, are involved yet in corporate social responsibility (CSR) and for this purpose they reserve certain budgetary measures. By communicating via social media, companies can rapidly engage the local community for various rescue operations, supporting them financially and materially. Through such activities they gain synergy and their aid is effective and not anonymous. Therefore, companies can expect positive effects in the dimension of public relations.

Pharmaceutical companies can achieve many different goals through the use of social media. They can improve the level of knowledge; build relationships; increase sales of its own products and finally serve general social purposes. As they seem not to take the possible advantages arising of e-pharmamarketing yet, it should be recommended they clearly re-orientate their marketing activity toward new instruments of communication available via Internet to stay up to date with the dynamic changes appearing in the social life and communication channels.

AUTHOR CONTRIBUTIONS

MS-Ś conceived the study and prepared draft of the paper. MS-Ś and PR contributed to paper preparation and study. EP provided new information necessary to revise the paper.

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GENERAL COMMENTARY
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Commentary: Do health care workforce, population, and service provision significantly contribute to the total health expenditure? An econometric analysis of Serbia

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A commentary on

Do health care workforce, population, and service provision significantly contribute to the total health expenditure? An econometric analysis of Serbia

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With interest we have been reading the recent article entitled: "Do health care workforce, population, and service provision significantly contribute to the total health expenditure? An econometric analysis of Serbia" (Santric-Milicevic et al., 2016). Authors provided a decent piece of econometric modeling analysis. Here they evaluated on a supply side a considerable burden imposed by the pool of professional health workforce employees. Authors have pointed out that "*the growth of the health workforce number in the previous year has strongly contributed to the growth of total health expenditure in Serbia from 2003 to 2011.*" Time series modeling approach adds to the scarce body of evidence on health expenditure determinants in post-socialist Eastern European societies.

However, there are few significant gaps in the article deserving to build them up with the omitted evidence. In the explanatory background section a lot has been said about the structural reforms of the national health system. These reforms were to a large extent led by the external consultancies provided by the World Bank through the Health Project Serbia[1] and Second Serbia Health Project[2] whose recommendations were adopted by frequently changing national governments since the early 2000s. These changes took place for well over a decade and a half. Some of them, like the attempt to establish the national health technology assessment (HTA) agency, did that with a very limited success (Jakovljevic et al., 2011). Understanding of these background processes is necessary to catch a glimpse of the big picture in the Balkan health systems (Bredenkamp et al., 2011). Actual lack of confidence of health care professionals in many of these reform initiatives has been shown in large scale national surveys of clinical physicians (Jakovljevic et al., 2016a). Others point out to the significant growth of inequalities in terms of medical care access and affordability among the ordinary citizens in recent years (Radevic et al., 2016).

[1]Health Project (Serbia). http://www.worldbank.org/projects/P077675/health-project-serbia?lang=en. Accessed: 01 October 2016.

[2]Second Serbia Health Project. http://www.worldbank.org/projects/P129539/second-serbia-health-project?lang=en. Accessed: 01 October 2016.

In the section entitled "Drivers of health expenditure in the Republic of Serbia" little has been said about the microeconomic drivers of local medical spending. Mostly top-down national health reports were cited in this chapter. However, there is a strong body of quantified, bottom-up assessments on real-world costs of care in Serbian health system. Over the past 15 years academic health economists have identified core drivers of high costs of inpatient and outpatient medical care. Innovative pharmaceuticals imaging diagnostics, interventional radiology procedures, dental care and radiotherapy in oncology are among the highest impact ones (Jakovljevic et al., 2013, 2014, 2015a; Rankovic et al., 2013; Rančić et al., 2015). A set of regional cost of illness analysis have been conducted as well pointing out that non-communicable prosperity diseases sharing the highest budget impact were high risk pregnancies, diabetes, depression, alcohol addiction, HIV/AIDS, COPD and cancer (Jakovljevic et al., 2008; Biorac et al., 2009; Jovanovic and Jakovljevic, 2011; Dagovic et al., 2014; Cupurdija et al., 2015; Jakovljević et al., 2015; Arnlöv, 2016). Good example as well is the structural trend analysis on long term health expenditure evolution in Serbia published few years ago (Jakovljevic, 2014). Since the focus of the source article is health spending we should emphasize the evolving role of evidence based resource allocation in all of former Yugoslavia's republics (Jakovljevic, 2013). When explaining the growing availability of professional staff in Serbia, authors properly notice: "*Throughout that period, the accessibility of physicians, nurses, and midwives per 10 000 population has increased by 14 % but with significant inequity across districts.*" However, they miss to mention the scale of geographical inequality in density of staff distribution. Most of this pool of physicians, nursing and associated medical staff is concentrated in four largest cities with heavily neglected rural periphery. Heavy migration of skilled labor force toward rich urban cores happens due to higher living standards and stronger employment prospects (Stilwell et al., 2004). Some relief could be found in a skillful financing and provision of primary care services throughout the country (Konstantinović et al., 2012). This exceptional centralization of health workforce capacities in capital cities is not unique to Serbia. It presents a landmark of many Eastern European health systems (Simai, 2006). This is even more prominent in dental workforce and pharmaceutical spending evolution going in different directions in Eastern and Western Europe alongside former Cold War borderlines (Jakovljevic et al., 2016b,c).

In conclusion, authors noticed the role of the growing size of an aging population coupled with strong emigration net rates (Santric-Milicevic et al., 2014). Probably the most typical challenge of rising portion of elderly to the long term sustainability of health care financing could be found in the eldest of nations—Japanese one (Ogura and Jakovljevic, 2014). Nevertheless we should not forget the broad perspective of the population aging in Europe which might be bringing some opportunities together with the difficulties (Jakovljevic, 2015a). Keeping in mind Eastern European perspective, there has been straight forward evidence on connection between the health expenditure long term dynamics and the extension of human longevity (Jakovljevic et al., 2015b). Other major drivers of spending such as the chronic illnesses could be efficiently tackled by more effective provision and financing of hospital care (Mihailovic et al., 2016). Even more promising is the investment into the preventive screenings and other primary outpatient care and life style interventions as was the case in nearby Hungary (Sándor et al., 2016). One of the cost-effective strategies is improved quality of pharmacotherapy nationwide in terms of better patient compliance (Gustafsson et al., 2011). Another complimentary approach is dissemination of good clinical practice guidelines controlling the rate of drug adverse events in hospital and outpatient care (Godman et al., 2013). Pharmaceuticals acquisition costs could be contained by ongoing transformation of the local market targeted to strengthen generic substitution of brand name drugs (Woerkom et al., 2012; Howard et al., 2015). Authors are right in their rather pessimistic opinion on prospects of national health expenditure growth in Serbia up to 2020. But to have these long term projections more reliable, due to their peculiarity, we should look toward more similar health systems such as those of the leading BRICS emerging markets (Jakovljevic, 2015b). Many of these nations share the historical legacy of health care establishments similar to that of Serbia to a large degree. Getzen's excess growth model in forecasting health expenditures gives us hints of what is going on in these nations up to 2025 (Jakovljevic et al., 2016d). Since they have been burdened with similar issues and constraints far earlier and too a far larger extent, small post-socialist nations might be capable to learn valuable lessons for their own future (Jakovljevic et al., 2016e).

AUTHOR CONTRIBUTIONS

MJ and MV have jointly designed the research question, prepared the manuscript and revised it for important intellectual content. They share equal authorship responsibility.

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ORIGINAL RESEARCH
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Relationship between Statin Utilization and Socioeconomic Deprivation in Hungary

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The risk of premature mortality caused by cardiovascular diseases (CVDs) is approximately three times higher in the Central Eastern European region than in high income European countries, which suggests a lack and/or ineffectiveness of preventive interventions against CVDs. The aim of the present study was to provide data on the relationship between premature CVD mortality, statin utilization as a preventive medication and socioeconomic deprivation at the district level in Hungary. As a conceptually new approach, the prescription of statins, the prescription redemption and the ratio between redemption and prescription rates were also investigated. The number of prescriptions for statins and the number of redeemed statin prescriptions were obtained from the National Health Insurance Fund Administration of Hungary for each primary healthcare practice for the entire year of 2012. The data were aggregated at the district level. To define the frequency of prescription and of redemption, the denominator was the number of the 40+-year-old population adjusted by the rates of 60+-year-old population of the district. The standardized mortality rates, frequency of statin prescriptions, redeemed statin prescriptions, and ratios for compliance in relation to the national average were mapped using the "disease mapping" option, and their association with deprivation (tertile of deprivation index as a district-based categorical covariate) was defined using the risk analysis capabilities within the Rapid Inquiry Facility. The risk analysis showed a significant positive association between deprivation and the relative risk of premature cardiovascular mortality, and a reverse J-shaped association between the relative frequency of statin prescriptions and deprivation. Districts with the highest deprivation showed a low relative frequency of statin prescriptions; however, significantly higher primary compliance (redemption) was observed in districts with the highest deprivation. Our data clearly indicate that insufficient statin utilization is strongly linked to the so-called physician-factor, i.e., a statin prescription. Consequently, statin treatment is poor and represents a significant barrier to reducing mortality, particularly among people living in highly deprived areas of the country.

Keywords: statin, prescription, redemption, deprivation, cardiovascular mortality, health services research

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INTRODUCTION

The health status of the population of Central Eastern European (CEE) member states of the European Union is less favorable than that of the countries that became members before May 2004 (EU15 countries). Although the period of epidemiological crisis plateaued between 1980 and the early 1990s in CEE countries and although the mortality caused by cardiovascular diseases (CVDs) is continuously decreasing, the relative risk of premature death, i.e., the ratio between the death rates for CEE countries compared with that of EU15 countries, is highly unfavorable. In the Visegrad Group countries (Czech Republic, Hungary, Poland, and Slovakia), the relative risk of early death caused by CVDs varies between 1.96 and 3.18 (Czech Republic, 1.96; Poland, 2.57; Slovakia, 2.91, and Hungary, 3.18) according to the latest available data (WHO HFA, 2015). These figures clearly indicate that the effectiveness of preventive interventions against CVDs is not sufficient in these countries; therefore, identifying gaps and improving the scale and effectiveness of preventive interventions are necessary in the region.

In addition to lifestyle modifying interventions, considerable benefit can be derived from preventive medication, including lipid-lowering therapy, particularly statin treatment (Perk et al., 2012; Kypridemos et al., 2015). A meta-analysis of 10 randomized trials enrolling a total of 70,388 people with a mean follow-up of 4.1 years clearly showed that statin treatment significantly reduced the risk of all-cause mortality (odds ratio 0.88), major coronary events (0.70), and major cerebrovascular events (0.81). In patients without established CVD but with cardiovascular risk factors, statin use was associated with significantly improved survival and large reductions in the risk of major cardiovascular events (Brugts et al., 2009). It was clearly demonstrated that every 1 mmol/l decrease in LDL cholesterol results in a 21% decrease in cardiovascular events (Yusuf et al., 2009). Therefore, statins are considered the first choice of drugs for patients with hypercholesterolemia or combined hyperlipidemia to reduce their risk of CVDs. Despite the presently growing number of publications on certain adverse effects of statin medication, it is considered to be obvious that the benefits of statins far outweigh the risks for the vast majority of patients (Godlee, 2014).

Although epidemiological data clearly demonstrate that cardiovascular mortality is much higher in CEE countries (WHO HFA, 2015), no studies on the relationship between statin utilization and socioeconomic characteristics of certain population groups were performed in these countries thus far. For the most developed countries, a large number of studies were published on the effect of socioeconomic status on statin utilization, with highly contradictory findings. Studies from Australia, Sweden, Denmark and the US (Stocks et al., 2004; Thomsen et al., 2005; Franks et al., 2010; Ohlsson et al., 2010) suggest that statin prescription in these countries has a socioeconomic gradient, typically among men, with women having a lower prevalence of statin use with increasing socioeconomic status. Furthermore, there is a less than expected utilization among the more disadvantaged. In a pharmacoepidemiological cohort study (Wallach-Kildemoes et al., 2012) it was clearly demonstrated that the Danish implementation of the high-risk strategy to prevent CVD by initiating statin therapy is inequitable across socioeconomic groups, reaching primarily high-risk individuals in groups with lower risk socioeconomic position. However, independent reports from the UK confirm that statin prescription is higher in more deprived areas (Ashworth et al., 2007; Wu et al., 2013). Similarly in New Zealand, those in the most deprived socioeconomic areas were most likely to receive statins. At ages of up to 75 years old, the use was higher among Maoris than non-Maori, particularly in middle age range (in the 45–54 age group, 11.6% of Maori received a statin prescription compared with 8.7% of non-Maoris) (Norris et al., 2014). In these studies, statin utilization was characterized by the frequency of prescription for statins, but no data were published on whether the patients redeemed their statin prescription (the rate of primary non-compliance). However, previous studies found that the overall adherence to treatment is low if statins are used for primary prevention, such as for patients with no previous cardiovascular events; with elevated cholesterol levels, only half of those patients prescribed a statin takes this medication on a regular basis (Mann et al., 2007). Long-term adherence to preventive statin therapy was also found to be decreased with decreasing income, especially in men aged 40–64 years in Denmark (Wallach-Kildemoes et al., 2013).

The aims of our present study were to provide data on statin prescription and its relation to the socioeconomic characteristics of various population groups in Hungary and, as a conceptually new approach on the redemption and relationship between redemption and prescription rates, to define the contribution of patient and/or physician factors to the inefficiency of statin utilization, if one exists, on CVD prevention. Because physicians in general practice are the key persons that initiate, coordinate, and provide long-term follow-up for CVD prevention (Mauskop and Borden, 2011), our study was performed as a cross-sectional analysis utilizing data on statin prescription and redemption rates from all general practices in Hungary. Furthermore, and the ratios of the statin prescription and redemption rates were analyzed as functions of deprivation in the areas served.

MATERIALS AND METHODS

This study focused on the comparative analysis of data for prescriptions by general practitioners (GPs) and redeemed prescriptions for statins in Hungary during 2012, the last year for which all data necessary for the analysis were available in validated databases in a district level study design. The ratios between the number of redeemed prescriptions and that of the prescriptions for statins were used to characterize the level of primary non-compliance. The associations between deprivation and premature mortality caused by diseases of the circulatory system (ICD-10: I00-I99), particularly ischemic heart disease (ICD-10: I25), as well as deprivation and statin utilization (prescription, redemption, and ratio) were also assessed.

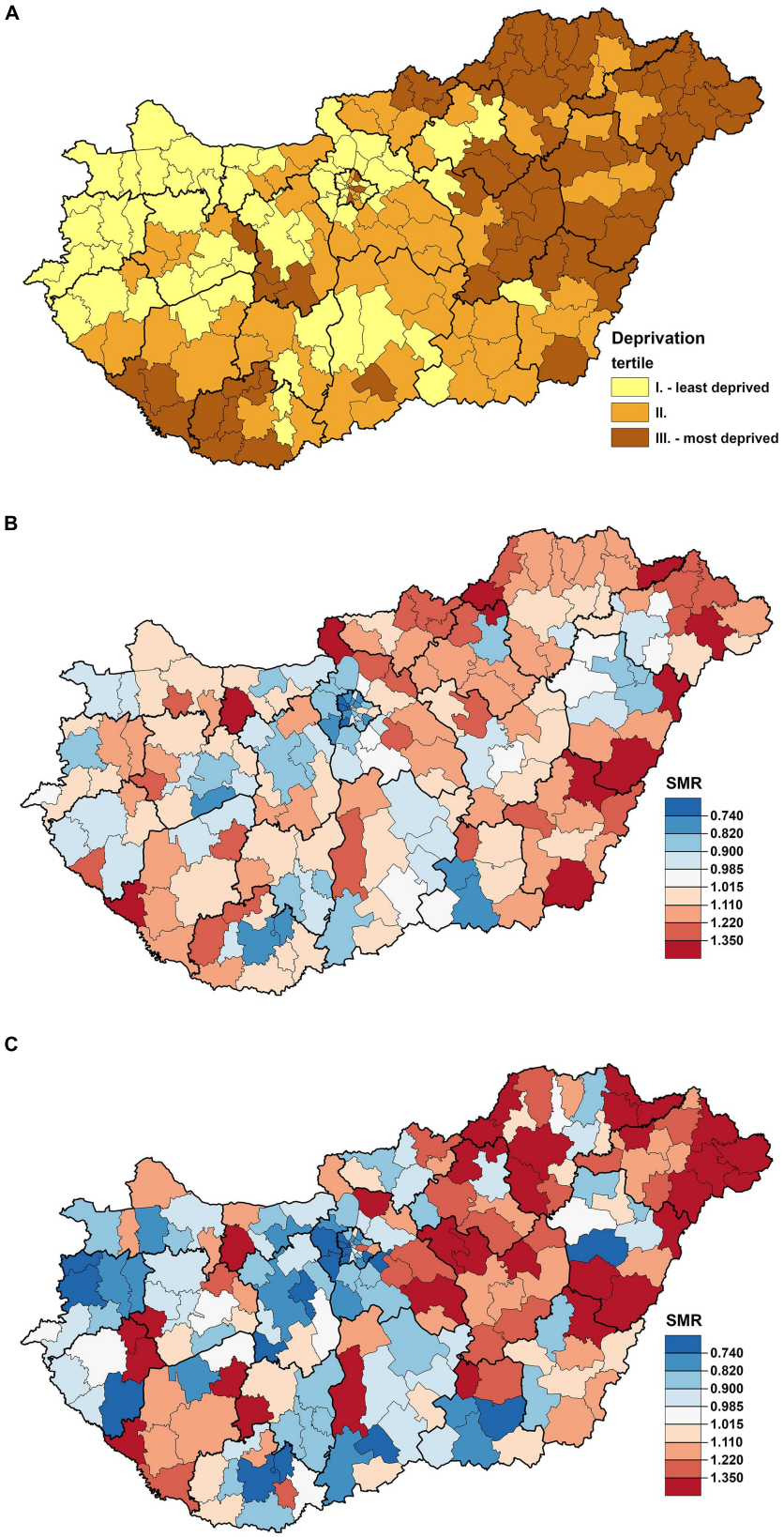

FIGURE 1 | The spatial distribution of deprivation (A) and premature mortality due to diseases of the circulatory system (ICD-10.: I00-I99) (B) as well as premature mortality due to chronic ischemic heart disease (ICD-10.: I25) (C) at the district level in Hungary, 2012.

TABLE 1 | Mortality due to diseases of the circulatory system and chronic ischemic heart disease at district level by DI tertiles, Hungary, 2012.

DI tertiles	Mortality due to diseases of the circulatory system (ICD-10.: I00-I99)	Mortality due to chronic ischemic heart disease (ICD-10.: I25)
	Relative risk (95% CI)	Relative risk (95% CI)
I (Least deprived)	0.926 [0.914–0.938]	0.888 [0.870–0.906]
II	0.996 [0.984–1.009]	0.980 [0.961–1.000]
III (Most deprived)	1.137 [1.120–1.155]	1.233 [1.205–1.262]

Data

Administratively, Hungary is divided into 19 counties as well as the capital Budapest; thus, it has 20 European regions at the third level of the Nomenclature of Territorial Units for Statistics (NUTS). The counties are further subdivided into 198 districts constituting Local Administrative Units 1 (LAU1), formerly known as NUTS level 4 of Hungary[1].

For the year 2012, the mortality data were obtained from the Hungarian Central Statistical Office, whereas population data were obtained from the Central Office for Administrative and Electronic Public Services. Both mortality and population data for the districts were stratified by 5-year age bands and sex.

The number of prescriptions for statins and the number of redeemed statin prescriptions were obtained from the National Health Insurance Fund Administration of Hungary for each primary healthcare practice for the entire year of 2012. According to Hungarian regulations, GPs can prescribe only one type of medicine as a 1-month dose for one prescription for people who are taking long term medications. The data were aggregated at the district level. To define the frequency of prescription and that of redemption, the denominator was the size of the 40+-year-old population that was adjusted for by the rate of the 60+-year-old population of the district.

Deprivation Index (DI) Calculation

Deprivation index was used to provide information about socio-economic deprivation at the district level compared with the national average for 2011, the year of the last census in the country. Socio-economic indicators for the DI were selected from available data stored at the Regional Informational System of the Ministry of Local Government and Regional Development. The data were originally obtained from the Hungarian Central Statistical Office (Census, 2011) and the Hungarian Tax and Financial Control Administration (2011).

The method to calculate DI values was described previously (Juhasz et al., 2010) and was successfully used in former studies designed to characterize the association between deprivation and mortality amenable to healthcare (Nagy et al., 2012) as well as between deprivation and premature mortality due to alcoholic liver disease (Nagy et al., 2014) in Hungary. Briefly, the DI is based on seven elementary socio-economic indicators, including income, level of education, rate of unemployment, rate of one-parent families, rate of large families, density of housing and car ownership. The variables were transformed using the natural log transformation and standardization (z-scores). The district-specific index is a weighted sum of the z-scores, with higher values representing greater deprivation. The weight of each variable was determined on the basis of the standardized scoring coefficients using a principal component analysis. The areas with positive index values are districts with a lower socio-economic status compared with the national average, and the converse is shown in districts with negative index values.

Study at the District Level

In Hungary, the number of GP practices operating in 1 781 municipalities was 6 658 in 2012. The size of the practices, as the number of clients served, varied widely (800–3000 persons/practice), and the average size was 1488 persons/practice. Generally, more family practices operate in higher populated municipalities, whereas one family practitioner serves more than one municipality in less populated areas. In addition, there are primary healthcare practitioners with obligations to provide in-area care and those without such obligations. Considering the facts, that the free choice of family physician is a norm in Hungary and the detailed population data for practices, as well as the statin utilization data by age group are not available due to personal privacy, and the DI is not available at the practice

[1]http://ec.europa.eu/eurostat/ramon/statmanuals/files/KS-RA-07-005-EN.pdf

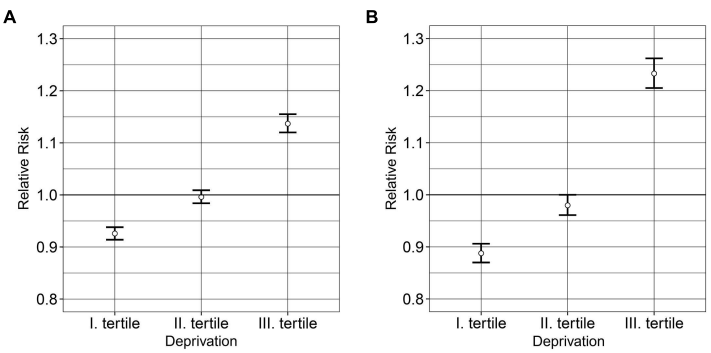

FIGURE 2 | Relationship between the deprivation tertiles and the relative risk of premature mortalities caused by diseases of the circulatory system (A) and chronic ischemic heart disease (B) for 2012 in Hungary.

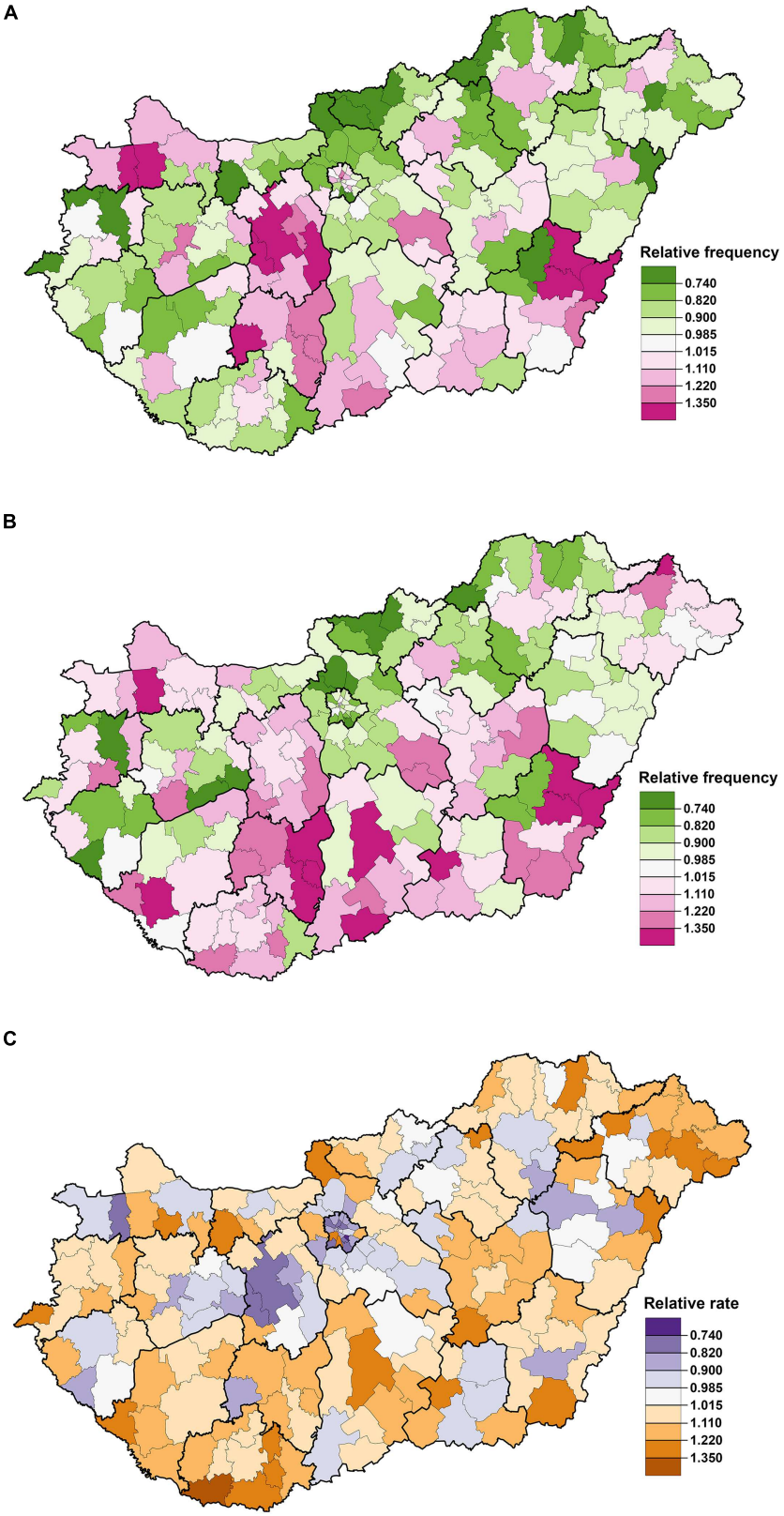

FIGURE 3 | The spatial distribution of the relative frequencies of statin prescription (A), redemption (B) and the relative redemption rate (relative compliance) (C) at the district level in Hungary, 2012.

level to reduce the risk of misclassification, we aggregated all data to the district level. The deprivation for each district was calculated using the population weighted average of DI. All districts included in the analysis were classified into 3 groups or tertiles, ranging from the least deprived (tertile I) to the most deprived (tertile III), with each containing a third of the population.

Using the "disease mapping" option within the Rapid Inquiry Facility (RIF)(Beale et al., 2010), spatial patterns of cardiovascular mortality (ICD-10: I00-I99) and mortality due to chronic ischemic heart disease (ICD-10: I25) for the 40+ age group for 2012 were investigated and visualized at the district level. Indirectly, standardized mortality ratios were calculated using sex- and age-specific death rates for the Hungarian population. The frequency of prescriptions for statins, redeemed statin prescriptions, and the ratios for compliance in relation to the national average were also mapped using the RIF and their association with deprivation was defined using tertiles of DI as a district-based categorical covariate and the risk analysis capabilities of the RIF. Chi-square tests for homogeneity and linear trend were also performed to test the global association of DI and mortality as well as statin utilization.

RESULTS

Association between Deprivation and Premature Mortality Caused by CVDs

Deprivation index values defined by districts varied widely from −3.76 to +5.83, which indicates a high level of socio-economic inequalities in the country. The tertiles based on the DI values were defined as ranges of $-3.76 \leq DI \leq -0.6$,

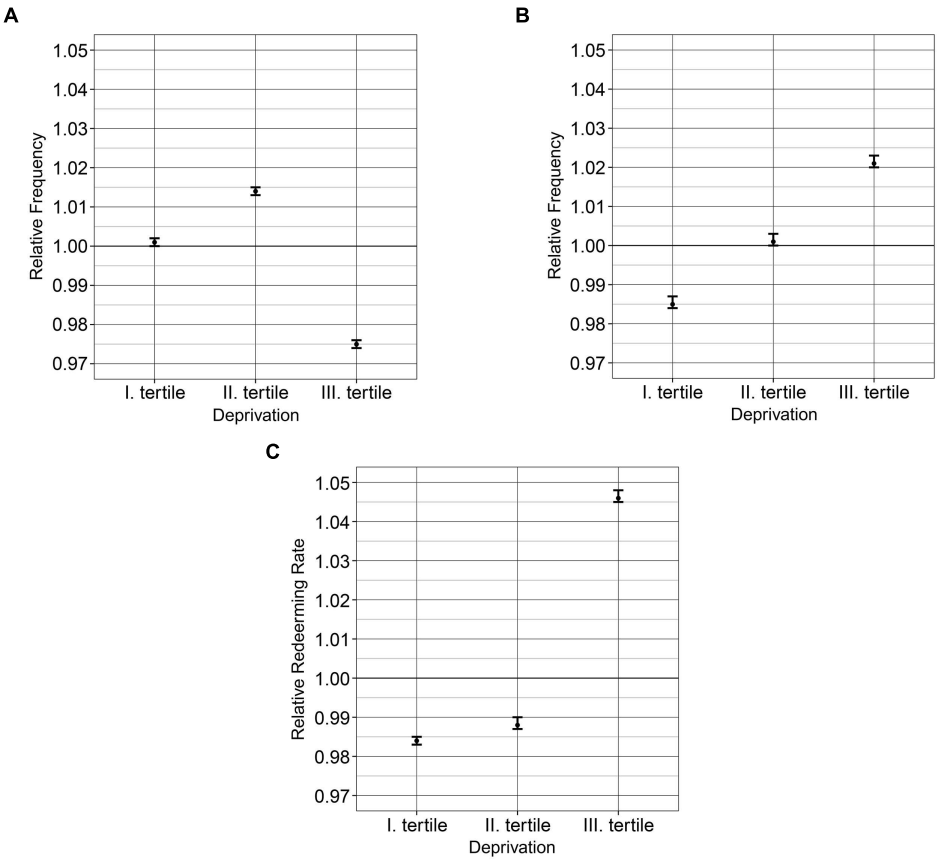

FIGURE 4 | Relationship between the deprivation tertiles and the relative frequencies of statin prescription (A), redemption (B) as well as the relative redemption rate (C) for 2012 in Hungary.

TABLE 2 | Relative frequencies of prescription of statins, statin redeeming, and relative redeeming rates at district level by DI tertiles, Hungary, 2012.

DI tertiles	Prescription of statins	Statin redeeming	Relative compliance
	Relative frequency (95% CI)	Relative frequency(95% CI)	Relative redeeming rate (95% CI)
I (Least deprived)	1.001 [1.000–1.002]	0.985 [0.984–0.987]	0.984 [0.983–0.985]
II	1.014 [1.013–1.015]	1.001 [1.000–1.003]	0.988 [0.987–0.990]
III (Most deprived)	0.975 [0.974–0.976]	1.021 [1.020–1.023]	1.046 [1.045–1.048]

with an average of –1.32 (tertile I); $-0.6 < DI \leq 0.58$, with an average of –0.04 (tertile II); and $0.58 < DI \leq 5.83$, with an average of 1.59. The least-favored districts were found in the northeastern and southwestern parts of Hungary in 2011, whereas the least deprived districts were located in the northwestern part of the country and in the capital city of Budapest and neighboring areas (**Figure 1A**). The spatial distribution of premature mortality due to diseases of the circulatory system (**Figure 1B**) and chronic ischemic heart disease (**Figure 1C**) in Hungary was also characterized by significant inequalities. The districts with the highest estimated SMRs are localized in the more deprived areas, particularly for chronic ischemic heart disease (**Figures 1A–C**; **Table 1**). This is supported by the results of the risk analysis showing a significant association between the relative risk of premature cardiovascular mortality and deprivation (χ^2 homogeneity = 405.15, $P = 0$, χ^2 linearity = 391.57, $P = 0$) as well as between deprivation and premature mortality caused by chronic ischemic heart disease (χ^2 homogeneity = 443.89, $P = 0$, χ^2 linearity = 412.96, $P = 0$) (**Figures 2A,B**).

Statin Utilization (Prescription, Redemption, and Their Ratios)

In Hungary, a total of 10 044 005 statin prescriptions (simvastatin, atorvastatin, rosuvastatin, pravastatin, and fluvastatin) were prescribed in 2012, and only 63.39 [63.37–63.43] % (6 367 738) were redeemed. The frequency of prescription was 1.971 [1.9701–1.9725] and the frequency of redemption was 1.249 [1.248–1.251] per person aged 40+ years. These values were considered the national average.

The frequency of statin prescriptions in relation to the national average was higher in districts in the northwestern and southeastern parts of Hungary and in the middle of the country (**Figure 3A**). The districts with a higher relative frequency of statin redemption were primarily located in the southern part of Hungary (**Figure 3B**). Districts with a higher redemption (primary compliance) rate were located along the axis in the northeastern-to-southwestern direction of Hungary, although the spatial distribution does not show clustering (**Figure 3C**).

The results of the risk analysis showed a reverse J-shaped association between the relative frequency of statin prescriptions and deprivation (**Figure 4A**). The areas of highest deprivation showed a low relative frequency of statin prescriptions (1.89 per person). A positive association was observed for the frequency of statin redemption by degree of deprivation (**Figure 4B**). Significantly higher compliance was observed in districts with the highest deprivation (67.88% [67.812–67.951]) (**Figure 4C**; **Table 2**).

DISCUSSION

Our present study was designed to answer the question whether a lack and/or ineffectiveness of preventive medication may also exist behind the about three times higher risk of premature mortality caused by cardiovascular diseases in the Central Eastern European region than in high income European countries; hypothesising that preventive medication is not adequately reaching people characterized by having higher risk of CVD, especially in groups living in socioeconomically deprived conditions. Analysing data on the relationship between premature CVD mortality, statin utilization (the prescription of statins, the prescription redemption and the ratio between redemption and prescription rates) as a preventive medication and socioeconomic deprivation at the district level in Hungary, a significant positive association between deprivation and the relative risk of premature cardiovascular mortality, and a reverse J-shaped association between the relative frequency of statin prescriptions and deprivation were found. In districts with the highest deprivation a low relative frequency of statin prescriptions was detected; however, significantly higher primary compliance (redemption) was observed in these districts.

The 2012 guidelines from the Fifth Joint Task Force of the European Societies on CVD Prevention in Clinical Practice recommend that all hypertensive patients with established CVD or with type 2 diabetes and patients with an estimated 10-year risk of cardiovascular death ≥5% based on the SCORE chart should be considered for statin therapy (Stone et al., 2014). The 2013 AHA/ACC (American College of Cardiology Foundation/American Heart Association) guidelines on the management of elevated blood cholesterol for the primary and secondary prevention of atherosclerotic CVDs recommend appropriate levels of statin therapy for different risk groups (high intensity in patients with atherosclerotic CVD, moderate or high intensity in patients with diabetes depending on their 10-year risk of atherosclerotic CVD, and moderate or high intensity in individuals aged 40 to 75 years without CVD or diabetes but with a 10-year risk of clinical events >7.5% and an LDL-cholesterol level of 1.8–4.9 mmol/l) (Yancy et al., 2013). The WHO guidelines for the prevention of CVDs propose preventive medication to the lower cholesterol level in all individuals with total cholesterol at or above 8 mmol/l, but if the ten-year CVD risk is 20% or higher, adults aged >40 years with a cholesterol level >5.0 mmol/l and/or LDL cholesterol > 3.0 mmol/l despite a lipid-lowering diet should be given a statin.

It is generally accepted, with minor limitations, that for dyslipidemic persons who have not already had a vascular event but are at a higher cardiovascular risk, combined statin therapy substantially reduces the CVD mortality risk, thereby "potentially being an ideal risk-reducing factor with added risk reduction by lifestyle changes" (Opie, 2015). The evidence for statins for secondary prevention in patients after a heart attack is more robust, decreasing the risk of a second heart attack by approximately one-third (Wei et al., 2005). Because in CEE countries, including Hungary, the premature mortality caused by CVDs is significantly higher than in the most developed countries of the European Region, it is reasonable to suggest that preventive interventions, such as preventive medication with statins, have not been considered or implemented sufficiently.

Our results are consistent with findings published for different countries (Mackenbach et al., 2000, 2003) and clearly show that standardized mortality rates caused by CVDs, particularly from chronic ischemic heart disease, are significantly

higher in districts with the highest DIs (grouped into tertile III) in Hungary. Although premature mortality caused by CVDs, particularly by ischemic heart disease, is highest in the same districts, the frequency of statin prescriptions at the primary care level was significantly lower than the national average. However, the rate of redemption, and consequently, the ratio between redemption and prescription rates were significantly higher. These data clearly indicate that insufficient statin utilization is highly linked to the so-called physician-factor; i.e., statin prescription, consequently statin treatment is poor and represents significant barriers to mortality reductions, particularly among people living in highly deprived areas of the country. Because the socio-economic gap in health and mortality is widening in Europe – as the largest study to have explored the association between social factors and serious outcomes of chronic diseases, particularly cardiovascular outcomes clearly demonstrated (Mackenbach et al., 2003) – the identification of gaps in preventive services in deprived areas is of the utmost importance. The statement "reducing socio-economic inequalities in mortality in Western Europe critically depends upon speeding up mortality declines from CVDs in lower socioeconomic groups, and countering mortality increases from several other causes of death in lower socioeconomic groups" can be interpreted as an imperative on how to improve the health of the population for the low- and middle-income countries of the European Region. Our study identifies a gap in current cardiovascular prevention practice by showing that many patients are likely under-treated and others remain untreated.

Regarding the reasons and remedies for under-treatment, it seems likely that the lack of financial incentives for primary prevention at the level of primary care (Adany et al., 2013) has a strong effect, particularly if it meets the low health literacy of people living in the most deprived districts. Although a survey (UNDP/World Bank/EC regional Roma survey 2011) revealed a high percentage of households unable to afford prescription medication in eleven countries of the CEE region, including Hungary, our result showing significantly higher redemption rates in the most deprived districts of the country indicates that for statin prescription, the primary non-compliance, for any reason, is not a factor highly defining the insufficient preventive medication. Based on our results, the importance of determining why GPs do not follow guideline recommendations regarding lipid-lowering treatment should be emphasized. Benefits provided by the National Health Insurance Fund of Hungary include cost-free healthcare services, such as preventive examinations, primary healthcare, and drug reimbursement on grounds of equity. For persons who are low income or on social welfare, medical exemption certificates are available, such that they are exempt from prescription charges in the case of defined medicaments, including the majority of statin medicines.

The limitations of our study deserve mention. All three factors (patient, physician, and health system) that have an effect on statin utilization cannot be covered in a single study. The effects associated with socio-economic factors may be mediated by other factors that were not included in our analyses. Health system factors were only partially studied, and access to care requires particular attention in further studies. Information about various elements that may influence a patient's likelihood to take statin medications should also be collected to understand the relatively low redemption rate in areas with the lowest deprivation indices.

AUTHOR CONTRIBUTIONS

The study was designed and the manuscript was written by RÁ. KB, AJ, CN, and KBíró have contributed to the analysis of the data. All authors stated above have contributed to the interpretation of the results, and helped to draft the manuscript.

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Critical Appraisal of Reimbursement List in Bosnia and Herzegovina

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Keywords: health care system, legislation, reimbursement list, price differences, economic effects

PHARMACEUTICAL MARKET OF BOSNIA AND HERZEGOVINA

One of the most challenging issues in health systems of middle-income countries is unequal access to medicines. When it comes to determining prices and reimbursement, different frames of price regulation and distribution margins, various methodological approaches, and tools for assessing the eligibility of costs for the insured are used (Jakovljevic et al., 2016a). Most countries in the European Union (EU) decided to regulate prices, at least when it comes to reimbursement lists (Rosian et al., 1998; Freemantle et al., 2001; Mrazek, 2002; Mossialos et al., 2004, 2006; Mossialos and Oliver, 2005; Vogler et al., 2005, 2008, 2009, 2011, 2015; Vogler and Habimana, 2014; Walley et al., 2005; Habl et al., 2006; Kazakov, 2007). Health legislation is one of the key elements in national and international activities related to health, as it plays a major role in development of a comprehensive support for individual and community health (Salihbasic, 2011).

The different and complex constitutional division as well as arrangement of price regulation in the healthcare system in BH causes huge losses. Because of lack of uniform legislation in this field and huge diversification in decision-making there is no adopted and unique methodology in price determination thus the key role in price determination in each entity have decision-makers involved in process.

The article's objective is to critically assess the methodological quality of decision-making process and Bosnian legislation for price determination as well as the reimbursement policy. Bosnian authority strives toward for regulation of prices according to external referent prices model, so this article also presents and outlines clear benefits that could be achieved if the method of price determination is homogenized between each entity according to referent prices especially in terms of price deviation outlined in this article.

Health system in Bosnia and Herzegovina (B&H) has fully divided jurisdiction between two entities and State District (Federation of Bosnia and Herzegovina, Republic of Srpska, and the Brcko District of B&H) further divided in entity Federation of B&H to 10 Cantons. This complex structure follows the administrative, constitutional frame of B&H which consist of two entities, State District and 10 Cantons in entity Federation of B&H. There is no single segment in this area, which would be a part of the jurisdiction of BH's state level authorities except for the BH's Law on Medicines and Medical Devices and the Agency for Medicines and Medical Devices[1]. Jurisdiction of the Agency for Medicines and Medical Devices at the state level is reflected in conducting the process of registration of medicines and medical devices.

In the Federation of B&H, the jurisdiction over the health sector is divided between the federal government and the Cantons, which means that the health sector is organized at the cantonal level and coordinated at the federal level (Salihbasic, 2011). As a part of the commitment

[1] Medicinal Product Act. "Official Gazette of Federation" BH No. 51/10 and 29/05.

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to honor the citizen's rights to health care, it is essential that all countries ensure accessibility of essential medicines, i.e., medicines that meet the priority needs of the population (Hogerzeil, 2004, 2006; Hogerzeil et al., 2006). Reimbursement list in the Federation of BH (hereinafter: the Federal reimbursement list) contains only generic names. In addition to this, the cantonal positive lists of medicines are coordinated based on this list[2], while the cantons are free in choosing trade names of a drug[1]. When creating a positive list of medicines in the cantons, the cantons must comply with the general and specific criteria for inclusion of drugs on the canton's positive lists of medicines. This list should contain information about a medicine as well as the mandatory acceptance of the prices established by the Federal Ministry of Health[3]. Medicine prices are established during negotiations of the Federal Ministry of Health with drug manufacturers. The price includes a manufacturing price of a drug, relevant customs duties, and other related costs of imports for imported drugs and the amount of wholesale margins (the maximum allowed margin is 8%)[4].

In contrary to entity Federation of B&H, the health system in entity Republic of Srpska (RS) is fully centralized. Compulsory health insurance is regulated by the Health Insurance Fund of RS as an independent organization, while the control over the legality of the Fund is overseen by the ministry responsible for public health (Salihbasic, 2011). A reimbursement list in the Republic of Srpska is determined by the Health Insurance Fund. Afterwards, the entire determined list of drugs becomes available at the whole territory of RS[5]. In this entity, the Ministry of Health and Social Welfare and the Health Insurance Fund establish the system of pricing (Petrusic and Jakovljevic, 2015). The price of drugs stated on the list is formed based on the wholesale prices of medicines from the price list of the largest wholesalers, which includes VAT (internal pricing)[6].

When it comes to Brcko District of B&H (BD), basic provisions of the entity's legal regulations are in place (Hogerzeil, 2004). The organizational structure of the health sector in BD was determined through forming of the Department of Health. This department is in charge of making a proposal of a reimbursement list containing generic names of drugs. It was modeled after the most favorable drug list in one of the entities, either the Federation B&H or the RS[6]. Prices for the list of medicines of BD are determined by the sum of the minimum manufacturer prices and margins, which the Government of BD set in the amount of 20%[7].

THE DATA REPORT METHODS

Materials and Methods

The study features critical analysis of drug prices for period 2011–2015, current methods of price determination, and impact on a budget. We performed a cross-sectional study using the official published data for the period 2011–2015.

The data from the official documents of Bosnia and Herzegovina relating to the price of drugs on reimbursement lists from certain regions in Bosnia and Herzegovina, spanning the period from 2011 to 2015, was compared. Each region has published different price list and it is available for each region, Brcko District,[6,7,8], Federation BH[9], and Republic of Srpska[10].

In more recent times in Bosnia and Herzegovina, there is a legislative tendency to determine prices for medicines according to external reference pricing takes into account benchmark countries, namely: Serbia, Croatia, Slovenia, and Italy and Bulgaria, as substitute countries (Jakovljevic, 2013). In accordance with the current proposals of institutions in Bosnia and Herzegovina, this paper presents economic effects of the actual situation in Bosnia and Herzegovina, compared with the prices in Serbia (the prices of drugs on List A—Group A. Drugs that are prescribed and dispensed via a medical prescription, and List A1—drugs which are prescribed and dispensed via medical prescriptions, which have a therapeutic parallel with the medicines from List A, in the period from 2011 to 2015.)[11]. Each year, the exchange rate for the month of June is used for the stated period. The prices are calculated and presented in convertible marks (BAM)[12].

The total number of different INN's listed on the reimbursement lists in the Federation BH and the RS is the same—138. This number is significantly lower in BD, where

[2]Health Care Act. "Official Gazette of Federation" BH No. 30/97, with amendments Nos. 7/02 and 70/08.

[3]The decision of Essential list of medicines. "Official Gazette of Federation BH" No. 75/11; The decision of List of medicines, Solidarity Fund of Federation BH. "Official Gazette of Federation BH" No. 67/11.

[4]The decision on the criteria for inclusion of medicinal products on the list of medicines on prescription reimbursed from Health Insurance Fund of the Republic of Srpska. "Official Gazette of Republic of Srpska" No. 2/10.

[5]Ministry of Health and Social Care, The strategy in the field of medicine by 2012, 16.

[6]Health Insurance Act, Brcko District BH, "Official Gazette of Brcko District" BH No. 1/02, 7/02, 2/8, 19/7, and 34/08.

[7]The decision on the methodology of determining the reference price of medicine from List of essential medicines for the needs of insured persons, the Health Insurance Fund of Brcko District BH, "Official Gazette Brcko District BH," No. 52/11.

[8]The decision on establishing the list of essential medicines for the needs of insured persons the Health Insurance Fund of Brcko District, 04.04.2013; Table with established changes in prices of medicines with the list of essential medicines for the needs of insured persons of Health Insurance Fund of Brcko District B&H, 2014; Established prices of essential medicines for the needs of insured persons the Health Insurance Fund of Brcko District, Health Insurance Fund, 07.05.2015.

[9]The decision for the list of essential drugs required to provide health care within the standards of the mandatory health insurance in Federation BH, "Official Gazette of Federation" BH, Nos. 75/11, 56/13, 74/14, and 94/15.

[10]Pricelist for List of medicine from A, A1, B list. Health Insurance Fund of Republic of Srpska, 21.10.2008, 01.10.2013, and 15.03.2015.

[11]Ordinance of List of medicines prescribed and issued at the expense of mandatory health insurance, "Official Gazette of the Republic of Serbia" No. 28/11.; Ordinance of List of medicines prescribed and issued at the expense of mandatory health insurance, "Official Gazette of Republic of Serbia," dated 20.03.2012. Prices in Serbia in 2013. Available: http://media.dzindjija.rs/2013/09/Lista-lekova-Sl-glasnik-76_13.pdf (accessed: 21.06.2013). Ordinance of List of medicines prescribed and issued at the expense of mandatory health insurance, "Official Gazette of Republic of Serbia," No. 7/14. Ordinance of List of medicines prescribed and issued at the expense of mandatory health insurance, "Official Gazette of Republic of Serbia," No. 7/14.

[12]Exchange rate, dated 01.06.2011.: https://www.unicredit.ba/ba/stanovnistvo/tecajna_lista.html; Exchange rates, dated 01.06. 2012: https://www.unicredit.ba/ba/stanovnistvo/tecajna_lista.html; Exchange rate, 03.06.2013: https://www.unicredit.ba/ba/stanovnistvo/tecajna_lista.html; Exchange rate, dated 02.06.2014: https://www.unicredit.ba/ba/stanovnistvo/tecajna_lista.html; Exchange rate, dated 01.06.2015.: https://www.unicredit.ba/ba/stanovnistvo/tecajna_lista.html (accessed: 06.12.2016).

it only amounts to 75. What is interesting is that there is no representative on the BD reimbursement list within the two ATC groups (the D group—preparations for skin application and S group—medicines which affect the sensory organs). Average prices of medicines on lists of medicines in the Federation B&H, RS, and BD, show considerable variations, both regarding the average price, and the average price per individual ATC group. To be specific, the average price of drugs on the reimbursement list of the Federation B&H is 12.71 BAM. This price is much higher in RS and BD, as it amounts to 29.44 and 17.07 BAM, respectively. This difference is most striking when it comes to the average price of medicines from Group L. Although, the average price in this drug group in the Federation B&H was only 34.26 BAM, the RS reimbursement list of drugs shows that the medium price was as high as 139.64 BAM.

Prices Inequalities and Impact on Healthcare System

The consequences of price differences and differences in the structure of the reimbursement lists for individual regions have had the most impact on the treatment and quality of life of the patients and the entire healthcare system.

The data from the Federation BH presented in **Table 1**, show a decline in prices in accordance with the reference prices, but significant deviations are still present. Reduction of referent prices from 2011 to 2015 was clearly showed. Regardless gradual reduction of prices of every region, some INNs, such as valproic acid + sodium valproate, did not follow the trend of referent price reduction. In 2015 price deviation of valproic acid + sodium valproate in FBH was 54%, in RS was 72%, and in BD 72%.

For example, the deviation in prices for lamotrigine in 2011 was 9% from the reference price, in 2012 36%, 2013 was 17%. 2014 witnessed a deviation of 1%, which is a subtle deviation from the reference price, however, in 2015, there was a sudden increase in the difference in prices, which amounted to 42%. This is rather significant given that this was the year of great market preparations and policy changes related to the new regulations on the method of price control, the method of forming prices of medicines and the manner of reporting on the prices of medicines in B&H. Also, the prices between entities are significantly different, and the higher prices were observed in the Republic of Srpska.

However, in RS, the deviations for the same medicine are even greater. For example, in 2011 was 59%, in 2012, 71%, in 2013, 40%, in 2014, 42%, and in 2015, 69%. It is worrying that according to reports of the Agency for Medicinal Products and Medical Devices, there was no reduction of total costs for the aforementioned drug considering reduction of prices[13] (Supplementary Table 1).

In 2013, there was a sudden drop in the price of medicines in RS, but also a slight decline in other regions as well. That year, there was a reduction in the costs for the drug lamotrigine, however, what followed was a growth trend of total costs which should be worrisome. It is tough to establish adequate monitoring of reimbursement lists in BH due to lack of price control mechanisms, control of consumption, and drug prescriptions, as a result of decentralized regulations. It is also becoming increasingly difficult to monitor the drug supply within a payer rights.

The dataset has been submitted to a public repository Figshare, and it is available on https://figshare.com/s/07fa8d6d5a1e7a0eeaa4. Data has been uploaded as Excel file while the Appendix with all INNs (https://figshare.com/s/506f6aea67ab6208aaad) and the results are in PDF formats. Readers are free to access and reuse these publicly available data at the links provided above.

Reimbursement and Pricing Policies

These results indicate that there are a high inequality and instability in the health sector. If we take into account the reference prices in the Republic of Serbia, as well as the mechanisms of rationalization of prescribing drugs, the result could be to reduce the cost of treatment, which would consequently lead to large savings in financial resources. These resources could further be allocated toward the prevention and stabilization of the health care system.

Significant expenses that occur due to the inability to control the prices, impede the progress of the health system and the introduction of new therapies, which are more efficient and cost-effectiveness.

Limitations of a decentralized health care system in BH, whether political, administrative, or fiscal, call into question financial sustainability of the health sector in BH[14].

Inefficiency of the organizational model present in BH and limitations of institutional capacities and institutional fragmentation of every region, present the biggest problem of this concept of health care organization and causes an unequal access to health care (Jakovljevic and Ogura, 2016). However, this is not the case in developed countries with decentralized systems. In fact, this concept proved to be very convenient because it allowed access to medicines and other health care services to the marginalized population and population living in geographically remote areas (Forouzanfar et al., 2016). Lack of adequate homogeneous legislation within BH and apparent differences in prices, constitutional and administrative fragmentation, as well as health sector jurisdiction fragmentation contribute to enormous economic losses, which further weaken the overall health system in Bosnia and Herzegovina. One of the ways to approach solving of this problem should be centralization of the decision-making processes related to medications, clear guidelines, and policies on drugs as well as the laws and by-laws in BH, preferably through a better implementation of these regulations and policies in a decentralized system of supply, necessary complemented with in-depth constitutional, and administrative reform. Only this way full effect on health care system could be achieved.

Most of the EU countries have developed detailed criteria (e.g., cost-efficiency, relative efficiency, the need for medication), to

[13]The report of distribution of medicines licensed for BH market for period from 2011 to 2015. The Agency for medicinal products and Medical Devices, Banja Luka, 2012, 2013, 2014, 2015, 2016.

[14]Strategic Plan and the development of health in Federation of Bosnia and Herzegovina for period 2008 till 2018, Ministry of Health Federation of Bosnia and Herzegovina, Sarajevo 2008. Available: http://www.fmoh.gov.ba/images/federalno_ministarstvo_zdravstva/zakoni_i_strategije/strategije_i_politike/dokumenti/usvojeni_strateski_plan_1_.pdf

TABLE 1 | Differences in prices for Reimbursement list for epileptic group of medicines in Bosnia and Herzegovina in comparison with reference prices for the period from 2011 to 2015.

ATC	INN	Form and pack size	Prices 2011	Ref. prices 2011	(%)[a]	Prices 2012	Ref. prices 2012	(%)[a]	Prices 2013	Ref. prices 2013	(%)[a]	Prices 2014	Ref. prices 2014	(%)[a]	Prices 2015	Ref. prices 2015	(%)[a]
FEDERATION BOSNIA AND HERZEGOVINA																	
N03AX09	Lamotrigine	Tablet, 30 × 100 mg	25.5	23.1	9	25.5	16.32	36	22.1	18.29	17	17.87	17.65	1	16.08	9.29	42
N03AX11	Topiramate	Tablet, 60 × 100 mg	72	73.58	−2	72	44.88	38	72	49.03	32	52.58	44.42	16	47.32	30.06	36
N05AH02	Clozapine	Tablet, 50 × 100 mg	35.36	35.33	0	35.36	24.27	31	35.35	28.35	20	31.36	27.36	13	31.36	17.79	43
N03AA02	Phenobarbitone	Tablet, 30 × 100 mg	3.27	2.93	10	3.27	2.48	24	3.3	2.89	12	3.3	2.67	19	3.3	2.75	17
N03AE01	Clonazepam	Tablet, 30 × 2 mg	N/A	3.08	N/A	N/A	2.57	N/A	N/A	3.01	N/A	N/A	2.51	N/A	N/A	1.63	N/A
N03AF01	Carbamazepine	Tablet, 50 × 200 mg	6	3.88	35	6	3.23	46	13.7	4.52	67	10.28	4.34	58	10.28	4.27	58
N03AF02	Oxcarbazepine	Oral suspension	N/A	43.08	N/A	N/A	N/A	N/A	59.25	41.78	29	50.36	N/A	N/A	45.32	N/A	N/A
N03AG01	Sodium valproate	Tablet, 100 × 300 mg	34.52	N/A	N/A	34.52	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	24.15	N/A	N/A
N03AG02	Valproic acid, Sodium valproate	Film-coated tablet, 30 × 500 mg	N/A	9.47	N/A	N/A	7.89	N/A	17.3	8.86	49	12.11	5.59	54	12.11	5.61	54
N03AX12	Gabapentin	Capsule, 50 × 300 mg	26	19.48	25	26	16.07	38	24.1	18.62	23	22.17	17.43	21	19.95	12.58	37
N03AX14	Levetiracetam	Film-coated tablet, 60 × 500 mg	N/A	126.38	N/A	N/A	93.06	N/A	N/A	103.69	N/A	68.46	38.73	43	54.77	20.38	63
THE REPUBLIC OF SRPSKA																	
N03AX09	Lamotrigine	Tablet, 30 × 100 mg	56.83	23.1	59	56.83	16.32	71	30.41	18.29	40	30.41	17.65	42	29.82	9.29	69
N03AX11	Topiramate	Tablet, 60 × 100 mg	158.77	73.58	54	158.77	44.88	72	84.23	49.03	42	84.23	44.42	47	84.23	30.06	64
N05AH02	Clozapine	Tablet, 50 × 100 mg	44.44	35.33	20	44.44	24.27	45	41.37	28.35	31	41.37	27.36	34	41.37	17.79	57
N03AA02	Phenobarbitone	Tablet, 30 × 100 mg	3.63	2.93	19	3.63	2.48	32	3.63	2.89	20	3.63	2.67	26	3.63	2.75	24
N03AE01	Clonazepam	Tablet, 30 × 2 mg	6.26	3.08	51	6.26	2.57	59	N/A	3.01	N/A	N/A	2.51	N/A	6.26	1.63	74
N03AF01	Carbamazepine	Tablet, 50 × 200 mg	4.33	3.88	10	4.33	3.23	25	4.32	4.52	−5	4.32	4.34	0	4.32	4.27	1
N03AF02	Oxcarbazepine	Oral suspension	54.02	43.08	20	54.02	N/A	N/A	54.02	41.78	23	54.02	N/A	N/A	54.02	N/A	N/A
N03AG01	Sodium valproate	Tablet, 100 × 300 mg	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	20.23	N/A	N/A
N03AG02	Valproic acid, Sodium valproate	Film-coated tablet, 30 × 500 mg	20.83	9.47	55	20.83	7.89	62	20.83	8.86	57	20.83	5.59	73	20.23	5.61	72

(Continued)

TABLE 1 | Continued

ATC	INN	Form and pack size	Prices 2011	Ref. prices 2011	(%)[a]	Prices 2012	Ref. prices 2012	(%)[a]	Prices 2013	Ref. prices 2013	(%)[a]	Prices 2014	Ref. prices 2014	(%)[a]	Prices 2015	Ref. prices 2015	(%)[a]
N03AX12	Gabapentin	Capsule, 50 × 300 mg	28.31	19.48	31	28.31	16.07	43	28.31	18.62	34	28.31	17.43	38	28.15	12.58	55
N03AX14	Levetiracetam	Film-coated tablet, 60 × 500 mg	96.81	126.38	−31	96.81	93.06	4	96.81	103.69	−7	96.81	38.73	60	96.81	20.38	79
BRCKO DISTRICT																	
N03AX09	Lamotrigine	Tablet, 30 × 100 mg	N/A	23.1	N/A	36.65	16.32	55	29.85	18.29	39	20.9	17.65	16	20.9	9.29	56
N03AX11	Topiramate	Tablet, 60 × 100 mg	N/A	73.58	N/A	N/A	44.88	N/A	N/A	49.03	N/A	N/A	44.42	N/A	N/A	30.06	N/A
N05AH02	Clozapine	Tablet, 50 × 100 mg	N/A	35.33	N/A	44.44	24.27	45	41.35	28.35	31	36.7	27.36	25	36.7	17.79	52
N03AA02	Phenobarbitone	tablet, 30 × 100 mg	3.1	2.93	5	3.1	2.48	20	3.1	2.89	7	3.1	2.67	14	3.63	2.75	24
N03AE01	Clonazepam	Tablet, 30 × 2 mg	N/A	3.08	N/A	N/A	2.57	N/A	N/A	3.01	N/A	N/A	2.51	N/A	N/A	1.63	N/A
N03AF01	Carbamazepine	tablet, 50 × 200 mg	3.7	3.88	−5	3.7	3.23	13	3.7	4.52	−22	3.7	4.34	−17	4.32	4.27	1
N03AF02	Oxcarbazepine	Oral suspension	N/A	43.08	N/A	N/A	N/A	N/A	N/A	41.78	N/A	N/A	N/A	N/A	N/A	N/A	N/A
N03AG01	Sodium valproate	Tablet, 100 × 300 mg	34.53	N/A	N/A	34.53	N/A	N/A	34.53	N/A	N/A	28.25	N/A	N/A	28.25	N/A	N/A
N03AG02	Valproic acid, Sodium valproate	Film-coated tablet, 30 × 500 mg	17.8	9.47	47	17.8	7.89	56	17.8	8.86	50	17.8	5.59	69	20.23	5.61	72
N03AX12	Gabapentin	Capsule, 50 × 300 mg	N/A	19.48	N/A	N/A	16.07	N/A	N/A	18.62	N/A	N/A	17.43	N/A	N/A	12.58	N/A
N03AX14	Levetiracetam	Film-coated tablet, 60 × 500 mg	N/A	126.38	N/A	N/A	93.06	N/A	N/A	103.69	N/A	N/A	38.73	N/A	N/A	20.38	N/A

N/A, not available.

[a]*(%), prices deviation in percent.*

help them decide when and how much is refundable. Health Economics also called the 'Fourth Hurdle' (Cohen et al., 2007; Forouzanfar et al., 2016) is something that is increasingly being used in the decision-making process (Drummond et al., 1997, 2010; Cohen et al., 2008). The pricing policy is most often determined institutionally, where drug prices are determined by legal regulations (e.g., legislation, regulations, and so forth). One such example should be implemented in the health care system in B&H with presented clear benefits of such system implementation.

CONCLUSIVE REMARKS

The relationship between economic development and health care system are interrelated and dependent on one another. In most cases, the primary concern are financial costs of health care services and social security schemes. However, one major impact on all of the above are primarily the overall costs of illness and early death for the society and the individual. The concept of developing a health care system has many similarities with the economic development (Jakovljevic et al., 2016b). Both processes are the result of activities which involve many sectors of society, as well as the population as a whole, through individual and collective decisions and actions. Social deprivation, along with economic inequalities and housing conditions, results in a lower quality of life and shorter life expectancy (Jakovljevic et al., 2015). Medicines are a paramount segment of every health system, not only for treating a disease but also because of a high consumption of available resources in the health care system toward drugs. The analysis of the current situation shows that, most often, significant funds are spent on drugs that do not have adequate therapeutic value, and this is in addition to losses occurring as a result of a jurisdiction conflict and overlaps in all regions of the country. This means that the medicine sector, as well as the entire health care system in Bosnia and Herzegovina is in need of re-organization. One of the more important factors affecting the financial condition of our overall health care system is the present deviation in pricing and the inability to control them. Reimbursement regulations and reference pricing are the key mechanisms employed by government and regulatory bodies to manage pharmaceutical costs (Seget, 2003). Following new trends and introducing new methods of determining the efficiency of drugs in relation to the resources expended, the health care services in B&H can be improved to a great extent which would clearly present biggest benefit to end users of healthcare system of Bosnia and Herzegovina.

AUTHOR CONTRIBUTIONS

All authors listed, have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fphar.2017.00129/full#supplementary-material

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Does the Strategy of Risk Group Testing for Hepatitis C Hit the Target?

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In the European Union, it is estimated that there are 5.5 million individuals with chronic infection of hepatitis C. Intravenous drug abuse is undoubtedly the key source of the hepatitis C epidemic in Europe and the most efficient mode of transmission of HCV infections (primarily due to short incubation time, but also because the virus is introduced directly into the blood stream with the infected needle). Potentially high-risk and vulnerable populations in Europe (and the world) include immigrants, prisoners, sex workers, men having sex with men, individuals infected with HIV, psychoactive substance users etc. Since there is a lack of direct evidence of clinical benefits of HCV testing, decisions related to testing are made based on indirect evidence. Clinical practice has shown that HCV antibody tests are mostly adequate for identification of HCV infection, but the problem is that this testing strategy does not hit the target. As a result of this health care system strategy, a large number of infected patients remain undetected or they are diagnosed late. There is only a vague link between screening and treatment outcomes since there is a lack of evidence on transmission risks, multiple causes, risk behavior, ways of reaching screening decisions, treatment efficiency, etc. According to results of limited number of studies it can be concluded that there is a need to develop targeted programmes for detection of HCV and other infections, but there also a need to decrease potential harms.

Keywords: hepatitis C infection, testing strategies, risk groups, cost-effectiveness

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SOME FACTS ABOUT HCV PRESENCE

In 2014, 35,321 new cases of hepatitis C were reported from 28 EU/EEA member states, while a "crude" rate was 8.8 cases per 100,000 population (European Centre for Disease Prevention and Control, 2013). Out of these cases, 1.3% were classified as acute, 13.3% as chronic, 74.7% as "unknown," and 10.7% were not classified. Intravenous drug abuse is undoubtedly the key source of the hepatitis C epidemic in Europe and the most efficient mode of transmission of HCV infections (primarily due to short incubation time, but also because the virus is introduced directly into the blood stream with the infected needle).

The prevalence of HCV among drug addicts is between 60 and 80% which is in direct correlation to the period of psychoactive substance abuse. This way HCV infection is transmitted 10 times faster and more efficiently than HIV infection (Mosley et al., 2005; Wang et al., 2016b).

In the European Union, it is estimated that there are 5.5 million individuals with chronic infection. Intravenous drug use is the key issue in dispersion of HCV infection in Europe—national estimates of antibody-prevalence range from 15 to 84% (European Monitoring Centre for Drugs Drug Addiction, 2016).

Potentially high-risk and vulnerable populations in Europe (and the world) include immigrants, prisoners, sex workers, men having sex with men, individuals infected with HIV, psychoactive substance users etc. (Forouzanfar et al., 2016).

In Serbia, which geographically belongs to the Western Balkans, the situation is similar to other countries in the region—epidemiological characteristics of HCV infection have not been studied reliably since there is no continuous and comprehensive disease monitoring. Moreover, there are only few limited studies on socio-economic background of this disease in Serbia. Regardless the advancement in the disease treatment, it is of vital importance to have epidemiological and pharmacological data in order to make the plan of prevention and control more efficient (Mitrovic et al., 2015).

Based on limited range studies, the prevalence of HCV in Serbia is higher than 1% (i.e., the estimated prevalence in general population is 1.13% (95% CI: 1.0–1.26%) (European Centre for Disease Prevention and Control, 2013), while in Europe it is about 1.5% (Cooke et al., 2013). In our population, the most common HCV genotypes are genotype 1 (63%) and genotype 3 (27%), while genotype 2 and 4 account for 7 and 3% of the cases, respectively. Genotypes 5 and 6 have not been registered (Mitrovic et al., 2015).

Jakovljević et al. carried out a study in 2013 which compared the costs of patients with genotypes 1 or 4 (group I) and patients with genotypes 2 or 3 (group II). It showed that the patients with genotypes 1 and 4 caused significantly higher direct medical costs which did not include medicine purchase costs. When the costs of the consumed pegylated interferon alfa plus ribavirin were added, the expenses moved toward patients with genotype 2 or 3 infection. Finally, when indirect costs (e.g., lost productivity costs) were taken into account, the total costs were even 25% higher among patients with genotype group 2. The conclusion was that an average patient belonging to either of the groups incurred €18,121.04 costs per protocol for the treatment period less than a year (Jakovljevic et al., 2013).

To make a comparison, the estimates from the Health Protection Agency (HPA) in Great Britain (Hepatitis, 2013) show, based on the research carried out by the National Institute for Health and Clinical Excellence (NICE), that the cost of antiviral treatment of individuals with hepatitis C varies between £6,246 for those requiring 24-week treatment (mainly genotypes 2 and 3) and £12,741(14,714.80 euros) for those requiring a standard treatment of 48 weeks (mainly genotype 1) (Ramsay, 2011).

This means that the treatment of an individual infected with hepatitis C in Great Britain is almost €3,500 cheaper than in Serbia. From 2006 to 2014, GDP in Serbia ranged from $3,700 to 4,300, while in Great Britain it was $39,511[1].

[1]http://www.penzin.rs/koliko-drzave-sveta-prave-novca-po-stanovniku-a-koliko-srbija/

The costs given by the HPA are in compliance with the costs reported in 2011 by the British National Formulary for peginterferon alfa-2a (Pegasys), peginterferon alfa-2b (ViraferonPeg), and ribavirin (Copegus, Rebetol) (British National Formulary, 2015-2016), including the treatment monitoring costs taken over from Hartwell et al. (2011).

However, the budget impact of HCV treatment has been significant. Classic treatments resulted in more significant side effects and they were less effective than newer treatments. The most important issue (always) is the price. Health stakeholders should use scientific information to increase the efficiency and availability of treatment and reduce costs. Some studies show that the prevalence growths associated with the increase in annual health cost are, for example, from £82.7 m in 2012 to £115 m in 2035. Also, productivity losses were estimated to rise from between £184 and £367 m in 2010 to between £210 and £427 m, in 2035 (Hepatitis, 2013).

HCV SCREENING AND OUTCOMES

Hepatitis C is an important public health issue not only in Europe but all around the world, considering high costs associated with morbidity and mortality (ECDC, 2015; Wang et al., 2016a). The Global Burden of Disease (GBD) is 42% for mortality as a result of liver cancer caused by hepatitis C. Approximately 700,000 people die each year from the consequences of this infection (Lozano et al., 2012).

Monitoring does not always give a clear picture of the situation in a particular country. For example, it is estimated that 2.2–3.2 million people are chronically infected with hepatitis C in the USA, but half of them is unaware of that (CDC, 1998).

Despite the limitations of routine monitoring of HCV infection, the available data clearly indicate that the largest number of reported cases was associated with drug injecting and other groups at risk.

There are two kinds of **tests** typically used to **diagnose** HCV infection (**Figure 1**):

(1) **Serological assays** that detect antibody to hepatitis C virus (anti-HCV);

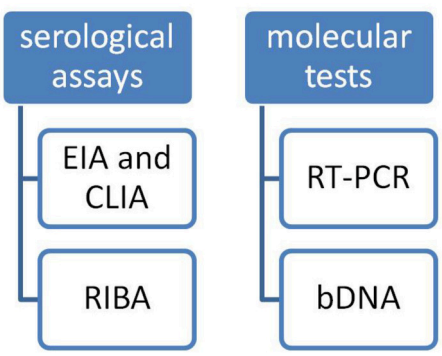

FIGURE 1 | HCV tests.

(2) **Molecular assays** that detect, quantify, and/or characterize HCV RNA genomes

Serological assays can be subdivided into:

(1) Screening tests for anti-HCV such as EIA and CLIA (Chemiluminescence Immuno Assay).
(2) And supplemental tests such as RIBA (Recombinant Immunoblot Assay) test.

In the 1980s first generations of **serological assays** were developed. The first-generation anti-HCV EIA detected antibodies 12–26 weeks after exposure to infection, thus creating a long window period of infectivity. With the second generation of tests the window period of infectivity was reduced to 10–24 weeks. So far three generations of serological assays have been developed in order to improve sensitivity and specificity (Marwaha and Sachdev, 2014). Nowadays, the third-generation of EIA assays is used to detect antibodies against reconfigured hepatitis C proteins: C, NS3, and NS4, as well as NS5A antigen which the previous generation of assays did not contain (Gretch, 1997).

The third-generation EIA brought about a new reduction in the window period by a week. Despite many attempts to increase sensitivity of assays, the problem of serology negative but "infectious" window period remained, which with the second-generation assays was 82 days (Busch et al., 1995) and with the third-generation remained around 66 days (Couroucé and Pillonel, 1996).

Combination antigen-antibody assays were introduced few years ago, when, two markers of the same infection were detected at the same time. These assays are called "fourth-generation" or "antigen-antibody combo" tests. They are suitable for testing in blood banks where a large numbers of samples need to be tested in a short period of time. The average window period for these assays is 26.8 days (CDC, 2013).

RIBA tests are used to confirm a positive enzyme immunoassay, while the same serum samples can be used. RIBA use recombinant antigens and synthetic peptides similar to EIA. They are in immunoblot format, so that they can detect antibodies for specific proteins.

The test result is reported positive if antibodies to two or more antigens are detected, inconclusive or indeterminate if antibodies to one antigen are detected, or negative. These tests are recommended to be used primarily for patients at low risk for HCV like volunteer blood donors (Alter et al., 2003; Narciso-Schiavon et al., 2008). A positive anti-HCV antibody test does not distinguish between a current and a past infection, but it indicates the need for further medical evaluation (Fonseca et al., 2011). Among immunocompromised individuals, serological tests can have false-negative results, for example with HIV-infected patients, with patients with renal insufficiency and with patients with essential mixed cryoglobulinemia caused by HCV (Alter et al., 2003) (**Table 1**).

Qualitative molecular tests are based on RT-PCR technique. These tests have a detection limit of 50 IU/ml and they are used to confirm viremia and to monitor treatment response[2]. If the test result is positive, there is an active infection. Qualitative PCR tests are also used with EIA negative patients with suspected acute infection, with patients diagnosed with hepatitis of unknown cause, as well as with those with known causes of false-negative results of antibody tests.

Qualitative molecular tests, PCR, and bDNA (branched DNA assay) are used to monitor anti-HCV treatment (Alter et al., 2003).

A very significant non-specific alanine aminotransferase measurement (ALT) test used to monitor infections and treatment effectiveness should be also mentioned here (Alter et al., 2003).

The AASLD (American Association of the Study of Liver Diseases) and the IDSA (Infectious Disease Society of America) strongly recommend annual HCV testing for persons who inject drugs and for HIV-seropositive men who have unprotected sex with men[1].

WHAT ABOUT TESTING STRATEGIES?

Since there is a lack of direct evidence of clinical benefits of HCV testing, decisions related to testing are made based on indirect evidence (Chou et al., 2012). Furthermore, clinical practice has shown that HCV antibody tests are adequate for identification of HCV infection. The problem is that this testing strategy does not hit the target. As a result of this health care system strategy, a large number of infected patients remains undetected or are diagnosed late. Potentially, these patients are permanent sources of infection, which is very important especially for groups at risk. This way, our understanding of the actual risks and the real dimensions of this problem remains incomplete. In order to make screening more effective, besides strategies to identify HCV infected individuals, there should be strategies for further actions including counseling, education, medical treatment, physiological, and psychiatric support etc., with the aim to improve treatment outcomes. At this time, there is only a vague link between screening and treatment outcomes since there is a lack of evidence on transmission risks, multiple causes, risk behavior, ways of reaching screening decisions, treatment efficiency, etc.

Retrospective studies that analyzed strategies that target several risk factors showed sensitivity of over 90% and the need to test up to 20 people in order to identify one HCV-infected person (Gunn et al., 2003; Zuure et al., 2010).

However, there have been no prospective studies to compare different screening strategies or consider a new (alternative) approach to screening or possible outcomes. In the USA, epidemiological data show that about two-thirds of people with chronic hepatitis C were born between 1945 and 1965. Birth-cohort screening may be a useful future screening strategy. The only published birth-cohort is a cost-effectiveness study from 2012 (Rein et al., 2012).

Some studies published in the last decade suggest the knowledge of being infected reduces risk behavior of some patients (Hagan et al., 2006; Scognamiglio et al., 2007; Trepka et al., 2007), but prospective studies show that this behavior is not sustained over time (Tsui et al., 2009).

[2]Available online at: http://www.hcvguidelines.org/printpdf/12

TABLE 1 | Testing for HCV infection.

Test result	Interpretation	Further action
HCV antibody non-reactive	No HCV antibody detected	Sample may be non-reactive for HCV antibody. No further action is required. If there was a recent exposure, test for HCV RNA.
HCV antibody reactive	Presumptive HCV infection	A repeatedly reactive result indicates current HCV infection, past HCV infection that has resolved or biologic false positivity for HCV antibody. Test for HCV RNA is order to identify current infection.
HCV antibody reactive HCV RNA detected	Current HCV infection	Organize testing with appropriate counseling and link the tested person to future treatment.
HCV antibody reactive HCV RNA not detected	No current HCV infection	In most cases, no further action is needed. If there is desired distinction between true positivity and biologic false positivity for HCV antibody, and if the sample is repeatedly reactive in the initial test, test with another HCV antibody assay. In certain situations, continue with HCV RNA testing and appropriate counseling.

CDC. Testing for HCV infection: An update of guidance for clinicians and laboratorians. MMWR 2013; 62 (Gretch, 1997).

Nevertheless, there are many uncertainties concerning potential harms and benefits of HCV testing. There is a need to study psychological aspects of testing such as fear, anxiety, acute stress reaction, impact on quality of life, impact on partner relationships, family, and social relations, etc. There is also a question whether a wider concept of counseling would contribute to reduction of potentially harmful influences of the given factors.

Testing efficiency and cost-effectiveness are present additional problems. How reasonable is to repeat rapid antibody detection tests?

Patient testing as part of PAS addiction treatment programmes is a good way to target chronically infected individuals which enables implementation of potentially new approaches to treatment which might become more efficient that the existing ones (Afdhal et al., 2013; Frimpong, 2013).

A research carried out within the programme for community-based treatment of addicts by the National Drug Abuse Treatment Clinical Trials Network (CTN), showed that only 28% of the USA programmes offered HCV testing as part of their programme or in the nearest reference center (Pollack and D'Aunno, 2010; Bini et al., 2012). The latest researches show a significant reduction in HIV and HCV testing within opiate addiction treatment programmes between 2005 and 2011 and a significant increase of testing within public treatment programmes (D'Aunno et al., 2014), which suggests that scarce resources can play an important role in deciding whether to invest into private-profitable or unprofitable programmes.

Between 2003 and 2014, Serbia received ∼$30 million from the Global Fund for development and implementation of HIV and HCV prevention and treatment in Serbia. However, as a middle income country, Serbia lost the funding abruptly when its HIV burden was estimated as "moderate" (The Global Fund, 2015). Furthermore, in 2012 Serbia was removed from the list of countries eligible for support in 2013 (Jakovljevic et al., 2017).

In 26 opiate addiction treatment centers in Serbia, HCV testing was drastically reduced because they were no longer financed by the Global Fund. The testing programmes included rapid tests within the treatment centers or at the nearest reference centers. Since 2014, the number of tests has been constantly decreasing (Jakovljević and Jovanović, 2011).

The World Health Organization states that the Global Fund supports comprehensive harm reduction packages that include preventive activities, testing and treatment of hepatitis C (World Health Organization, 2014).

Based on the available evidence, on-site rapid HIV and hepatitis C testing at addiction treatment centers is an excellent investment in public health (Jakovljevic et al., 2016).

Legal authorities should identify the ways to improve and implement on-site HCV and HIV rapid testing at addiction treatment centers and ensure that the individuals with positive results proceed to further treatment and further evaluation (Schackman et al., 2015).

One of major concerns is liver biopsy which is an invasive procedure with potentially serious adverse effects which is still the only reliable method to determine the histological state of the liver in HCV-infected individuals. A possible alternative would be to develop non-invasive techniques and tests to determine the stage of the disease (Chou et al., 2012). However, further comparative studies are needed to determine the significance of the liver biopsy in relation to further treatment courses.

There is also the issue of testing and education of specific groups and the impact of testing on the public health.

Testing and education should not be limited only to groups at risk such as PAS users, it should include other groups in need for immunization such as vaccination of alcoholics against hepatitis A and B and implementation of a known HCV detection strategy.

Hepatitis C virus infection is the most prevalent infection among intravenous drug users. According to the study conducted in Serbia in 2008, the prevalence among intravenous drug users was 69% in Belgrade, 50% in Niš, and 45% in Novi Sad.

The same study showed that after voluntary, free of charge and confidential testing on HCV, HIV and syphilis, more than 55.3% of the tested individuals in Belgrade and 43.5% in Niš failed to return for their test results. (Mickovski, 2010). The future studies should take into account the cost of testing, motivation and other psychological characteristics of the studied patients, as well as the outcomes of these interventions.

Studies conducted in other countries also show that only a small number of people injecting drugs returns for their results (Hagan et al., 2006; McDonald et al., 2010). Since this is a high-risk population, an adequate strategic approach is needed to enable frequent testing, preferably free of charge and an easy way to get to an infectologist and further treatment. To be more precise, testing should be done in places where the therapy is administered.

Although screening can positively identify adults with chronic HCV infection, more research is needed to understand the effects of different screening strategies on the clinical outcome. The evidence on effects of knowledge of HCV status, counseling, and vaccination of HCV diagnosed patients are still scarce. There should also be more studies on interventions that could successfully prevent vertical transmission. A comprehensive assessment of benefits and harms of screening includes evaluation of the effectiveness of antiviral regimes is also necessary.

Furthermore, there is a need for a cost-effectiveness study of the fourth-generation HCV antigen and antibody assay (combination EIA) two HCV in the same assay. Molecular testing for HCV-RNA using nucleic acid amplification technology (NAT) is today the most sensitive assay that shortens the window period to only 4 days. Implementation of NAT in many developed countries in the world has resulted in dramatic reductions in transfusion transmitted HCV infections, so now the relative risk is <1 per million donations (CDC, 2013).

If we bear in mind all the facts stated above, it becomes obvious that future studies will have to consider testing costs in relation to potential benefits in specific, high-risk populations.

CONCLUSION

The current hepatitis C testing strategy is not efficient, as concluded by numerous studies.

Research, development, validation, and cost-effectiveness studies should yield best practices for detecting HCV viremia and for developing new possibilities to distinguish between people with resolved HCV infection and those with biologic false positivity for HCV antibody, in whom HCV RNA has not been detected. The results of these studies should provide comprehensive guidelines for testing, reporting, and clinical management and improve definitions for disease reporting and surveillance. (Gregory and Dodd, 2009; Marwaha and Sachdev, 2014).

Based on the presented facts, it can be concluded that there is a need to develop targeted programmes for detection of HCV and other infections, but there also a need to decrease potential harms. Furthermore, public health programmes have to be made according to the local epidemiological picture and taking into account new research evidence on efficiency and effectiveness. Also, there is a need to include innovation in health system products, processes, and delivery systems and to optimize the performance of medical care through better understanding causes and courses of HCV infection and also, treatment consequences.

AUTHOR CONTRIBUTIONS

All authors listed, have made substantial, direct and intellectual contribution to the work, and approved it for publication.

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Pharmaceutical Expenditure and Burden of Non-communicable Diseases in Serbia

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In the low- and middle-income countries some non-communicable diseases (NCDs), such are cardiac diseases, strokes, chronic lung diseases, certain cancers, and diabetes, tend to overtake the morbidity and mortality of poverty diseases (Adams and Butterly, 2015; Jakovljevic and Getzen, 2016). Such diseases, conditionally labeled as diseases of affluence (Nutrition Health Topics, 2016), are growing rapidly in the developing countries, making almost 80% of deaths due to NCDs (New WHO report: deaths from noncommunicable diseases on the rise, with developing world hit hardest, 2011). Until a century ago, infectious diseases were the leading cause of morbidity and mortality worldwide. For example, in the United States at the beginning of the twentieth century, the crude death rate for the infectious diseases amounted to 800 per 100,000 population per year, reaching nearly 1000 during influenza pandemic at the end of the WWII. Afterwards, significant drop in the morbidity and mortality due to infectious causes was noticed, mostly as a consequence of a variety of the conducted preventive measures in sanitation and hygiene area, vaccination strategies and the development of different antimicrobial agents (Achievements in Public Health, 1900–1999: Control of Infectious Diseases, 1999; Wang et al., 2016). Due to the globalization, the flow rate of people, ideas and financial capital increased worldwide (Jakovljevic et al., 2016).

Non-communicable diseases have achieved high morbidity and mortality rates, first in the developed (affluent) and afterwards in the low- and middle-income countries, dislodging the rich-countries exclusivity premise. On the contrary, the wealthier people live, socially and economically, the better their health (Fair Society Healthy Lives, 2010). Morbidity and mortality rates are rising faster in developing countries; inequalities in health access within particular country favor the growth of such rates (Human Development Report 2013, 2013). The chronic illnesses make a profound impact on patients and society, regarding complex and expensive treatment strategies, decreased quality of life and working disability. Most of them are treatable, but not curable, which additionally prolongs the enormous influence on the health funds (Jakovljevic and Milovanovic, 2015; EU Reflection on Chronic Disease, 2016). The objectives of this study were to estimate the impact of drug utilization related to NCDs on Serbian health funds, and compare it with the Gross National Income (GNI) per capita values for the observed period.

NON-COMMUNICABLE DISEASES IN SERBIA

Although, the life expectancy at birth for both sexes was increased by 3 years over the period of 2000–2012, in 2012 the loss of healthy life expectancy due to morbidity and disability was 9 years lower than overall life expectancy at birth (Country Statistics Global Health Estimates by WHO UN Partners, 2015; Jakovljevic et al., 2015a). Significant increase in treating cardiovascular diseases (CVDs) contributed to such progress, although the adult risk factors as raised blood glucose,

obesity, tobacco usage and raised blood pressure are slightly higher in Serbia then the European average (Possible Directions for Increasing Efficiency of Healthcare System in Serbia, 2015). Mortality range for CVDs reached 762–744.9 per 100,000 population for a 10 years period (2004–2013), 259.4–294.4 for malignant neoplasms, 34.4–39.1 for diabetes and 34.2–36.0 for chronic obstructive pulmonary disease (COPD; Health statistical yearbook of Republic of Serbia, 2013). NCDs in Serbia are estimated to account for 95% of all deaths, which is significantly higher compared to the 86% of the European region (EU Reflection on Chronic Disease, 2016). Mortality due to cardiovascular diseases reached 54% of all deaths, followed by cancers (23%), COPD (4%), and diabetes (3%) (Noncommunicable Diseases (NCD) Country Profiles, 2015).

THE DATA REPORT METHODS—DATABASES

Data obtained from the World Bank and OECD National Accounts files concerning Serbia (Serbia, 2016) and from the publications *Marketing and consumption of medicinal products for human use of Medicines and Medical Devices Agency of Serbia* (ALIMS) were observed for each year of a ten-year period (2004–2013) (Marketing and consumption of medicinal products for human use (2004–2013), 2016). The quantum of Gross National Income per capita, obtained by Atlas method and originally expressed in currency US$, was observed and converted into euros using yearly average exchange rates for each year. GNI per capita presents the gross national income, converted to U.S. dollars using the World Bank Atlas method, divided by the mid-year population. GNI is the sum of value added by all resident producers plus any product taxes that were not included in the valuation of output plus net receipts of primary income from abroad.

Medicine consumption for pharmacotherapy of the most common NCDs and financial expenses were calculated based on the World Health Organization (WHO) ATC classification, for the following groups of drugs: A08-Antiobesity preparations, excl. diet products, A10-Drugs used in diabetes, B01-Antithrombotic agents, C-Cardiovascular system, L-Antineoplastic and immunomodulating agents and R03-Drugs for obstructive airway diseases. Expenses were expressed in euros (EUR), consumption of medicines in Defined Daily Doses per 1000 inhabitants per day (DDD/1000 inh/day) and ratios as a percentage of a total quantum (%).

DRUG UTILIZATION REGARDING THE GNI

Values of GNI per capita in Serbia recorded a rapid growth, starting from 2004 to 2010, when a slight regression occurred with a modest re-growing tendency in the period from 2011 to 2013. The expenses for indicated medicines followed the GNI trend line, expressing an even more rapid growth of the financial assets, especially in 2007 and 2008 (**Figure 1**; Jakovljevic et al., 2015b).

In every particular year within the observed period, the greatest funds were dedicated to the pharmacotherapy of cardiovascular diseases. In the year 2008, it reached the highest share of 25.5% regarding total medicine expenses. In the terms of drug utilization in DDDs/1000 inh/day, the highest consumption was in 2013 with the share of 44.38% of all prescribed medicines.

The funds for antineoplastic and immunomodulating agents almost doubled their share within the observation period, reaching the highest values in 2013, both in the financial and utilization terms.

The expenses for drugs used in diabetes nearly tripled their value in 2013 in comparison to 2004, whereby that was not the case with the relative ratio regarding entire medicine funds, which has remained more or less constant. The consumption and its ratio followed the above-mentioned path of expenses (Jakovljevic and Souliotis, 2016).

The drugs for obstructive airway diseases are at the fourth place among pharmacotherapy resources, with the constant growth in both terms, reaching the peak of the expenses and consumption in 2011, in the nominal values as well as in ratio terms.

The prescription of antithrombotic agents shows an increasing tendency, together with increasing costs of treatment, while decrease of consumption and consequently costs cutting concerning antiobesity preparations, excl. diet products, was noticed.

PHARMACOTHERAPY DATA COMPARED TO THE COST OF ILLNESS

Approximately 10% of Serbian GDP was spent on the total health care, thereof the share of government expenditure amounted 62%. Total pharmaceutical market in Serbia, with included prescription and over-the-counter medicines, is estimated at €645.6 million, with per capita expenditure estimated at €89.37. National health insurance funds for medicines amounted €45.32 per capita in 2012, and reached 18% of total budget. Considering the fact that NCDs are the most common cause of death, current morbidity and mortality rates have to be reduced in order to maintain sustainability of health care funds (Godman and Gustafsson, 2014).

As a part of NCDs, cardiovascular diseases impose a significant burden on the society, not only in terms of morbidity and mortality, but also as a significant economic impact. Amongst CVDs, stroke remains the main cause of death, followed by cardiomyopathy and ischemic heart disease; however, those diseases show no changes in the crude death rate in 2012 compared to 2000. Hypertensive heart disease shows growing tendency in the same time period (Noncommunicable Diseases (NCD) Country Profiles, 2015). In order to estimate the economic burden of cardiovascular diseases, a study conducted in Serbia referring year 2009, evaluated their direct and indirect costs from the point of view of the society. Total costs reached 514.3 million euros, the greatest part of which was influenced by medications (29.94%; Lakić et al., 2014). According to the ALIMS data, for the cardiovascular system disorders medicines only, it

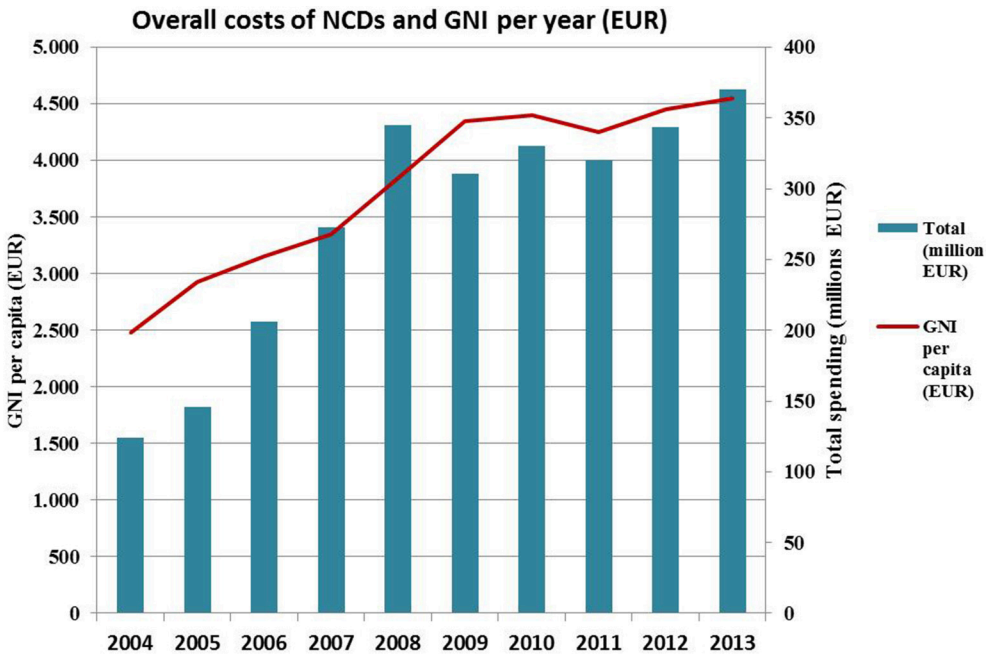

FIGURE 1 | Overall costs for pharmacotherapy of the most common NCDs compared with GNI for the selected time period. It can be observed that the expenses for medicines followed the GNI trend line, expressing an even more rapid growth of the financial assets in years 2007 and 2008.

was necessary to refund between 80 and 180 million Euros per each observed year (2004–2013; **Table 1**). If the expenses of the antithrombotic agents are added to the cardiovascular medicines, we can conclude that the cardiovascular diseases are a highly costly group of diseases with a heavy burden on the society. It is even more if we consider the fact that the total cost of illness amounted to approximately 1.8% of the Serbian GDP (Lakić et al., 2014).

Ischemic heart disease is the leading cause of mortality and morbidity, expressed in terms of disability-adjusted life years (DALY). In Europe, ischemic heart disease accounted for 24.8% of all the DALYs caused by other diseases, while in Serbia it accounts for only 1% less (23.8%). In highly developed countries, the mortality rate of ischemic heart disease has been decreasing, due to better socio-economic conditions, increased health protection service quality and healthy life styles promotion (Jakovljevic et al., 2016). At the same time, mortality is high in the east-European countries. In 2009, standard mortality rate for Serbia amounted to 113.8 compared to the European Union average of 87.2 per 100,000 inhabitants (Mickovski et al., 2011). Serbian age standardized death rate regarding CVDs in 2014 of 400.8 per 100,000 males, was amongst highest in the whole European region; e.g., in United Kingdom it amounted 140.6, Denmark 134.6 and France 111.8 per 100,000 males (Global status report on noncommunicable diseases 2014, 2014).

Calculated from the point of view of the society, the peculiarity in the Serbian cost of illness calculations would be the fact that only one fourth of all the expenses were made up of indirect costs. That differs from the developed countries data concerning the treatment of CVDs in which indirect costs would reach almost half of the total costs (Chan et al., 1996; Liu et al., 2002).

Worldwide, cancer represents an important public health and economic issue, as the global cancer incidence in 2012 was 14.1 million with 8.2 million death cases (Worldwide cancer statistics, 2014). In 2014 the age standardized death rate from cancers in Serbia reached 218.1, while in UK, Denmark and France it amounted 153.9, 179.9, and 179.8 per 100,000 males, respectively (Global status report on noncommunicable diseases 2014, 2014). Cancer treatment costs impose considerable expenses on the national health system budgets, reaching in average 9.1% of the Gross Domestic Product Expenditure on Health (GDPHE) for developed European countries, up to 17.1% in USA in 2010 (Pritchard et al., 2016). On average, 10% of total health care costs in developed countries are also spent on treating cancer (Bosanquet and Sikora, 2004).

Differences in costs occur not only due to different types of cancer, but also as a consequence of the stage of the disease (Dagovic et al., 2014). Based on the research conducted in the central Serbian region the same authors concluded, that in the total costs of cancer care the medication share reached 5%, while malignant breast neoplasm turned out to be the most expensive overall treatment. For the patients with the advanced stage of cancer, the greatest impact on total medical treatment costs was observed concerning medicines expenditures (Kovacevic et al., 2015a). Significant costs are obtained for colorectal cancer pharmacotherapy, depending upon the stage of cancer. In Serbian settings, it was necessary to pay from 4200 to 20,600 Euros per patient with metastatic disease (Kovacevic et al., 2015b). The data obtained from the ALIMS show a significant fivefold increase in the expenses and more than twofold increase of consumption of antineoplastic and immunomodulating agents in 2013 compared to 2004 (Jakovljevic et al., 2014a).

TABLE 1 | Expenses (EUR) and consumption of the specific medicine groups for the selected years and ratios regarding their total spending and consumption (%).

Year	Expenses (EUR)	% of total spending on medicines	Consumption (*DDD/1000 inh/day)	% of total consumption
C—CARDIOVASCULAR SYSTEM				
2004	78.716.560,68	23,20	331,02	30,54
2005	83.534.063,75	21,94	334,63	30,57
2006	122.294.456,31	23,94	387,81	38,26
2007	158.399.085,91	23,04	400,06	36,89
2008	203.799.903,76	25,50	481,70	39,51
2009	161.297.625,34	21,74	414,67	35,21
2010	162.352.661,21	22,89	384,73	39,82
2011	163.667.924,49	22,66	474,31	42,94
2012	176.571.683,75	23,80	526,98	42,44
2013	182.656.566,45	22,99	568,28	44,38
L—ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS				
2004	19.166.161,32	5,65	1,52	0,14
2005	23.112.621,92	6,07	1,49	0,14
2006	30.880.478,61	6,05	2,12	0,21
2007	49.424.984,02	7,19	2,32	0,21
2008	60.977.545,27	7,63	2,32	0,19
2009	68.839.374,51	9,28	2,71	0,23
2010	77.515.115,27	10,93	2,38	0,25
2011	68.873.960,86	9,54	2,19	0,20
2012	75.968.428,70	10,24	3,32	0,27
2013	89.944.696,11	11,32	3,61	0,28
A10—DRUGS USED IN DIABETES				
2004	13.673.374,33	4,03	15,88	1,46
2005	21.607.559,81	5,68	27,51	2,51
2006	23.647.892,69	4,63	41,82	4,13
2007	28.566.352,17	4,15	41,18	3,80
2008	35.355.225,48	4,42	59,68	4,90
2009	30.357.067,89	4,09	49,31	4,19
2010	34.022.142,79	4,80	45,73	4,73
2011	36.770.569,28	5,09	45,19	4,09
2012	37.668.755,11	5,08	74,50	6,00
2013	42.739.770,26	5,38	79,97	6,25
R03—DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES				
2004	8.758.308,28	2,58	18,40	1,70
2005	9.751.546,83	2,56	17,47	1,60
2006	16.558.281,51	3,24	26,87	2,65
2007	16.745.056,96	2,44	23,09	2,13
2008	19.043.385,18	2,38	25,53	2,09
2009	24.353.872,40	3,28	18,40	1,56
2010	26.190.593,19	3,69	23,17	2,40
2011	26.784.686,01	3,71	23,22	2,10
2012	22.604.678,59	3,05	15,06	1,21
2013	25.425.617,85	3,20	18,55	1,45
B01—ANTITHROMBOTIC AGENTS				
2004	2.994.811,70	0,88	11,00	1,01
2005	7.020.869,89	1,84	19,80	1,81
2006	11.245.999,68	2,20	29,08	2,87
2007	18.433.025,18	2,68	55,44	5,11
2008	24.131.961,20	3,02	54,32	4,46
2009	24.750.838,47	3,34	69,16	5,87
2010	29.334.215,64	4,14	58,82	6,09
2011	23.823.928,51	3,30	67,94	6,15
2012	30.130.846,05	4,06	73,34	5,91
2013	29.289.470,21	3,69	89,68	7,00
A08—ANTIOBESITY PREPARATIONS, EXCL. DIET PRODUCTS				
2004	711.589,90	0,21	0,10	0,01
2005	1.033.497,60	0,27	0,17	0,02
2006	1.313.206,95	0,26	0,22	0,02
2007	1.320.202,45	0,19	0,23	0,02
2008	1.413.316,40	0,18	0,25	0,02
2009	1.295.245,35	0,17	0,30	0,03
2010	524.148,20	0,07	0,10	0,01
2011	474.353,52	0,07	0,09	0,01
2012	402.346,66	0,05	0,08	0,01
2013	402.979,73	0,05	0,08	0,01

	Total medicines expenses(EUR)	Total *DDD/inh/day
2004	339.279.303,77	1.083,97
2005	380.716.701,39	1.094,61
2006	510.833.609,54	1.013,70
2007	687.588.174,80	1.084,34
2008	799.082.221,00	1.219,07
2009	741.981.960,19	1.177,72
2010	709.317.344,16	966,26
2011	722.207.154,57	1.104,57
2012	742.013.975,72	1.241,66
2013	794.560.044,61	1.280,47

**DDD/1000 inh/day, Defined Daily Doses per 1000 inhabitants per day.*

The cost of diabetes mellitus, with its high morbidity and mortality rates, imposes significant burden on the national healthcare system of Serbia. The Institute of Public Health of Serbia mortality estimates were 39.1 per 100,000 population, but morbidity data show the presence of almost half a million people with this illness (Health statistical yearbook of Republic of Serbia, 2013). Compared to some European countries, e.g., Greece, the death rate equals only 6.6 per 100,000 males (Global status report on noncommunicable diseases 2014, 2014). The theoretical cost of handling this disease would even reach 6% of the total Serbian health care expenditure or 11% of the annual Health insurance fund budget (Jakovljevic, 2014). In real life, these costs would be considerably lower, since not all the population is covered by health insurance. Data concerning developed countries, such as Switzerland, show that 2.2% of the total health care expenditure is spent on the specific diabetes care (Schmitt-Koopmann et al., 2004), while in the United States 10–20% of the health budgets are spent on diabetes mellitus treatment (American Diabetes Association, 2008). Based on the research conducted by Biorac et al. (2009), medicine share in overall costs of illness for the year

2007 reached 38% in Serbia. An increasing trend in insulin and its analogs as well as oral antidiabetics consumption was observed. The ALIMS showed a fourfold increase in drug consumption for diabetes treatment and a threefold increase in expenses in 2013 in comparison to 2004. Antidiabetic medication share in the overall consumption showed a rapid growth in the observed period, but that was not the case with the costs, whose share in total expenses was only 5.38% in 2013 compared with 4.03% in 2004 (**Table 1**).

As a severe disabling and irreversible illness, COPD is standing among top five most expensive chronic disorders due to its high healthcare budget impact. Its estimated prevalence in developed countries makes 4–6% among adult males as well as 1–3% among females, with smoking as a dominant risk factor. The COPD patients often have different severe comorbidities that rise costs of treatment and make distinction from the basic illness difficult. The greatest contributing factors in overall treatment costs are periodic exacerbations of the disease, which are getting higher with the COPD severity degree (Andersson et al., 2002). The major cost drivers in the developed countries would be physician consultations and surgery, while in the middle-income eastern countries, pharmaceuticals and oxygen costs are dominant. In Serbia, the incidence of COPD mortality is almost equal to the one of the diabetes (Health statistical yearbook of Republic of Serbia, 2013). COPD related pharmaceutical prescription reached the peak of the value turnover in 2011, with almost 27 million Euros, while the consumption of such medicines remained constant, with lesser pop outs, in the entire observational period (**Table 1**). The similar situation was observed in the entire western Balkan market, when value of medicines for the treatment of the respiratory diseases rose to 46.5 million Euros in 2012. COPD comorbidities significantly contributed to the greater costs of medical care, e.g. costs of community acquired pneumonia (CAP) clinical treatment accounted for an average 717 Euros in a 1 month, while COPD and CAP together accounted for 970 Euros during the same time period (Cupurdija, 2015). According to the results from a recent published study, concerning comparison of two different markets, Serbian and Belgian, drug acquisition costs (in- and outpatient consumption) of COPD treatment reached up to 54% in Serbian and 46% in Belgian sample. The greatest difference actually occurred in the relative number of hospital bed days and hospital admissions due to exacerbation of the disease, per person, which were significantly smaller in Belgian population (Jakovljevic et al., 2013).

Obesity is present in the Serbian population in 24.8% of the adult population. This ratio is increasing; some forecasts predict that in 2020, 44% of men and 31% of women will be obese (Nutrition, Physical Activity and Obesity, 2013). Consumption and expenses of medicines concerning this disease are not following the predicted path, since their significant decrease occurred in 2008, making only 0.01% of total drugs consumption as well as 0.05% of the overall expenses (**Table 1**). We strongly support other anti-obesity measures, such as promoting healthy life style, which would make a significantly higher contribution in the management of this problem, rather than pharmacotherapy (Jakovljevic and Ogura, 2016).

CONCLUSION

Almost 80% of all deaths due to chronic diseases like CVDs, cancer, COPD and diabetes occur in the low- and middle-income countries. The rapid aging of the Serbian population (Jakovljevic and Laaser, 2015), with higher demands for the healthcare services, along with the difficulties in transitional national health insurance fund functioning, have resulted in the huge impact on the national budget as well as household expenditures (Ogura and Jakovljevic, 2014).

This data report shows that the total pharmacotherapy costs of treating CVDs in Serbia followed the GNI trend line, with noticeably constant growth of the financial assets. Expenses of medicines reached highest values in 2008 and 2013, even overgrowing the GNI rising trends.

Together with measures of prevention, chronic disease morbidity and mortality can be significantly reduced if pharmacotherapy is accessible and affordable. There have to be more initiatives and real-life activities in order to alleviate one's access to the treatment, as well as to improve governmental interventions aiming to facilitate the affordability of the drugs used to treat chronic diseases (Jakovljevic et al., 2015c).

One of the efficient measures could involve expanding the National Health Insurance Fund Drug List, both with brands and generic equivalents (Jakovljevic et al., 2014b). In addition, a certain part of health funds must be dedicated to substantial promotion of healthy life styles and minimizing verified risk factors for the occurrence of NCDs.

Possible limitations of the study would likely be the underestimated drugs utilization and pharmacotherapy costs for the particular diseases. In treating most NCDs, many different medications are used, not only those within specified ATC groups, but for other concomitant diseases, which could elevate calculated costs. Calculations did not comprehend the out-of-pocket expenses for different Over the Counter medicines due to no published data regarding their consumption. Drug prices data within the ALIMS publications database are calculated using regulatory approved drug prices, not the real values ensued from the special terms of sale.

AUTHOR CONTRIBUTIONS

All the authors listed have made substantial contribution to the conception, design, analysis and interpretation of data for the work, and approved it for publication. AK, VD developed research questions, designed the study and prepared the manuscript. NR, ZS searched the literature, analyzed and interpreted the data for the work. VD, ZS critically reviewed the manuscript.

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GENERAL COMMENTARY
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Commentary: Patient Cost Sharing and Medical Expenditures for the Elderly

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Keywords: cost sharing, medical expenditure, elderly, Japan, population aging

A commentary on

Patient Cost Sharing and Medical Expenditures for the Elderly
by Fukushima, K., Mizuoka, S., Yamamoto, S., and Iizuka, T. (2015). J. Health Econ. 45, 115–130. doi: 10.1016/j.jhealeco.2015.10.005

Fukushima et al. recently published research on the relationship between cost sharing policies and medical spending by the elderly (Fukushima et al., 2016). Japan, as the nation in the most advanced stage of population aging, is indeed the best place to search for answers (Ogura et al., 2007). The authors provided us with a valuable contribution on the effects of such policies on the demand for medical services and costs within the subpopulation of senior citizens. The study has been conducted within a sound methodological framework and significantly expands our knowledge on the oldest among the world's large nations. I would like to complement their revealing findings with few additional facts crucial for understanding these issues.

One of the baseline results of the study claims: "lower cost sharing significantly increases medical spending." This actually follows the natural logic that a patient is likely to consume more care if it is effectively free at the point of usage. Three decades ago policy makers believed it should be possible for a cost sharing mechanism to contain costs and induce net savings (Keeler and Rolph, 1983). It appears that the final balance is highly dependent on prevailing governing practices and legislative framework within the observed market (Remler and Glied, 2006). Besides there are studies showing that increased co-payments—especially for pharmaceuticals—have a detrimental effect on access and compliance—potentially leading to worse health outcomes (Shrank et al., 2006; Roberts et al., 2012a,b; Maimaris et al., 2013; Barnieh et al., 2014; Putrik et al., 2014; Simoens and Sinnaeve, 2014; Barbui and Conti, 2015; Tefferi et al., 2015). There are findings from Greece where major increases in patient co-payments were coupled with a reduction in public services in areas such as infection and mental health. This national case also adds to the literature (Ayuso-Mateos et al., 2013; Siskou et al., 2013; Kentikelenis et al., 2014). However, the impact of increased co-payments on health is still subject to ongoing debate (Mann et al., 2014). WHO had serious concerns on accessibility and co-payment. Therefore, it settled on a target of 80% availability for affordable essential medicines, including generics. Targeted therapeutic areas were major Non-Communicable Diseases (NCDs), such as diabetes and hypertension. This policy aimed to address global concerns with the impact of NCDs on morbidity and mortality[1].

The article conveys an important message with regards to the role of cost sharing in prescribing and dispensing medicines (Johnson et al., 1997). The authors noticed the concerning fact that

[1]Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013–2020. http://www.who.int/nmh/events/2013/revised_draft_ncd_action_plan.pdf?ua=1 (updated revised draft).

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reduced cost sharing after the age of 70 increases demand for brand-name medicines, unlike generics. This change ultimately leads to an expanding market share of original drug dispensing and sales. The roots of this change could be found in consumer behavior. There is traditionally a strong lack of confidence in the quality of copycat medicines attributed to the Japanese patient (Kobayashi et al., 2011). This explains the willingness to pay slightly more for an original drug compared to generic alternative in a reduced cost-sharing setting. The uniqueness of the Japanese pharmaceutical market and its global impact refers to its mammoth size (World's second largest) and the smallest share of generics compared to other major high-income OECD economies (Penner-Hahn and Shaver, 2005). National efforts to increase generic replacement of brand name drugs have long been a source of public debate among Japanese authorities (Jakovljevic et al., 2014). The surprising findings of Fukushima et al. appropriately indicate the need for differential cost sharing rates as a strategy to contain drug acquisition costs in future.

There is a variety of measures used to increase the prescribing of generics vs. originators in Europe. These include compulsory substitution, e.g., in Sweden (Andersson et al., 2005), compulsory INN prescribing, e.g., in Lithuania (Garuoliene et al., 2011), or high voluntary INN prescribing as in the UK (Godman et al., 2013). The high use of generics should not be troubled conditional to guaranteed quality. Some of these historical experiences might be applicable to Japanese policy challenges as well. We should be aware that a general provision of guidelines has limited impact visible in the demise of the RMO guidelines in France for GPs (Sermet et al., 2010). The comprehensive approach to instigating a limited list of well-proven medicines, coupled with simple advice, has worked well in Stockholm, Sweden. It leads to improved care through consistency in use of well-proven medicines as well as reduced pharmaceutical expenditure (Gustafsson et al., 2011).

The phenomenon of a shrinking labor force and threatened financial sustainability of health care provision was recognized in the Japanese market a few decades ago (Ogura, 1994). The development of policies aimed at meeting this challenge followed, with diverse success rates (Tsutsui and Muramatsu, 2007; Campbell, 2014). It has clearly been proven that the long term health expenditure pattern follows the pace of population aging (Stojkovic and Milovanovic, 2015). Outsourcing from Japanese regression discontinuity study there are valuable lessons with implications for other world regions. Nations of the European region age rapidly while key consequences for the national health sectors and economies are yet to be seen (Jakovljevic M. 2015). The pace of the process remains uneven but surprisingly, involves some of the traditional young nations historically famous for their high fertility rates (Jakovljevic and Laaser, 2015). Appliance of cost sharing approaches as a strategy to contain medical costs has become prominently popular even among Eastern European countries (Tambor et al., 2015). Administration of cost sharing as demand side intervention to limit medical consumption among the elderly is clearly beneficial for the society. There remain two essential issues likely to spark further professional debate coming from opposite angles of different stakeholders. Patient perspective focuses on how to protect senior citizens from vulnerabilities outsourcing from such policies. These citizens face falling household income after retirement and lower affordability of medicines and medical services (Miralles and Kimberlin, 1998). Such financial burden is lessened by generous provision of cost sharing after the age of 70 provided in Japanese health system. Another issue comes from the perspective of the society. How to limit the heavy burden of medical expenditure attributable to the elderly within the existing financial constraints of a large aging nation? (Ogura and Jakovljevic, 2014) Strategies complementing the evident success of cost sharing will be sought in the upcoming decades as expenditure continues to grow further (Jakovljevic M. M. 2016). The advanced stage of Japanese social care for the elderly shall probably remain a prime example of the rapidly evolving health systems of the Asia-Pacific region.

AUTHOR CONTRIBUTIONS

MJ has solely designed and authored this Commentary article without any external engagements by other contributor or professional services.

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Satisfaction with Health Services among the Citizens of Serbia

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SATISFACTION WITH HEALTH SERVICES

The health system in Serbia has changed a lot in the past 30 years. After falling apart of Yugoslavia in the 90s, all the weaknesses of the health system of that time have become more visible. The country has entered the period of transition, and the creators of health policies have been forced to start the reforms of the health system related to solving structural and functional issues, human resources issues, financing, organization, and availability of the health care in order to build a generally accepted and maintainable health system which shall include intensive controls of the expenses (Kutney-Lee et al., 2009; Kutzin et al., 2010; Jakovljevic et al., 2011; Jakovljevic, 2013).

Following democratic changes during 2000, Serbia has entered the period of intensive reforms and speedy recovery of the health system, due to the significant income of money through International charity help and affordable bank loans (Bajec et al., 2008). Quick development was stopped by the world economic crisis in 2007 (Marmot et al., 2013; Ruckert and Labonté, 2014; Tøge and Blekesaune, 2015). Today, Serbian government provides the health system with 10.4% of Gross domestic product (GDP), and alongside with Belgium, Denmark, and Canada, Serbia falls under the category of countries which provides health system with a significant part of GDP, but that percentage is considerably smaller than in the countries already mentioned (The World Bank, 2016).

The reform analysis of health systems going through a transition and the analysis of quality assessment of the provided services are conducted using the indicators for the subjective and objective assessment. The most common indicators for the subjective assessment are: the satisfaction of the patient with health care and self-assessment of a health condition. The satisfaction with health care is used in the reform analysis of the health systems all across Europe, Asia and America and it represents the ratio between the expected and achieved health services (Bleich et al., 2009; Browne et al., 2010; Rechel et al., 2012; Gupta et al., 2015).

The most common determinants of the satisfaction of the citizens with health care are: age, health condition, income, the type of the given service (state or private sector), communication, politeness of the staff, and hospital environment (Friese et al., 2008; Aiken et al., 2011, 2012; Al-Refaie, 2011; Xesfingi and Vozikis, 2016).

Due to the lack of universal instrument for measuring the level of satisfaction with health care and the lack of correlation of the satisfaction and economic power of the health system, the degree of satisfaction with health services is determined indirectly based on: waiting lists, quality of given services and communication with health workers (Sofaer and Firminger, 2005; Adang and Borm, 2007).

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THE DATA REPORT METHODS

Public Data Set Description—National Health Survey Serbia 2006 and 2013

The research has used the database of the two National Health Surveys in the Republic of Serbia, conducted in 2006 and 2013, funded by the Ministry of Health (National health survey Serbia, 2006, 2013). The survey was conducted in accordance with the methodology and instruments of the European Health Interview Survey wave 2 (Eurostat European Commission, 2013). Both surveys were conducted as cross sectional studies. Population presented in the research included adults, aged 19, and more. The researches excluded people living on the territory of Kosovo and Metohija, as well as people with residence addresses in Special institutions (retirement homes, prisons, psychiatric clinics).

The research used the national representation sample, such as stratified two-phase sample without repetition. The sample frame in the 2006 and 2013 researches included all the households listed in the censuses from 2002 to 2011. In order to obtain a random sample, two techniques have been used: stratification and multiple-phase sampling. Stratification was conducted in such a way that each of six geographical areas in 2006 (Vojvodina, Belgrade, west Serbia, central Serbia, east Serbia, and south-east Serbia) and 4 in 2013 (Vojvodina, Belgrade, Sumadija, and west Serbia, south and east Serbia) represented one main stratum in the sample. Each stratum was divided into cities and other regions. Total number of strata was 12 in 2006 and 8 in 2013. Based on such sample, it is possible to obtain a statistically accurate assessment of the health service quality on a national level as well as on the level of given geographical regions and on the level of cities and other areas.

Two-phase sampling includes local communities, as units of the first phase, selected on the basis of probability proportional to their size, and households as units of the second phase selected on the basis of linear sampling method with the random start and uniform selection steps. In this way, households are selected with the equal probability of being chosen, without repetition.

Acquired data are then united in the unique database according to the common key and organization principle.

Survey Data Description

The number of households which wanted to participate in the research was significantly different in 2006 and 2013. In 2006 out of 7673 contacted households, 6156 agreed to take part in the research, which represents the response rate of 86.5%. In 2013 the response rate was 64.4%, which means that only 6500 households out of 10,089 contacted ones agreed to participate in the research. Total number of the interviewed adults was 30,186. For the purposes of this paper, the sample of 19-year-olds and older was used, which amounts to the total number of 29,485 interviewees, namely 15,563, and 13,992 in 2006 and 2013 respectively.

Two types of questionnaires have been used in the research: the questionnaires about the household which provided information on the characteristics of the household, residence, and members and the face to face interview which provided data on demographic and socio-economic characteristics of the interviewees. Each interviewee was familiar with the type and the purpose of the research and each of them gave their written consent. Ethical standards in the research were in accordance with the international ethical standards as well as with the Serbian legislation.

Dependent variable in the research was the satisfaction of patients with the health service, measured with Likert-type scale.

Independent variables in the research were:

(a) Basic characteristics of the interviewees (age, gender, financial condition according to well-being index, region). Age is continuous, gender is coded as male, or female, financial condition according to well-being index for the purpose of this paper was coded into three categories: poor, middle class and rich and the listed regions were Vojvodina, Belgrade, Sumadija with West Serbia and South and East Serbia;
(b) Health condition of the interviewees (presence of some illness or certain pathological conditions in the past 12 months, sick leave). Illnesses or pathological conditions which were diagnosed in the past 12 months included: asthma, chronic bronchitis, chronic obstructive pulmonary disease, emphysema, myocardial infarction, coronary heart disease, hypertension, stroke, osteoarthritis, diabetes, kidney problems, depression, malignant diseases, and interviewees were or were not on a sick leave during the past 12 months;
(c) Using hospital and non-hospital health care services and prevention check-ups (hospital treatment choosing a GP or pediatrician, using the private practice services, prevention check-ups, lab analysis, and tension measurement in the health institutions). All these variables are dichotomic;
(d) Unachieved need for health care (lack of some type of health care service due to long waiting lists, financial reasons, long distance of the health institution). Interviewees could or couldn't get the necessary health treatment in the past 12 months due to long waiting lists;

The data set has been submitted in a public repository Figshare and it is a available on: https://figshare.com/s/b1ede3b1bbcdf166eac7.

Satisfaction with Health Services in Serbia

During the analyzed period, the percentage of the interviewees satisfied with health care rose from 42.8 to 54.8%. Both with men and women, there is a noticeable increase of the satisfaction level and the satisfied patients were 1 year older in 2013 in comparison to 2006 (52.27 ± 17.45, in comparison to 53.86 ± 17.98, $p < 0.001$). The inhabitants of the region of Sumadija and West Serbia were the most satisfied in 2006, while in 2013 the people of Vojvodina were the most satisfied ones. The least satisfied were the rich, namely 39.2% in 2006 and 48.1% in 2013. The interviewees which were diagnosed with some disease in the past 12 months were equally satisfied as those who were not diagnosed with any disease. Patients who were on sick leave in the past 12 months were less satisfied while the difference in satisfaction between hospitalized and not hospitalized patients which was noticed in 2006 (55.6% of hospitalized as opposed to 41.9% not hospitalized) faded away and the percentages became identical in 2013. The biggest difference in patient

TABLE 1 | The comparison of the patients who were satisfied with health care in 2006 and 2013.

Variables	Year 2006		Year 2013		*p*
	Total	n (%)*	Total	n (%)*	
Total	15563	6119 (42.8)	13922	7154 (54.2)	<0.001
GENDER					
Female	7586	3526 (46.5)	7276	4032 (55.4)	>0.05
Male	6703	2593 (38.7)	5927	3122 (52.7)	
REGION					
South and East Serbia	3667	1587 (43.3)	3211	1752 (54.6)	<0.001
Vojvodina	3555	1321 (37.2)	3218	1617 (50.2)	
Belgrade	2559	1049 (41)	2724	1409 (51.7)	
Sumadija and West Serbia	4508	2162 (48)	4050	2376 (58.7)	
WELL-BEING INDEX					
Poor	3176	1365 (43)	2947	1741 (59.1)	<0.05
Middle class	8661	3792 (43.8)	7964	4336 (54.4)	
Rich	2452	962 (39.2)	2292	1077 (47)	
ILLNESSES IN THE PAST 12 MONTHS					
No	11881	5096 (42.9)	6139	3246 (52.9)	<0.001
Yes	2408	1023 (42.5)	7064	3908 (55.3)	
SICK LEAVE					
No	14056	6030 (42.9)	3588	1782 (49.7)	<0.001
Yes	233	89 (38.2)	652	250 (38.3)	
HOSPITALIZATION					
Yes	959	533 (55.6)	1179	664 (56.3)	>0.05
No	13258	5555 (41.9)	12024	6490 (54)	
SELECTED GP					
No	7113	3593 (50.5)	937	356 (38)	<0.001
Yes	7166	2522 (35.2)	12250	6792 (55.4)	
PRIVATE PRACTICE					
No	11631	5196 (44.7)	11112	6292 (56.6)	<0.001
Yes	2645	918 (34.7)	2091	862 (41.2)	
PREVENTIVE CHECK-UPS					
More than 12 months ago	5105	2301 (45.1)	4486	2430 (54.2)	<0.001
In the last 12 months	9145	3803 (41.6)	8672	4699 (54.2)	
UNACHIEVED NEED					
No	11897	5017 (42.2)	11413	6665 (58.4)	<0.001
Yes	2378	1094 (46)	1751	473 (27)	

n (%), the number (percentage) of whose satisfied with health care.*

satisfaction (apart from the variable of unachieved need) was recorded in choosing a general practitioner. In 2006, 50% of the interviewees had their own GP and one third of the total number of the interviewees were satisfied. The percentage of those who used the private practice services and who were satisfied with them was 34.7 and 41.4% in 2006 and 2013 respectively, and the percentage of those who had preventive check-ups in the last 12 months was 41.6 and 54.6% respectively. Almost half of the total number of interviewees in 2006 expressed their satisfaction although they did not get the necessary treatment on time. On the other hand, in 2013 only one quarter of the total number of the interviewees who did not get the necessary treatment on time, were satisfied with the provided services (**Table 1**).

The results of the binary logistic regression of the patient satisfaction with health care in the period from 2006 to 2013 show that the following variables give a statistically significant contribution to the model: age, illnesses diagnosed in the past 12 months, hospitalization, selected GP, using the private practice services and preventive check-ups in the past 12 months. In 2006, there were more statistically significant predictor variables: region and well-being index, and in 2013 there was sick leave and unachieved need for some type of health care (**Table 2**).

The older the interviewees were, the less satisfied they were. Odds ratio with patients who were diagnosed with some illness was 1212 (1102–1333) in 2006 and 1182 (1027–1361) in 2013. Patients who were not hospitalized in the last 12 months were 1.5 or 1.4 times more dissatisfied with health care in comparison

TABLE 2 | Binary logistic regression for Health Services Satisfaction in 2006 and 2013.

Variables	Year 2006		Year 2013	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Age	0.992 (0.990–0.994)	<0.001	0.993 (0.987–1.000)	<0.05
REGION				
South and East Serbia	1		1	
Vojvodina	1.337 (1.213–1.475)	<0.001	1.141 (0.944–1.379)	>0.05
Belgrade	1.293 (1.153–1.449)	<0.001	0.878 (0.722–1.066)	>0.05
Sumadija and West Serbia	0.0804 (0.734–0.880)	<0.001	0.917 (0.769–1.094)	>0.05
WELL-BEING INDEX				
Poor	1		1	
Middle class	0.900 (0.825–0.982)	<0.05	0.985 (0.802–1.208)	>0.05
Rich	0.994 (0.880–1.122)	>0.05	1.123 (0.888–1.421)	>0.05
ILLNESSES IN THE PAST 12 MONTHS				
No	1		1	
Yes	1.212 (1.102–1.333)	<0.001	1.182 (1.027–1.361)	<0.05
SICK LEAVE				
No	1		1	
Yes	1.249 (0.948–1.646)	>0.05	1.390 (1.141–1.694)	<0.05
HOSPITALIZATION				
Yes	1		1	
No	1.551 (1.349–1.783)	<0.001	1.465 (1.070–2.006)	<0.05
SELECTED GP				
No	1		1	
Yes	2.010 (1.867–2.164)	<0.001	0.506 (0.391–0.655)	<0.001
PRIVATE PRACTICE				
No	1		1	
Yes	1.556 (1.417–1.708)	<0.001	1.626 (1.359–1.944)	<0.001
PREVENTIVE CHECK-UPS				
More than 12 months ago	1		1	
In the past 12 months	1.124 (1.047–1.207)	<0.05	1.199 (1.055–1.364)	<0.05
UNACHIEVED NEEDS				
No	1		1	
Yes	0.914 (0.833–1.003)	>0.05	4.576 (3.553–5.892)	<0.001

with those who were hospitalized. Less satisfied were those who had preventive check-ups in the last 12 months with those who did not. The biggest difference was recorded with the predictor variable of the selected GP, namely $OR = 2.010$ (1867–2164) in 2006 and in 2013 $OR = 0506$ (0391–0655). The interviewees who used private practice services were 1.5 and 1.6 times less satisfied in comparison to those who did not use them.

Based on the research from 2006, people coming from Vojvodina and Belgrade were 1.3 and 1.2 times less satisfied in comparison to the people from South and East Serbia.

Based on the research from 2013, patients who were on sick leave had $OR = 1390$, which means that they were 1.3 times less satisfied in comparison to the interviewees who were not absent from work. The strongest predictor of patient satisfaction with health care was unachieved need for some type of health protection. Namely, in 2013 patients who did not get the necessary treatment were Four times less satisfied with health care in comparison to those who did not have such problems ($OR = 4579$ (3553–5892).

In Comparison to the World

The analysis of the patient satisfaction with the health protection services has a goal of improving the quality of the given services, defining priorities, understanding patients' expectations and reducing inequality (Chow et al., 2009; Gupta et al., 2014; Radevic et al., 2016) The researches of the patient satisfaction on a national level enable monitoring of trends, defining problems, analyzing predictors for certain population groups in relation to gender, age, the type of the provided service and the type of the medical institution (U. S. Department of Health Human Services., 2011; Republic of Serbia Ministry of health, 2014). Regardless of possibilities, patient satisfaction with health protection, as a subjective indicator, hasn't still been used in its full scope (Jenkinson et al., 2002; Al-Abri and Al-Balushi, 2014).

In the period between 2006 and 2013, the population in the Republic of Serbia reduced for 3.3% (247,437). In the same time, life expectancy increased during the period of about 3 years (it rose from the average 72,37–75,05 years of age for both genders; Institute of Public health of Serbia, 2007, 2014). Health care expenses, by looking at GDP, rose from 9 to 10.4% of GDP (The World Bank, 2016). However, patient satisfaction as a subjective factor does not have to correlate with the budget and real performance of the health system (Adang and Borm, 2007). Due to the influence of the transition and the related socio-economic changes on patient satisfaction with health care, they have been used in an analysis of relations and attitudes of patients toward the reforms of the health system (Footman et al., 2013). The analysis of the quality indicators related to medical services shows that the satisfaction has significantly decreased in the countries going through a period of transition, especially following the world economic crisis in 2007 (Habibov and Afandi, 2015). Although inequality in using medical services is constantly present (Abebe et al., 2016), there are certain differences related to the period before and after 2007. So the number of those people who consider their health worse after the world economic crisis increased among the inhabitants of Greece, Lithuania, Poland, and Estonia (Vandoros et al., 2013; Zavras et al., 2013; Hessel et al., 2014; Reile et al., 2014).

The analysis conducted in the countries of West and East Europe shows diverse results. The research conducted in six countries of Central and East Europe, shows that there were 10–14% dissatisfied patients. However, some differences could be noticed, namely, patients from Hungary were the most satisfied while the most dissatisfied patients came from Bulgaria and Ukraine (Stepurko et al., 2016). However, the research of patient satisfaction trends conducted in the Netherlands in the period between 2003 and 2009 showed opposing arguments. Namely, according to one group this period recorded a global rise of patient satisfaction while the others argue that the satisfaction among hospitalized patients decreased from 76 to 66% (Kleefstra et al., 2015).

Patient satisfaction is related to the positive results of treatments, and such patients are easier to treat although they often ask for additional services, but researches show that satisfaction remains even when the additional requests have not been met (Zolnierek and Dimatteo, 2009; Deyo et al., 2010; ACCORD Study Group et al., 2011; Bertakis and Azari, 2011; Wiener et al., 2011). The research of satisfaction factors shows that the communication with medical workers, along with employment status, education and gender is one of the most important factors influencing patient satisfaction. Moreover, women, less educated people, and unemployed people estimate their own health condition as worse (Zolnierek and Dimatteo, 2009; Sánchez-Piedra et al., 2014).

Similar to our research, there was a research conducted in nine countries of the former SSSR which showed increased patient satisfaction with health care from 19.4% at the beginning to 40.6% in the period between 2001 and 2010. Similarly to our country, these countries also recorded that the most satisfied patients were young people, less educated people, people coming from rural places, and those people with generally good health condition (Footman et al., 2013). The analysis of the type of medical services shows that people who rarely use services of the Emergency center and, as in our research, those people who often use hospital services were more satisfied (Fenton et al., 2012). It is interesting that there is no significant relation between the satisfaction of hospitalized patients and hospitalization rate while nursing care, medical care and hospital organization are the most important factors determining the level of satisfaction among hospitalized patients in Germany (Sacks et al., 2015; Kraska et al., 2016).

CONCLUSIVE REMARKS

Patient satisfaction with health care represents the path toward the improvement of its quality. However, this instrument is most often used in order to define the factors which determine the satisfaction. In order to use it as means of monitoring and improving the quality, it is necessary to acquire additional knowledge about specific aspects of patient experience in relation to their characteristics, but also about the type and characteristics of the health institution which provided the services as well as the type of the provided services.

AUTHOR CONTRIBUTIONS

All authors listed, have made substantial, direct, and intellectual contribution to the work, and approved it for publication. NM: drafting of manuscript; SK: interpretation of data; GT: analysis of data; MJ: conception and design of the manuscript.

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Self-Assessed Health and Socioeconomic Inequalities in Serbia: Data from 2013 National Health Survey

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SOCIOECONOMIC INEQUALITIES—IMPACT ON HEALTH

Health inequities are differences in health status or health determinants between population groups, which are unjust because they reflect an unfair distribution of the underlying social determinants of health (Marmot, 2005; World Health Organization, 2013; Arcaya et al., 2015). This is a global phenomenon, seen in low, middle (Jakovljevic and Getzen, 2016) and high income countries (Ogura and Jakovljevic, 2014).

The largest contribution to inequalities in health is attributable to socio-economic determinants of health, or the societal conditions in which people are born, grow up, live, work, and age, which in turn are determined by wider economic, social, and political conditions (Liu et al., 2002). Socialeconomic inequalities are defined as "differences in the prevalence or incidence of health problems between individual people of higher or lower socioeconomic status" (World Health Organization, 2013). Commission on Social Determinants of Health of the World Health Organization (WHO) has singled out 10 determinants of health important for injustice in health: social gradient, stress, early life, social exclusion, employment, unemployment, social support, addiction, food, and transport (World Health Organization, 2008). Socialeconomic inequalities are usually measured by income, education, and occupation (Mackenbach et al., 2008; World Health Organization, 2010).

Strong associations between health and socioeconomic determinants have been documented in many studies (Mackenbach et al., 2008; Kaikkonen et al., 2009; Mackenbach, 2012). Considerable evidence suggests that lower socioeconomic status are associated with a poor self-perceived health, higher prevalence of chronic diseases (Radovanović et al., 2011; Lazic et al., 2012), and injuries, unhealthy behaviors such as smoking, inadequate diet, alcohol use (Jovanovic and Jakovljevic, 2011), and lack of physical exercise (De Looper and Lafortune, 2009; Dorjdagva et al., 2015). People of lower SES can expect to live less years in good health, have higher rates of mortality and die at younger ages (Mackenbach, 2012).

Socioeconomic inequalities are measured by various indicators of health such as life expectancy (Jakovljevic et al., 2015c), incidence of various diseases (Jakovljevic and Milovanovic, 2015), mortality, and self-assessment of health (Vuković et al., 2012). Self-assessment of health is one of the most commonly used health indicators recommended by WHO and European Union Commission (Janković et al., 2012). Self-assessed health is a commonly used measure of health status that asks individuals to rate their general health on five-point Likert scale with with five possible answers: very good; good; fair; bad; or very bad. The measure provides a valid and reliable assessment of overall health status, and has been found to be predictive of future health outcomes when used in

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national population health surveys (Park et al., 2015; Jakovljevic et al., 2016c). Also, it was found that the self-assessment of health is one of the important predictors of mortality, morbidity, functional limitations, and health care use in the population (Burström and Fredlund, 2001; Müters et al., 2005).

Comparative study of 22 European countries indicating that in almost all countries the prevalence of poorer self-assessments of health were significantly higher in groups of lower socioeconomic status (Mackenbach et al., 2008). People with lower level of education or income and unemployed persons are more likely to have poor self-assessed health (McFadden et al., 2008).

Despite the global wealth (Jakovljevic, 2016) and application of the best evidence-based interventions, socioeconomic inequalities in health are important, and ongoing public health problem in all European countries (Jakovljevic et al., 2016a) and a major challenge for the enactment and implementation of health policy (Jakovljevic, 2014). In Serbia, as in many countries in transition, socioeconomic inequalities in health have not been sufficiently studied, neither they receive due attention in public health policies (Jakovljevic et al., 2016b).

THE DATA REPORT METHODS

Public Data Set Description—Serbian 2013 National Health Survey

Data belonging to the 2013 National Health Survey for Serbia were observed (Results of the National Health Survey of the Republic of Serbia, 2013).These data were acquired using a cross-sectional studies on a representative probability sample of adult citizens aged 15 years or more (excluding Kosovo). The survey was conducted in accordance with the methodology and instruments of the European Health Interview Survey wave 2 (EHIS-wave 2). It was implemented by the Ministry of Health of the Republic of Serbia.

The sample consisted of all households listed by all enumeration areas of Census 2013. The mechanism used to generate a random sample of households and respondents is a combination of two sampling techniques: stratification and multi-stage sampling. Two-stage stratified sample of the population of Republic of Serbia was selected so as to provide a statistically reliable estimate of indicators that indicate the health of the population at the national level. As the main strata in the sample four geographic regions were identified: Vojvodina, Belgrade, Šumadija and Western Serbia, South-East Serbia. Their further division into urban and rural areas obtained a total of eight strata. The units of the first stage consisted of a total of 670 enumeration areas. The units of the second stage were households. Within each enumeration area 10 households were chosen (plus three backup households). Households were selected by means of linear sampling method of start and equal step of choice. In this way, households were selected with equal probability of selection and without repetition.

Survey Data Description

Out of total 10,089 households contacted, 6500 of them agreed to participate in the survey, so that the response rate of households is 64.4%. Of the total of 16,474 registered household members aged 15 years and over 14,623 of them agreed to be interviewed, giving a response rate of 88.9%. Of this number of people who agreed to be interviewed, 13,756 of them accepted to fill in the questionnaire (response rate 94.1%). For the purposes of this study, the data on the adult population aged 15 years and over were used.

Data on demographic and socio-economic characteristics of the respondents and their own health assessment was obtained through a face-to-face interview carried out at home, while information at the level of the household was obtained by means of a household questionnaire. The questions were validated instruments based on the standard questionnaires from similar types of surveys were. Fieldwork was conducted in the period from 7 October to 30 December 2013, and for the purposes of the research 68 teams were formed. Each team consisted of two interviewers and one health worker. All respondents were informed about the purpose of the study and agreed to participate. Ethical Standards in Health study are in compliance with the international (World Medical Association Declaration of Helsinki) and the specific legislation of our country.

Of the independent variables, the researchers used demographic characteristics (age, gender, type of settlement, and marital status) and socioeconomic status (education, employment, and well-being index). Age of respondents was categorized into age groups of ten years: 20–29 years, 30–39 years etc. Gender is coded as male and female, place of residence as urban and rural, while the marital status was categorized as marriage or common law marriage and not married, divorced or widowed. Variables that reflect the socio-economic situation are education, which is designated as higher, secondary, and elementary, employment status as employed and unemplyed and household well-being index, according to which the population of Serbia, for the purposes of this paper, was classified into three socio-economic categories: rich class, middle class, and poor class.

A self-perceived health was used as the dependent variable and measured through a single question: "How do you regard your health in general?" Available responses were: very good, good, fair, poor, and very poor. For the present analysis, these responses were dichotomised into good (very good, good) and poor (fair, bad, very bad) health.

The data set has been submitted in a public repository Figshare and it is a available on: https://figshare.com/s/cfb6a5a0ef28427c0cdd. Data has been uploaded as Excel file while questionnaires are in PDF formats. Readers are free to access and reuse these publicly available data at the links provided above.

Core Socioeconomic Inequalities in the Country

There were more women (54%) than men (46%) in the sample. The highest percentage of respondents of both sexes belonged to the age group of 55–64 years. In the age group over 65 years there were more women. Slightly more than two-thirds of the respondents lived in a marriage or common-law marriage

(69.3%). The highest percentage of respondents of both sexes has completed secondary education (60.8 and 48.6%), while there is the least of those who have higher education (17.4%). Among women there are significantly more of those who have completed elementary school or lower education (35.6%). In relation to the employment status the highest percentage belongs to the group of inactive population (59.4%). More than half of the respondents live in urban areas (55.3%). When it comes to well-being index, the largest percentage of respondents of both sexes belongs to the middle class (60.1%), followed by those who belong to the poor class (22.5%), and the rich class (17.4%). Distribution of health self-assessment of respondents by gender, age, marital status, type of settlement, education, employment status, and well-being index is shown in **Table 1**.

Women more often evaluated their health as poor (22.0%) compared to men (14.6%). The age of respondent was inversely proportional to good health, the smallest percentage of respondents with poor health is among the youngest (1.0%), while there are most of those who rated their health as poor in the oldest age group over 85 years (49.5%). The difference of mean values of completed years between patients with poor and good health was statistically significant ($p < 0.0005$). The mean value of the number of years of the respondents with poor health was 65.58 ± 12.80 and with good 48.63 ± 16.86. Respondents living in marriage or common-law in a small percentage rated their health as poor (17.3%) as compared to those who do not have a partner (21.3%). Respondents living in rural areas were more likely to assess their health as poor compared to those who live in the city. The proportion of respondents with elementary education or less who assessed their health as poor (36.5%) is three times higher than in those with secondary education (12.1%) and four times higher than those with associated and higher education (8.3%). When it comes to employment status, the unemployed are five times more likely to assess their health as poor (25.5%) compared to employed (4.9%). A similar pattern was observed when it comes to the well-being index, i.e., Members of the poor class are three and a half times more likely to assess their health as poor (30.3%) compared to those who belong to the rich class (8.4%). Significant differences were observed between gender and all independent variables.

The results of bivariate and multivariate logistic regression for self-assessment of health as poor show that poor health is affected by age, gender, marital status, employment status, education, and well-being index (**Table 2**).

With the aging, the number of respondents who assessed their health as poor increased. Odds ratio for the age is 1.058 (1.053–1.062), which means that each year more increases the risk of poor-health 5.8%. Women have 40.9% higher risk of poor health compared to men. Odds ratio for females is ($OR = 1.409$). Employees have about two times lower risk of poor-health in relation to the unemployed ($OR = 0.557$). The proportion of respondents who assessed their health as poor is inversely proportional to the level of education. Respondents with lower education are two and a half times more likely to assess their health as poor ($OR = 2.314$) compared to those with higher education. The same pattern was seen for the well-being index. Members of the poor and middle class more often evaluated their health as poor ($OR = 1.544$ and OR $= 1.311$) compared with those who belong to a rich layer of the population.

Comparison with Contemporary Momentum Elsewhere Throughout Europe

At the start of the 21st century, large differences in health still exist between and within all European countries, and some of these inequalities are widening (Mackenbach et al., 2007). Within EU countries, reported poor health among the population as a whole is most prevalent in Eastern European countries (Hungary, the Czech and Slovak Republics, Poland) (Mackenbach et al., 2008). Inequalities within countries between low and high income groups also exist in Western Europe (Iceland, Ireland, and the United Kingdom), but the proportion of persons reporting poorer health is low. The practice of unhealthy lifestyles, associated with a lack of information about health and healthy behavior, can contribute to poor health in Eastern Europe (Steptoe and Wardle, 2001). Differences in health status between East and West could be partly explained by differences in behavior related to health (smoking and alcohol consumption (Jakovljevic et al., 2013) and psychological factors (Laaksonen et al., 2001).

Substantial socioeconomic inequalities in self-assessed poor exist in Serbia (Jakovljevic et al., 2011). The results showed that there are significant differences in self-assessment of health, depending on the demographic and socio-economic variables (Jakovljevic et al., 2015b).

There is a positive correlation between age and health status of the population (Jakovljevic et al., 2015a). The older the respondents, the more they assess their health as poorer (Jakovljevic and Laaser, 2015). Women tended to report significantly worse health than men. For example, in the Ukraine the adjusted odds of women reporting their health as poor was 3.58 (Gilmore et al., 2002). Only in Estonia was no gender differential found in self-assessed health (Leinsalu, 2002). These findings are repeated in many studies that talk about the poorer health of women and the elderly (Szwarcwald et al., 2005; Espelt et al., 2008; Pappa et al., 2009). These findings could be explained by the fact that women have higher awareness of health issues and symptoms of the disease compared to men. The impact of place of residence on health varied by gender. In the Ukraine living in a village increased the risk of ill-health in women, but was not significantly associated with ill-health in men (Gilmore et al., 2002), whilst in Latvia rural men had a higher risk of ill-health, but place of residence was not a significant variable for women (Monden, 2002).

Education is one of the most important predictor of self-assessed health. In Baltic (Monden, 2005), as well as in many other European countries (Pikhart et al., 2001; Balabanova and McKee, 2002), people with a higher level of education in higher percentage assess their health as good. In Estonia, the risk of poor self-reported health amongst women with less than secondary education was 3.88 times higher than those with a university education, and for men the odds ratio was 2.32 (Leinsalu, 2002). These inequalities in health self-assessment could be explained by the fact that people with higher levels of education have

TABLE 1 | Distribution of individuals' self-assessed health according to demographic and socioeconomic characteristics.

Variables		Good health		Poor health		*p*
		N	%	N	%	
TOTAL NUMBER OF RESPONDENTS						
Age	20–24	855	99.0	9	1.0	<0.0005
	25–34	1918	97.9	42	2.1	
	35–44	2080	95.2	106	4.8	
	45–54	2006	86.3	318	13.7	
	55–64	2215	76.9	664	23.1	
	65–74	1269	64.9	685	35.1	
	75–84	753	54.4	632	45.6	
	85+	101	50.5	99	49.5	
Gender	Female	5800	78.0	1632	22.0	<0.0005
	Male	5397	85.4	923	14.6	
Marital status	Has a partner	7446	82.7	1556	17.3	<0.0005
	Has no partner	3751	78.7	1013	21.3	
Employment status	Employment	4295	95.1	221	4.9	<0.0005
	Unemployment	6902	74.7	2334	25.5	
Place of residence	Urban	6549	84.5	1200	15.5	<0.0005
	Rural	4648	77.4	1355	22.6	
Education	Elementary education	2549	63.5	1463	35.5	<0.0005
	Secondary education	6544	87.9	901	12.1	
	Associated and Higher education	2104	91.7	191	8.3	
Well-being index	Rich class	2160	19.3	938	36.5	<0.0005
	Poor class	6839	61.1	1428	55.6	<0.0005
	Middle class	2198	19.6	202	7.9	<0.0005

TABLE 2 | Odds ratios (OR) and 95% confidence intervals (CI) for poor self-assessed health depending on demographics and socioeconomic characteristics.

Variables		N	%	Binary logistic regression		*P*
				Univariate	Multivariate	
Age				1.070 (1.066–1.073)	1.058 (1.053–1.062)	<0.0005
Gender	Male	6328	46.0	1.00	1.00	
	Female	7437	54.0	1.645 (1.505–1.798)	1.409 (1.256–1.580)	<0.0005
Marital status	Has a partner	4764	34.6	1.00		
	Has no partner	9001	65.4	0.771 (0.705–0.842)	1.014 (0.899–1.145)	
Employment status	Employment	9244	67.2	1.0	1.0	
	Unemployment	4521	32.8	0.152 (0.132–0.176)	0.557 (0.466–0.666)	<0.0005
Education	Associated and higher education	2296	29.1	1.0	1.0	
	Elementary education	4012	29.1	6.322 (5.380.7.4309	2.314 (1.856–2.887)	<0.0005
	Secondary education	7457	54.2	1.517 (1.288–1.786)	1.515 (1.234–1.859)	<0.0005
Well-being index	Rich class	2400	17.4	1.0	1.0	
	Poor class	3098	22.5	4.767 (4.047–5.616)	1.544 (1.223–1.949)	<0.0005
	Middle class	8267	60.1	2.279 (1.950–2.662)	1.311 (1.063–1.616)	0.011

more skills in coping with everyday life problems that could negatively affect their health as well as in overcoming them (Pappa et al., 2009). Poor and less educated people have fewer financial resources to solve their health problems, and despite higher morbidity and mortality, they less use health care services (Jakovljevic et al., 2014), and for some of them they have to pay proportionately more, compared to their income than the rich (Gwatkin et al., 2003).

Several studies reported that unemployed and economic inactive persons were more likely to report poor self-perceived health than employed persons (Monden, 2002; Molarius et al., 2007). Unemployed and their families have increased risk of poorer outcomes for health. Health effects begin already when people feel that their employment is uncertain. As the uncertainty grows, it increasingly acts as a chronic stressor whose effects increase with the length of exposure.

Reducing socio-economic inequality is one of the leading challenges for the adoption and implementation of health policies in many countries (Jakovljevic, 2013). The UN's Millennium Development Goals focused on poverty and development and reducing inequalities between countries (United Nations Millennium Development Goals, 2015). New European Policy for Health—"Health 2020" as one of the main objectives highlights improving health while reducing health inequalities (World Health Organization, 2013). The post-2015 era presents an opportunity for WHO and its partners to strengthen health inequality monitoring across all health topics at global, national and subnational levels. Improving health and reducing inequalities in health must be a common goal for all sectors of society (government and non-government sectors, organizations and institutions at national, regional, and local levels), which is the only feasible through joint integrated policies, strategies, and programs (Stahl et al., 2006).

CONCLUSIVE REMARKS

The elderly, females, with a lower level of education, unemployed, and belonging to the lower socio-economic class, have poorer health. Socio-economic inequalities in health are a major challenge for health policy, not only because they represent social injustice but also because solving health problems of underprivileged groups of the population can influence the improvement of the health status of the population as a whole.

AUTHOR CONTRIBUTIONS

All authors listed, have made substantial, direct and intellectual contribution to the work, and approved it for publication. SR and MJ developed research questions, designed the study, and prepared manuscript for this Data report. SK participated in the presentation and interpretation of the results, reviewing of the manuscript.

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Socioeconomic Factors Associated with Psychoactive Substance Abuse by Adolescents in Serbia

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PSYCHOACTIVE SUBSTANCE ABUSE IN ADOLESCENCY

Adolescence is a period of transition from childhood to adulthood, characterized by efforts to achieve the objectives related to the expectations of the culture, as well as the requirements of the physical, mental, emotional, and social development. It has its own characteristics in the biological, psychological, and social terms, with a process of identity formation, the development of social, and moral norms of behavior (McCabe et al., 2017). Adolescence is a period of great settings in which experimentation with psychoactive substances is common and can, in some cases, lead to the development of long-term addictive behavior (Jeannin et al., 2013). Psychoactive substances include licit, illicit, and prescribed psychoactive medications. Alcohol and cigarette are among the licit and controlled drugs, while marijuana, cocaine, heroin, lysergic diethylamide (LSD), crack, and ecstasy are illicit drugs (Kassa et al., 2014). The use of psychoactive substances in adolescents is often associated with a socioeconomic factors, such as gender, age, type, race, ethnicity, family, and social structures, socioeconomic status of the family (Gebreslassie et al., 2013).

Significant risk factors for psychoactive substances use among adolescents were poor parental involvement in the child's education, conflictual family relationships, and drug abuse by the parents, friends, and neighbors (Kpozehouen et al., 2015; Pisarska et al., 2016). Also, parental alcoholism, parental divorce before age 18, and parental death before age 18 increased the odds of abuse psychoactive substances (Vaughan et al., 2017).

Socioeconomic environment in which young people were raised as children predicts their behavior in young adulthood. Understanding this relationship, is an important step in identifying persons at risk (Tobler et al., 2000). In order to identify the risk factors and protective factors associated with psychoactive substances abuse among young people, it is very important to measure how socioeconomic factors influence the attitudes and behavior of young toward the use of psychoactive substances (Carter et al., 2010; Patrick et al., 2012).

THE DATA REPORT METHODS

Public Data Set Description—Serbian 2013 National Health Survey

The study of health of population in Serbia conducted in 2013 was the source of used data. This was the third national population health survey conducted by the Ministry of Health of the Republic

of Serbia[1]. In the third Survey, a harmonization of research tools (methodology, questionnaires, instructions) with the instruments of the European Health Survey second wave (EHIS wave 2)[2] was carried out in order to achieve the highest degree of comparability of results with the countries members of the European Union, according to a defined, internationally accepted indicators (ECHI, OMC, WHO, UNGASS, MD).

Fieldwork was conducted in the period from 7 October to 30 December 2013, which respected the legislation relating to the European Health Research—second cycle: the collection of data in the field should take at least 3 months of which at least 1 month should be in the period from September to December, or in the fall. In order to achieve a high level of quality of the collected data, to provide a high response rate of households and in order to protect the representativeness of the sample, the election, and training of interviewers had been organized prior to the commencement of field work, and also guidelines for the monitoring and control of field work were given to them.

The study used the most complete population register that includes a sampling units defined within the target population—Census of Population, Households, and Dwellings in the Republic of Serbia conducted in 2011. In accordance with the recommendations for the implementation of population health research EUROSTAT, the European Health Research—Second Wave—Methodological guide (EHIS wave 2, Methodological manual) the National representative probability sample was used: two-stage stratified sample with a known probability of selection of sample units at every stage sampling. The sample was drawn so as to provide a statistically reliable estimation of a great number of indicators of population health condition at the national level, considering geographic areas/statistical regions of Belgrade, Vojvodina, Sumadija, Western, Southern, and Eastern Serbia, and at the level of urban and other settlements/areas. The mechanisms that have been used to obtain a random sample of households and respondents represent a combination of the two sampling techniques: stratification and multi-stage sampling.

Health Survey of the Serbian population was carried out through interviews, anthropometric measurements, and blood pressure measurements. Three types of questionnaires were used in the survey: Questionnaire for Household—collecting information on all household members, the characteristics of the household, as well as on the characteristics of the household residence. The questionnaire had to be completed in the course of verbal communication between the interviewers and interviewees who represented the main person in the household to answer questions of interest. The questionnaire "face to face" is to be filled in with each member of the household. Self-administered questionnaire which should be filled in by each household member aged 15 and over without the participation of the interviewer.

This type of questionnaire was used because it was estimated that the questions concerning sensitive items of alcohol use, sexual behavior, and so on were not suitable for filling by method "face to face." In order to complete the questionnaires a method of computer-assisted personal interviewing—CAPI was used as well as the process of interviewing through paper-and-pencil procedures—PAPI for self-administered questionnaire.

Ethical Standards in Health Research were harmonized with the international World Medical Association Declaration of Helsinki. This study was approved by the competent territorial Ethics Committee of the four major regions of Serbia, based in the Republic Institute of Public Health Batut in Belgrade, Institute of Public Health Novi Sad, Kragujevac and Nis.

In order to respect the privacy of the subjects of research and confidentiality of information collected, all necessary steps were taken in accordance with the Law on Personal Data Protection (Off. Gazette of RS No 97/08, 104/09)[3]. Field researchers were required to give a printed document that informed research participants about the Research (Notice of Survey signed by the Minister of Health) and the approval of the Ethics Committee on its implementation, on the rights of patients, and about where and how they can submit complaint/grievance if estimate that their rights have been in any way compromised. Also, interviewers needed to obtain the signed informative consent of each of the participants for accepting to participate in the survey. In research, the collection of data that identify the respondents was avoided to the greatest possible extent (necessary identifiers were removed at the earliest stage of statistical analysis and replaced with code).

Survey Data Description

In the Serbian National Health Survey 2013, a total of 6,500 households and 13,756 participants aged 15 and over were interviewed. Out of total of 10,089 households contacted, 6,500 of them agreed to participate in the survey, so that the response rate of households was 64.4%. Out of total of 16,474 registered household members aged 15 and over, 14,623 of them agreed to be interviewed, giving a response rate of 88.9%. Out of this number of people who agreed to be interviewed, 13,756 of them accepted to complete the self-administered questionnaire (response rate 94.1%). For the purposes of this study, we analyzed data on respondents aged 15–24 years (1,722 interviewed respondents).

Of the independent variables, the researchers used demographic characteristics (age, gender, type of settlement, region) and socioeconomic status (education, employment, and well-being index). Participants' age was categorized in to two age groups (15–19 years; 20–24 years). Gender is coded as male and female, place of residence as urban and rural, regions of Belgrade, Vojvodina, Sumadija, Western, Southern, and Eastern Serbia. Variables that reflect the socioeconomic situation are education, which is designated as higher, secondary, and elementary, employment status as employed and unemployed and household. The Wealth Index is based on household assets

[1]Institute of Public Health of Serbia "Dr Milan Jovanović Batut." Results of the National Health Survey of the Republic of Serbia 2013. Available online at: http://www.batut.org.rs/download/publikacije/2013SerbiaHealthSurvey.pdf

[2]European Health Interview Survey (EHIS wave 2) Methodological manual 2013. Available online at: http://ec.europa.eu/eurostat/documents/3859598/5926729/KS-RA-13-

[3]Law on Personal Data Protection Off. Gazette of RS No 97/08. Available online at: http://www.paragraf.rs/propisi/zakon_o_zastiti_podataka_o_licnosti.html

and housing characteristics, such as the possession of color TV set, cell phone, refrigerator, dish washer, washing machine, PC, AC, car, construction material of floors, roofs and walls, the number of bedrooms per household member, type of drinking water resources, and sanitation facility as well as heating fuel and Internet access. Based on the Wealth Index, households were classified into five groups of equal size—quintiles: (1) the poorest (Q1), (2) poorer (Q2), (3) middle (Q3), (4) richer (Q4), and (5) the richest (Q5). For the purposes of this paper, respondents were classified into three socio-economic categories: poor class, middle class, and rich class. As the dependent variable in this analysis were used: cigarette smoking (daily and occasional), alcohol abuse, and abuse of other psychoactive substances (drugs and illicit drugs).

The data set has been submitted in a public repository Figshare and it is available on: https://figshare.com/s/f55d3b9213f41fe79827. Data has been uploaded as Excel file while questionnaires are in PDF formats. Readers can retrieve and reuse publicly available information by visiting links given above.

DESCRIPTION OF NATIONAL SURVEY OUTCOMES

A total of 1,722 participants aged 15–24 years (Mean = 19, *SE* = 2.1 years) were included in the study. There were 51% women in the sample. The highest percentage of respondents has completed secondary education (55.9%), while there is the least of those who have high education (4.6%). In relation to the employment status the highest percentage belongs to the group of inactive or unemployment population (87.6%). More than half of the respondents live in urban areas (55.5%). When it comes to well-being index, the largest percentage of respondents belongs to the rich class (42.4%) followed by those who belong to the poor class (38%) and the middle class (19.6%).

The study depicted that in the past 12 months of the study period 72.9% smoked cigarettes (daily and occasional), 56.5% used alcohol, and 24.2% abused drugs. The prevalence of illicit psychoactive substances such as cannabis, ecstasy, LSD, cocaine, crack, heroin was 0.8%.

Binary logistic regression analysis has not shown a statistically significant impact of examined factors on the prevalence of cigarettes smoking. The only factor that is associated with the consumption of cigarettes is self-assessment of health, respondents who evaluate their health as good for 30% less often smokers than in those who evaluate their health as poor (*OR* = 0.700). Results of binary logistic regression showed that alcohol consumption can be determined by age, gender, education, type of settlement, well-being index physical, and psychological violence. The prevalence of alcohol consumption in men is 55.2%, whereas men are 1.8 times more likely to use alcohol than women (*OR* = 1.882). Compared to the younger population (15–19 years) members of the 20–24 age group are more likely to consume alcohol (*OR* = 0.508). Respondents with higher education have 55.3% greater chance of alcohol consumption compared to those with low education (*OR* = 0.477). Young people who live in urban areas are 1.8 times more likely to consume alcohol in relation to those who live in rural areas (*OR* = 1.843). Members of poor class for 33.9% less consume alcohol (*OR* = 0.661) compared with those who belong to the rich class of the population. Young people who are exposed to physical violence (*OR* = 6.702) and the physical (*OR* = 5.026) and mental bully (*OR* = 3.405), significantly more frequent alcohol consumption.

As the most important predictors of use of drugs/ illicit drugs were found to be gender and self-assessed health. Men 88% less likely to use drugs and illicit drugs than women (*OR* = 0.120). Also those who assess their health as good to make less frequently by 56.9% compared to those who assess their health as poor (*OR* = 0.431; **Table 1**).

COMPARISON WITH PUBLISHED EVIDENCE

Psychoactive substances abuse represents a significant problem of the individual, family, and society, leaving a lot of effects on mental and physical health (Milovanovic et al., 2016), family relationships, work ability, and social activities (Jovanovic and Jakovljevic, 2015). There are also significant costs borne by society due to the direct and indirect consequences of abuse and dependence on certain substances (Jakovljevic et al., 2014). Drug abuse is a global problem, and methods of use and consequences of individual and socio-cultural are specific. The consequences of the abuse of substances may be various: education and unemployment, reduced work productivity, poor health, higher rates of human immunodeficiency-HIV and hepatitis B, C infections (Jakovljevic et al., 2013a), social dysfunction, higher rate of violence, poverty, homelessness, a lower probability of recovery, poor treatment outcomes, and poor quality of life (Jakovljevic et al., 2013b). According to the World Health Organization, alcohol, and tobacco are the most commonly abused substances (World Health Organization, 2013, 2014). Eastern Europe and the Balkans region report the high rates of alcohol abuse (Jovanovic and Jakovljevic, 2011). Alcohol abuse is a health problem that significantly contributes to the global disability (liver-diseases, cardiovascular diseases, traffic accidents, fights, murders, suicides; Jakovljevic et al., 2015a), but also it is an economic problem (absenteeism, unemployment, reduced productivity, long-term treatment) (Jakovljevic et al., 2011). Psychoactive substances present a great challenge of public health issue worldwide particularly regarding to the social vulnerable population of adolescents (Jakovljevic et al., 2015b).

According to the results of the 2013 Serbian National Health Survey, distribution of smoking in adults population was 35.8%, daily using alcohol was 4.7%, while using of sedative, for sleeping and analgetics was 61.4%. Illegal drugs were used by less of 1% adults[1]. Aforementioned dataset showed that there are significant differences in the abuse of psychoactive substances among young people in Serbia, depending on the demographic and socioeconomic characteristics of the respondents. They are consistent with the findings of other studies that show that there

TABLE 1 | Bivariate logistic regression analysis showing socioeconomic correlates of psychoactive substance abuse by adolescents in Serbia.

Variables	Cigarette smoking		Alcohol use		Drugs/Illegal drugs abuse	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Gender[a]	0.900 (0.594–1.364)	$p = 0.620$	1.882 (1.535–2.306)	$p < 0.001$	0.120 (0.032–0.442)	$p < 0.001$
Age (years)	0.954 (0.621–1.467)	$p = 0.832$	0.508 (0.415–0.623)	$p < 0.001$	1.244 (0.400–3.867)	$p = 0.707$
Education[b]	1.185 (0.806–1.742)	$p = 0.389$	0.477 (0.396–0.574)	$p < 0.001$	0.867 (0.331–2.271)	$p = 0.771$
Emplyment status[c]	1.227 (0.701–2.148)	$p = 0.473$	1.335 (0.979–1.821)	$p = 0.068$	1.954 (0.249–15.320)	$p = 0.524$
Type of settlement[d]	0.940 (0.616–1.433)	$p = 0.773$	1.843 (1.504–2.258)	$p < 0.001$	0.686 (0.208–2.265)	$p = 0.536$
Well-being index[e]	1.222 (0.962–1.552)	$p = 0.101$	0.661 (0.580–0.752)	$p < 0.001$	1.013 (0.544–1.883)	$p = 0.969$
Self-assessed health[f]	0.700 (0.501–0.978)	$p < 0.05$	0.864 (0.734–1.017)	$p = 0.079$	0.431 (0.149–1.248)	$p < 0.05$
Exposure to physical violence (in the family, in school, on the street)	1.964 (0.674–5.772)	$p = 0.216$	6.702 (2.869–15.656)	$p < 0.001$	0.334 (0.069–1.612)	$p = 0.172$
Exposure to psychological violence (in the family, in school, on the street)	0.722 (0.225–2.316)	$p = 0.584$	2.210 (0.990–4.932)	$p = 0.053$	0.447 (0.054–3.693)	$p = 0.455$
The tendency to psychological violence	1.966 (0.814–4.751)	$p = 0.133$	3.405 (2.052–5.651)	$p < 0.001$	0.366 (0.094–1.430)	$p = 0.148$
The tendency to physical violence	0.937 (0.475–1.850)	$p = 0.851$	5.026 (2.839–8.896)	$p < 0.001$	0.280 (0.072–1.087)	$p = 0.066$
Risky sexual behavior	0.873 (0.546–0.873)	$p = 0.572$	1.383 (1.016–1.882)	$p < 0.05$	1.211 (0.322–4.563)	$p = 0.777$

[a] *Reference values for women.*
[b] *Reference values for low education.*
[c] *Reference values for employment.*
[d] *Reference values for urban.*
[e] *Reference values for poor class.*
[f] *Reference values for poor self-perceived health.*

is no difference between the sexes for cigarette smoking and experimentation with drugs. It is more connected with young men. Young people of lower age groups and those who attend the school are negatively associated with the abuse of cigarette, alcohol, and illicit drugs (Patrick et al., 2012; Malta et al., 2014).

Other studies have shown that young people with low levels of education are regarded as high risk for consumption psychoactive substances (Quek et al., 2013). Anxiety, low self-esteem, and self-control, as well as the low level of parental control also poses a risk for abuse belt (Roy et al., 2015). Characteristics of mental health, such as loneliness and insomnia are positively associated with the abuse of tobacco, alcohol, and illicit drugs. The lack of a friend is a positive correlation with the abuse of tobacco, and illicit drugs, and the negative with the abuse of alcohol (Malta et al., 2014). Also young people who abuse psychoactive substances, are more likely to have higher levels of psychological stress and decreased levels of self-efficacy to resist peer pressure (Champion et al., 2016). Other studies have in turn shown that the lower the level of education of parents associated with a higher risk of psychoactive substances abuse (Johnston et al., 2011), while the characteristics of the family in the sense that they live with their parents and have a parental control (when parents know what the child is doing in his spare time) negatively associated with such a high-risk behavior (Malta et al., 2014). Heavy episodic drinking are frequent among young people who live in incomplete families (Patrick et al., 2012).

Some studies have shown that there is no significant difference in substance abuse between urban and rural areas, but there is the presence of higher levels of knowledge about the psychoactive substances in urban areas (Martinotti et al., 2015). Other studies show that adolescents who live in urban areas significantly more abuse the psychoactive substances in relation to their peers who live in rural areas (Pawłowska et al., 2014).

Many studies that have investigated the correlation of demographic and socioeconomic variables with the abuse of psychoactive substances have shown that high degree of religiosity, higher parent's education living with one or both parents reduces the chance to abuse, while high the socioeconomic status of the family increases the likelihood of psychoactive substances use (Goodman and Huang, 2002; Hanson and Chen, 2007; Schoenborn and Adams, 2010). Children who come from wealthier families with higher socioeconomic status may be at increased risk for the abuse psychoactive substances which can be explained by the fact that their experience more pressure achievement combined with isolation of parents who have careers more demanding. In addition, parents with higher socioeconomic status in comparison with those in the lower socioeconomic status families can have positions that are tolerant of the substance abuse (Luthar and Goldstein, 2008). The higher income families may be related to the use of psychoactive substances because of increased access to, or to buy the substance and have a social association with others who also have financial resources. On the other hand, a lower revenue may be associated with the abuse of psychoactive substances such mechanism of survival due to increased stress and less access to alternative actions that can be a focal point for preventive strategies (Goodman and Huang, 2002). Despite worldwide concern and education

about psychoactive substances, many adolescents have limited awareness of their adverse consequences (Oshodi et al., 2010).

CONCLUSIVE REMARKS

Preventive activities should be carried out through the development of specific programs to promote healthy lifestyles, strengthening the implementation of existing programs, and the promotion of prevention through various forms of educational activities, including peer education, supporting youth initiatives for the implementation of actions aimed at the affirmation of healthy lifestyles, develop social skills, informing young people, and parents about the risks of consuming psychoactive substances through school programs and workshops in schools, identification, and reduction of risk factors in the school environment.

In perceiving the frequency of using illegal drugs, it should take in mind specific limited researches of health in national population, because the drugs abuse, as social non acceptable behavior endanger sincerity of patients during answering these questions.

AUTHOR CONTRIBUTIONS

All authors listed, have made substantial, direct and intellectual contribution to the work and approved it for publication. KJ and SMR drafted the manuscript. SRR, SK, and MJ contributed through data analysis and interpretation.

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Socio-Economic Inequalities, Out-of-Pocket Payment and Consumers' Satisfaction with Primary Health Care: Data from the National Adult Consumers' Satisfaction Survey in Serbia 2009–2015

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CONSUMERS' SATISFACTION AND HEALTH CARE QUALITY

For over 30 years, a movement for putting primary health care (PHC) in the driver's seat of the health care system has aimed at promoting values such as equity, patient-centeredness, community participation and self-determination (Saltman et al., 2006). While at the beginning these values were considered radical, they are now widely accepted in health care (World Health Organization, 2008). This paradigm shift becomes also obvious when WHO adopted Millennium Development Goals, whose achievements were most thoroughly studied by the Global Burden of Disease Project (Lim et al., 2016). As was shown by different authors, the efficiency of PHC depends primarily on factors, such as the historical background, the occurrence of health problems, the characteristics of the health system as well as the social features of consumers (Ros et al., 2000; Walshe and Freeman, 2002).

One of the characteristics of a good health care system is its capability to satisfy consumers' needs (Sándor et al., 2016). Unmet health care needs depend primarily on consumers' socio-demographic characteristics, their experience with health care services, the quality of the offered health care and the level of consumers' health literacy (Chaupain-Guillot and Guillot, 2015). The main reasons for unmet heath care needs are cost, distance, waiting lists, the lack of cultural sensitivities and discrimination (Eurostat, 2016). In the EU-28, the most common reason, affecting about one third of all reported cases and involving 2.4% of the population, for not having a medical examination or treatment were excessive high costs (Eurostat, 2016).

Satisfaction of customers/patients does not only map positive assessment to the different dimensions of health care (Linder-Pelz, 1982), but also represents an important quality indicator (Donabedian, 2003). Patients' satisfaction is regarded as a crucial issue with respect to the creation of a high quality, safe and effective health care system (Tucker, 2002; National Health Service Corporation, 2010; Hinchcliff et al., 2014). Satisfied patients are more willing to undergo recommended therapies, thus entailing better health outcomes including a lower mortality rate (Chue, 2006; Glickman et al., 2010).

Patients' satisfaction includes on the one hand the nature of the first contact with the health system *per se* and on the other hand the staff's interaction with patients (National Health Service Corporation, 2010). Apart from the strong relationship between patients' satisfaction and the structure and processes of the health care system (Rademakers et al., 2011), socio-demographic characteristics have also a significant influence on patients' satisfaction with respect to health care (Rahmqvist and Bara, 2010). Female and older patients, patients with a high school or university diploma or patients with a very good perceived household well-being (HWB) were more likely to be satisfied with health care than other patients (Kontopantelis et al., 2010; Davey et al., 2013).

Great efforts were undertaken in the past with respect to the development of instruments for measuring patients' satisfaction (Garratt et al., 2008). In Serbia, policy makers established the mechanisms for a sustainable continuous improvement of the health care system (Simic et al., 2010) including the continuing education of the general practitioners (GPs) (Santric Milicevic et al., 2011), the supply of drugs (Jakovljevic et al., 2015) and financing (Simic et al., 2010). In addition, the Serbian managers were educated how to apply knowledge to utilize the results for further quality improvement (Terzic Supic et al., 2010; Santric Milicevic et al., 2011).

POPULATION DEVELOPMENT AND HEALTH CARE EXPENDITURE IN SERBIA 2009–2015

Between 2009 and 2015, the population of Serbia decreased from 7,321,000 to 7,095,000, i.e., about 220,000 or 3.1%. In contrast, the proportion of the age group 65+ increased from 17.2 to 18.3% (World Health Organization, 2015).

In this 7-year period the Gross Domestic Product (GDP) enlarged between 2009 and 2013 from $5,821.30 to $6,353.80 per capita, decreased in 2014 to $6,200.17 per capita, only to reach its minimum in 2015 with $5,144.00 per capita. Total health expenditure as a percentage of GDP increased from 9.9% in 2009 to 10.4% in 2014 (the data for 2015 are not yet available), while in the same period public sector expenditures for health as a percentage of GDP varied between 6.1% in 2009 and 6.4% in 2014 (World Health Organization, 2015). A relationship between health expenditures per capita and longevity was revealed for the vast majority of European countries, notwithstanding they are members of the EU or not (Jakovljevic et al., 2016a).

Fenton et al. (2012) reported that higher patients' satisfaction is positive correlated with both total health care expenditure and expenditure on prescribed drugs. In contrast, political interventions with the objective of cost reduction have a negative impact on the perception of all health care professionals with respect to health care quality (Jakovljevic et al., 2016b). As regards the Serbian health care system, it is essential not only to consider the health care expenditure, but also existing socioeconomic inequities (Jankovic and Simic, 2012; Radevic et al., 2016) and the burden of disease (Sipetic et al., 2013).

PRIMARY HEALTH CARE SERVICE IN SERBIA 2009–2015

Public PHC is provided in Serbia on municipality level by PHC centers, which are established in almost all municipalities according to the Ministry of Health of Serbia Decree on the Health Care Institutions Network Plan (Ministry of Health of the Republic of Serbia, 2006). These health care centers provide a wide range of preventive and curative health care for all demographic groups and represent the places of first contact with the public health care system in Serbia (Simic et al., 2010). In Serbia, patients are required to register with one physician of their choice, representing the doctor of first contact with the health care system. The chosen doctor for the adult population is a medical doctor or a general practitioner (GP) specialist.

Health care in Serbia is financed primarily by mandatory contributions to the National Health Insurance Fund, whereby almost one quarter (24.6%) of the entire health budget is spent on PHC. Mandatory health insurance premiums are levied on the salaries of the employees, farmers and self-employed. Another source of financing is out-of-pocket payments for health care services and drugs (participation/official co-payments or full price). Between 2009 and 2015, the out-of-pocket payments as proportion of total health expenditure rose from 35.2 to 36.6% (World Health Organization, 2015). Though official co-payments represent a significant share of out-of-pocket payments in Serbia (Arsenijevic et al., 2014), they are much lower as compared with some neighboring countries (Atanasova et al., 2013). Co-payments for GP visits, specialist visits, diagnostic procedures and drugs are mandatory for all patients, with exceptions for children, pregnant woman, people who suffer from some chronic non-communicable diseases, disabilities, for members of the Roma population etc. (Ministry of Health of the Republic of Serbia, 2005).

Summarizing, it can be said that the Serbian health care policy has changed significantly over the past years toward patient's centeredness and quality improvement (Simic et al., 2010), which is well documented in different government papers (Kosanovic and Andelski, 2015) and by the Health Consumer Index (Health Consumer Powerhouse, 2017).

THE SERBIAN HEALTH CARE CONSUMERS' SATISFACTION SURVEYS BETWEEN 2009 AND 2015

Consumers' satisfaction surveys were conducted from 2009 to 2015 in all public PHCs in Serbia according to the methodology provided by the Institute of Public Health of Serbia "Dr. Milan Jovanovic Batut". The data were collected by using a questionnaire that was designed according to the WHO's recommendation for estimating availability, utilization, coordination and comprehensiveness of a health care system and that was, in addition, adopted with respect to the Serbian PHC system. It referred to socio-demographic characteristics (gender, age, the level of education, perceived HWB), received preventive care counseling, level of satisfaction (with PHC services, GPs,

nurses, equipment), utilization, official co-payments (for GP visits, visits to specialists and drugs) and overall satisfaction with the offered PHC services.

The data for the present study were gathered in the course of cross sectional surveys conducted in 158 PHC centers in Serbia, among adult patients who visited their GPs during the working hours between 7:00 and 20:00. The periods of the studies were the same for all PHC centers. Participation was voluntarily and all respondents were informed about the purpose of the study and they could quit the interview at any time. Anonymity, confidentiality and privacy of data were explained and guaranteed (name, address, phone number or other personal data were not collected). The participants were asked to answer the questions after having visited their GPs. In the period between 2009 and 2015 an overall of 206,088 patients were included in the surveys, thus yielding annual response rates of more than 70%.

In the present study demographic characteristics, such as age or gender, the socioeconomic status comprising education or the perceived HWB, the out-of-pocket payments for visiting GPs and specialists as well as for prescribed drugs were analyzed in combination with the patients' satisfaction with the offered PHC services. For this purpose, the five-grade Likert scale (used to measure consumers' satisfaction) was modified into a three grade version running "satisfied," "neither satisfied nor dissatisfied" and "dissatisfied". Patients' unmet needs were also analyzed in order to find out if necessary visits to a GP were avoided or postponed due to the inability to pay for them.

The data set was uploaded to a public repository *Figshare* and is available at https://figshare.com/s/bb621ab20afb39b611e3. Data were uploaded as an Excel file, the questionnaire as pdf-file.

CONSUMERS' SATISFACTION SURVEYS: DATA ANALYSIS BETWEEN 2009 AND 2015

Socio-Economic Characteristics of the Respondents

Among the respondents, there were more women (55.3%) than men (44.7%). The highest percentage of respondents was in the age class between 50 and 59 (22.2%). The average age was 51.2 ± 15.7, whereby male patients were older (52.1 ± 15.8) than female ones (50.5 ± 15.5). The majority of respondents had attended a secondary school (53.9%), while 6.2% had less than primary school. A statistically significant difference between the levels of education with respect to gender could be observed ($p < 0.05$). Women attended more frequently only a primary school (m: 18.7%, f: 19.5%) or even less (m: 5.5%, f: 6.6%), while men attended more frequently a secondary school (m: 54.8%, f: 53.3%) or had a high school or university diploma (m: 20.9%, f: 20.6%). Most of the respondents, regardless of gender, perceived their HWB as medium (47.4%), while only a minority perceived it as very good (4.4%). There was a statistically significant difference of the perceived HWB with respect to gender ($p < 0.05$). Men categorized their HWB more frequently as bad than women (m: 14.9%, f: 14.0%), very bad (m: 7.0%, f: 6.1%), but also as very good (m: 4.5%, f: 4.3%).

Consumers' Satisfaction with Public Health Care

More than three quarters of the patients (79.0%) were satisfied with public health care. There was a statistically significant difference between the numbers of satisfied patients with respect to the year of the Health Care Consumers' Satisfaction Survey. The largest proportion of satisfied patients was observed in 2010 with 83.1%, while the largest proportion of dissatisfied was found in 2014 with 8.5%. Apart from this, there was a statistically significant difference between the numbers of satisfied patients with PHC services with respect to gender, the education level and the perceived HWB ($p < 0.05$). Female consumers were more satisfied (79.1%) as well as older ones (81.1% for the age group 80+, 80.8% for the age group 60–69). Apart from the two previously mentioned age groups, the most satisfied patients were those with a high school or university diploma (80.0%) and those with a very good perceived HWB (84.9%). In contrast, the group of the most dissatisfied patients comprised the youngest (7.6%), people with an education level less than primary school (9.0%) and with very bad perceived HWB (13.9%). Consumers' satisfaction with PHC services by the year of survey and selected socio-demographic characteristics is shown in **Table 1**.

Out-of-Pocket Payment for Health Services

The majority of respondents (54.5%) did not have to pay for GP visits, but 42.5% had to pay a co-payment. Approximately a half (51.1%) had to pay their co-payment for drugs, 40.4% got drugs free of charge and 2.9% had to pay the full price, while 5.6% did not know the answer. Since 2009 the number of those who did not have to pay for GP visits increased by 10% and the number of those who did not have to pay for prescribed drugs increased by 7%. Most of the patients, who did not have to pay for GP visits, got also free of charge drugs (72.6%), while only a small portion had to pay participation (21.1%). About half of the respondents thought that visits to specialists (with GP's referral) were free of charge 45.9%, while 44.7% thought that they have to pay a co-payment.

Throughout the research period 74.3% of the respondents did not avoid or postpone a GP visit, because they could not pay for it or for drugs, respectively; only a minority of 13.6% avoided or postponed such a visit, while 12.1% could not remember. There was a statistically significant difference regarding the number of respondents who avoided or postponed GP visits with respect to different socio-demographic characteristics ($p < 0.05$). Avoiding and postponing was more frequent among female respondents (13.9%), patients in the age group from 50 to 59 (14.6%), respondents with an education less than primary school (20.7%) and among those patients who perceived their HWB as bad or very bad (together 32.0%).

Consumers' Satisfaction, Payment for Health Care Services and Unmet Needs

There was a statistically significant difference between the number of satisfied consumers with respect to payment or not for PHC services ($p < 0.05$). Satisfied consumers were those who paid participation for GP visits (80.2%) or got it for free of charge

TABLE 1 | Contingency table of consumers' satisfaction with PHC services by the year of survey and selected socio-demographic characteristics.

Variables		Dissatisfied		Neither satisfied nor satisfied		Satisfied		*p*
		N	%	*N*	%	*N*	%	
Year	2009	1.698	5.7	4.277	142	24.072	80.1	<0.05
	2010	1.463	4.8	3.726	12.1	25.510	83.1	
	2011	1.827	6.1	3.872	13.0	24.168	80.9	
	2012	2.111	7.7	4.122	15.0	21.336	77.4	
	2013	2.162	7.7	4.192	14.9	21.701	77.4	
	2014	2.129	8.5	4.079	16.3	18.892	75.3	
	2015	2.101	7.4	4.297	15.1	22.122	77.6	
Gender	Male	6.154	7.1	12.207	14.0	68.784	78.9	<0.05
	Female	6.916	6.4	15.726	14.5	85.731	79.1	
Age	19 through 29	1.491	7.6	3.430	17.6	14.616	74.8	<0.05
	30 through 39	2.240	7.0	5.304	16.7	24.234	76.3	
	40 through 49	2.581	6.6	5.877	15.1	30.408	78.2	
	50 through 59	3.023	6.8	5.906	13.3	35.430	79.9	
	60 through 69	2.419	6.6	4.670	12.7	29.824	80.8	
	70 through 79	1.331	5.9	2.652	11.8	18.445	52.2	
	80 and more	406	6.8	726	12.1	4.844	81.1	
Education	Less than primary school	1.084	9.0	1.646	13.5	9.448	77.6	<0.05
	Primary school	2.561	6.7	5.549	14.5	30.056	78.8	
	Secondary school	6.926	6.5	15.764	14.7	84.421	78.8	
	High school or university	2.809	6.8	5.449	13.2	32.984	80.0	
Household well-being	Very bad	1.789	13.9	2.376	18.5	8.701	67.6	<0.05
	Bad	2.275	8.0	5.200	18.2	21.116	73.9	
	Medium	5.862	6.2	14.242	15.1	74.212	78.7	
	Good	2.926	5.4	5.872	10.8	45.625	83.8	
	Very good	560	6.3	774	8.8	7.508	84.9	

(80.0%), got drugs for free of charge (82.2%) or thought visits to a specialist (with GP referral) were free of charge (82.0%). The most dissatisfied patients were those who got GP visits free of charge (7.2%), got drugs for free (5.0%), but had a co-payment for specialists' visits (4.9%) or missed or postponed visit to GP (5.3%). Consumers' satisfaction with PHC services by the cost of service and unmet needs is shown in **Table 2**.

There was a statistically significant difference between the number of consumers who were dissatisfied and consumers with unmet needs due to the inability to pay for health care services in the previous 12 months. As shown in **Table 2**, consumers who experienced unmet needs were dissatisfied in a much greater number (15.4%) than those without such an experience (5.3%).

Prediction of the Number of Dissatisfied Consumers for the Period 2016–2018

The temporal development of the number of those consumers who were either dissatisfied or very dissatisfied with the Serbian PHC system was analyzed. A first inspection of the data revealed that their percentage has continuously grown over the past years. The trend can thereby be described by the regression line $y = 0.0051x - 10.113$, with the corresponding Pearson correlation coefficient $r = 0.821$ ($p < 0.05$) indicating a strong linear relationship between these two variables. Based on this regression analysis, an attempt was undertaken to predict the percentage of those consumers that will be dissatisfied or very dissatisfied with the Serbian PHC system within the next 3 years. According to the respective calculations, the percentage of dissatisfied or very dissatisfied patients will increase in 2016 to 8.85% (with the 95% prediction interval ranging from 6.05 to 11.64%), in 2017 to 9.35% (with the 95% prediction interval ranging from 6.30 to 12.40%) and, finally, in 2018 to 9.86% (with the 95% prediction interval ranging from 6.53 to 13.19%).

CONCLUDING REMARKS

The Serbian Health Care Consumers' Satisfaction Surveys between 2009 and 2015 revealed that most of the consumers of PHC centers were satisfied with the services, though there are differences with respect to gender, age, educational level, perceived HWB, health care expenses and unmet needs. During the observation period, the number of dissatisfied consumers

TABLE 2 | Contingency table of patients' satisfaction with PHC services by cost of services and unmet needs.

Variables		Dissatisfied		Neither dissatisfied nor satisfied		Satisfied		*P*
		N	%	*N*	%	*N*	%	
Is today's visit to GP for free or not?	Free	7.557	7.2	13.474	12.8	84.092	80.0	<0.05
	Participation	4.122	5.0	12.137	14.8	65.860	80.2	
	Full price	304	25.8	313	26.5	562	47.7	
	I don't know	589	12.7	1.394	30.0	2.664	57.3	
Are today's prescribed drugs for free or not?	Free	4.402	6.2	8.225	11.6	58.394	82.2	<0.05
	Participation	4.512	5.0	12.831	14.2	72.747	80.7	
	Full price	794	15.7	1.468	29.1	2.790	55.2	
	I don't know	886	9.0	2.637	26.7	6.362	64.4	
Is the visit to a specialist for free or not?	Free	4.830	6.1	9.432	11.9	64.817	82.0	<0.05
	Participation	3.761	4.9	11.050	14.4	62.148	80.8	
	Full price	669	18.3	990	27.1	1.994	54.6	
	I don't know	1.006	8.1	3.119	25.0	8.362	67.0	
Have you in the last 12 months missed or postponed visit to the GP because you have to pay for it?	Yes	4.108	15.4	6.409	24.0	16.238	60.7	<0.05
	No	7.731	5.3	16.902	11.5	122.087	83.2	
	I don't remember	1.375	5.8	4.824	20.2	17.647	74.0	

increased and additional efforts will have to be undertaken to stop this trend. The evaluated data indicated that the most dissatisfied consumers were men, younger patients, patients with lowest educational level, patients with a bad perceived HWB and patients who had to pay the full price for GP visits, specialist visits and for drugs. Patients who missed or postponed visits because they could not pay for it, were also less likely to be satisfied with the offered PHC services.

Patients' satisfaction could be considered as a multidimensional quality indicator, depending on the structure and processes in healthcare delivery, as well as on the characteristics of the patients, their expectation from PHC etc. This multidimensionality is the reason why it is not so easy to explain the phenomenon of patient's satisfaction. Taking efforts to address the needs and expectations of consumers of different social, economic and demographic characteristics and to keep them satisfied with PHC could improve compliance with GP recommendations, thus ensuring better health outcomes and decreasing unnecessary health expenditures.

AUTHOR CONTRIBUTIONS

All authors made substantial, direct and intellectual contribution to the work and approved it for publication.

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DATA REPORT
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Socioeconomic Patterns of Tobacco Use–An Example from the Balkans

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Keywords: smoking cigarettes, socioeconomic factors, National Health Survey, Serbia, socioeconomic inequality

INEQUALITIES IN PATTERNS OF TOBACCO USE

The number of smokers in the world is about 1.4 billion and projections are that this number is going to reach about 1.8 billion by the year 2030 (Bosdriesz et al., 2014). In many countries, smoking is known to be the single biggest source of inequalities in mortality and morbidity among the rich and the poor (Yamada et al., 2013). Some independent studies at both national and international levels have shown a connection between the use of tobacco and social and economic factors such as nationality, place of living, profession, education, gender, and age. Inequalities in socioeconomic status and its impact on people's health represents a global issue (Guo and Sa, 2015; Radevic et al., 2016). In most high-income countries today, there is a negative gradient in smoking, and smoking is more common among countries of low socio-economic status. As a result, smoking is one of the most important factors contributing to health inequalities (Bosdriesz et al., 2014).

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THE DATA REPORT METHODS

Public Data Set Description—Serbian 2013 National Health Survey

The study of health of population in Serbia conducted in 2013 was the source of used data. This was the third national population health survey conducted by the Ministry of Health of the Republic of Serbia (IPHS, 2013). The first such survey was conducted in 2000 and another one in 2006. In the third Survey, a harmonization of research tools (methodology, questionnaires, instructions) with the instruments of the European Health Survey second wave (EHIS wave 2; EHIS, 2013) was carried out in order to achieve the highest degree of comparability of results with the countries members of the European Union, according to a defined, internationally accepted indicators (ECHI, OMC, WHO, UNGASS, MD).

Health Survey of the Serbian population was carried out through interviews, anthropometric measurements and blood pressure measurements. The target population were people 15 or more years of age who were living in private households on the territory of the Republic of Serbia at the time of data collection. Categories of persons who belonged to the target population, and who were not included in the study population, were persons living in collective households and institutions, as well as persons living on the territory of the Autonomous Province of Kosovo and Metohija, which is under the authority of UNMIK (UN Mission in Kosovo).

The study used the most complete population register that includes a sampling units defined within the target population—Census of Population, Households, and Dwellings in the Republic of Serbia conducted in 2011. In accordance with the recommendations for the implementation of population health research EUROSTAT, the European Health Research—Second Wave—Methodological guide (EHIS wave 2, Methodological manual) the National representative probability sample was used: Two-stage stratified sample with a known probability

of selection of sample units at every stage sampling. The sample was drawn so as to provide a statistically reliable estimation of a great number of indicators of population health condition at the national level, considering geographic areas/statistical regions of Belgrade, Vojvodina, Shumadija, Western, Southern, and Eastern Serbia, and at the level of urban and other settlements/areas. The mechanisms that have been used to obtain a random sample of households and respondents represent a combination of the two sampling techniques: Stratification and multi-stage sampling. Population data for Serbia were used in order to make the initial strata. Also, two variables were used in order to create strata and to assess their size and the percentage distribution of the sample—region (four territorial strata according to NUTS2) and type of settlement, or division of settlements into urban and other settlements. The variables: Region and type of settlement were simultaneously used both for stratification of the population, and for stratification of the sample and therefore the samples are stratified in two dimensions. As the main strata in the sample four statistical regions were identified: Vojvodina, Belgrade, Shumadija, and Western Serbia, Southern and Eastern Serbia. The further division of four strata in urban and other areas gave a total of eight strata in Serbia.

Units of the first stage were selected based on probability proportional to their size (Probability Proportional Sampling-PPS). In the first stage, a total of 670 EAs stratum was selected. The units of the second stage were households. Lists of all households in selected EAs stratums were updated before the final selection of households. After completion of the update, 10 households along with three reserve households were selected within each enumeration area. Selected households were chosen using a linear random beginning sampling method with the equal steps of choice (Simple Random Sample Without Replacement-SRSWoR). In this way, households were selected with equal probability of selection without repetition. The sample was selected so as to provide a statistically valid estimation of Serbia as a whole and then at the level of individual regions (Belgrade, Vojvodina, Shumadija, and Western Serbia, Southern and Eastern Serbia), as well as at the level of a single type of settlement (urban, rural). Starting with the precision requests for the assessment and the level of obtaining reliable assessments, and in accordance with the recommendations for the implementation of population health research, the number of respondents who would provide the required sample size by strata was planned. A sample of 6700 households with 19,284 members expected was planned. A sample of 6500 households in which there were 19,079 listed members was realized.

Three types of questionnaires were used in the survey: Questionnaire for Household—collecting information on all household members, the characteristics of the household, as well as on the characteristics of the household residence. The questionnaire had to be completed in the course of verbal communication between the interviewers and interviewees who represented the main person in the household to answer questions of interest. The questionnaire "face to face" is to be filled in with each member of the household. Self-administered questionnaire which should be filled in by each household member aged 15 and over without the participation of the interviewer. This type of questionnaire was used because it was estimated that the questions concerning sensitive items of alcohol use, sexual behavior and so on were not suitable for filling by method "face to face." In order to complete the questionnaires a method of computer-assisted personal interviewing–CAPI was used as well as the process of interviewing through paper-and-pencil procedures–PAPI for self-administered questionnaire.

Fieldwork was conducted in the period from 7 October to 30 December 2013, which respected the legislation relating to the European Health Research—second cycle: The collection of data in the field should take at least 3 months of which at least 1 month should be in the period from September to December, or in the fall. In order to achieve a high level of quality of the collected data, to provide a high response rate of households and in order to protect the representativeness of the sample, the election and training of interviewers had been organized prior to the commencement of field work, and also guidelines for the monitoring and control of field work were given to them. 68 teams with a total of 204 interviewers were formed to perform the fieldwork. Each team consisted of three members, one of which had to be a health worker or a doctor or a nurse-technician. 13 field supervisors were responsible for monitoring and control of field work. The control procedures of the whole process of research, in all its phases, included the control of sampling and control of work in the field. At the end of the field work phase the supercontrol was performed. In order to carry this out, 10% of EAs were randomly selected from the total sample. Supercontrol results showed that data collection procedures went well, which means that both the interviewers and supervisors followed the instructions received during the training process.

Ethical Standards in Health Research were harmonized with the international World Medical Association Declaration of Helsinki. In order to respect the privacy of the subjects of research and confidentiality of information collected, all necessary steps in accordance with the Law on Personal Data Protection (Off. Gazette of RS No 97/08, 104/09)[1] were taken. Field researchers were required to give a printed document that informed research participants about the Research (Notice of Survey signed by the Minister of Health) and the approval of the Ethics Committee on its implementation, on the rights of patients, and about where and how they can submit complaint/grievance if estimate that their rights have been in any way compromised. Also, interviewers needed to obtain the signed informative consent of each of the participants for accepting to participate in the survey. In research, the collection of data that identify the respondents was avoided to the greatest possible extent (necessary identifiers were removed at the earliest stage of statistical analysis and replaced with code).

SURVEY DATA DESCRIPTION

Out of total of 10,089 households contacted, 6500 of them agreed to participate in the survey, so that the response rate of households was 64.4%. Out of total of 16,474 registered

[1]http://www.refworld.org/pdfid/4b5718f52.pdf

household members aged 15 years and over, 14,623 of them agreed to be interviewed, giving a response rate of 88.9%. Out of this number of people who agreed to be interviewed, 13,756 of them accepted to fill in the questionnaire (response rate 94.1%). For the purposes of this study, the data on households and population age 15 and over were used, so that the final sample for analysis included 6834 patients (aged 20 and over).

Of the independent variables, the researchers used demographic characteristics (age, gender, type of settlement, and marital status) and socioeconomic status (education, employment, and well-being index). Participants' age was categorized in to 8 age groups (20–24, 25–34, 35–44, 45–54, 55–64, 65–74, 75–84, and 85 years or more). Gender is coded as male and female, place of residence as urban and rural, while the marital status was categorized as marriage or common law marriage and not married, divorced or widowed. Variables that reflect the socio-economic situation are education, which is designated as higher, secondary and elementary, employment status as employed and unemployed and household. The Wealth Index is based on household assets and housing characteristics, such as the possession of color TV set, cell phone, refrigerator, dish washer, washing machine, PC, AC, car, construction material of floors, roofs and walls, the number of bedrooms per household member, type of drinking water resources and sanitation facility as well as heating fuel and Internet access. Based on the Wealth Index, households were classified into five groups of equal size–quintiles (1) the poorest (Q1), (2) poorer (Q2), (3) middle (Q3), (4) richer (Q4), and (5) the richest (Q5). For the purposes of this paper, respondents were classified into three socio-economic categories: Poor class, middle class, and rich class. The use of tobacco, as a dependent variable in this analysis, refers to smoking every day and occasionally.

The data set has been submitted in a public repository Figshare and it is available on: https://figshare.com/s/6ca73e2f4911b89b50f7. Data has been uploaded as Excel file while questionnaires are in PDF formats. Readers can retrieve and reuse publicly available information by visiting links given above.

TABLE 1 | Binary logistic regression of factors associated with tobacco use in Serbia.

Variables	*N*	%	Binary logistic regression	*p*
			OR (95% CI)	
GENDER				
Female	2185	49.3	1	<0.001
Male	2248	50.7	1.298 (1.166–1.444)	
Age (Years)			1.036 (1.032–1.040)	<0.001
MARITAL STATUS				
Not married, divorced, widowed	1468	40.9	1	
Married or living with a partner	2965	66.9	1.253 (1.115–1.409)	<0.001
EDUCATION				
Low	1019	23.0	1	
Middle	2779	62.7	1.329 (1.154–1.531)	<0.001
High	635	14.3	1.851 (1.534–2.233)	<0.001
EMPLYMENT STATUS				
Employment	1884	42.5	1	
Unemployment	2549	57.5	1.123 (0.994–1.267)	>0.05
TYPE OF SETTLEMENT				
Urban	2622	59.1	1	
Rural	1811	40.9	1.128 (0.096–1.277)	>0.05
WELL-BEING INDEX				
Poor class	907	20.5	1	
Middle class	2737	61.7	1.156 (0.992–1.349)	>0.05
Rich class	789	17.8	1.436 (1.168–1.765)	<0.05

SOCIOECONOMIC FACTORS ASSOCIATED WITH TOBACCO USE

The highest percentage of respondents belonged to the age group of 55–64 years (22.8%). There were more men (53.9%) than women (46.1%) in the sample. The highest percentage of respondents has completed secondary education (61.2%), while there is the least of those who have high education (16.4%). In relation to the employment status the highest percentage belongs to the group of inactive population (60.3%). More than half of the respondents live in urban areas (59.8%). When it comes to well-being index, the largest percentage of respondents belongs to the middle class (61.3%).

Results of binary logistic regression showed that cigarette smoking is under the influence of age, gender, marital status, education and well-being index (**Table 1**). The prevalence of cigarette consumption in males is 50.7%, whereas males are 1.3 times more likely to use tobacco than females. Compared to the younger population (<24 years) members of the group of the elderly population (25 and older) are more likely to consume cigarettes. Married or living with a partner are 1.4 times more likely to smoke compared to not married, divorced, widowed. Respondents with higher education have 1.8 times greater chance of cigarette smoking compared to those with low education (OR = 1.851). For an index of wealth, odds ratios are calculated by taking the poorest category of wealth as a reference. Members of rich class are more often smokers (OR = 1.436) compared with those who belong to a poor class of the population.

LANDSCAPE OF TOBACCO ADDICTION ACROSS THE GLOBE

Aforementioned dataset showed that there are significant differences in the consumption of cigarettes depending on the demographic and socioeconomic characteristics of the respondents. They are consistent with the findings of other studies that show that the prevalence of cigarette consumption varies among regions of the world, considerably depending on gender, level of education and well-being index (Janković and Simić, 2012). Also, smoking is a behavior that has the greatest impact on health inequalities (Giovino et al., 2012).

In most countries, smoking is more prevalent among men than women as represented in the Global Adult Tobacco Survey

conducted in Brazil, Mexico, Philippines, Uruguay, Bangladesh, China, Thailand, India, Turkey, Egypt, Poland, Russia, Ukraine, and Vietnam (Barbeau et al., 2004). Also, the prevalence of tobacco consumption is increasing with age in almost all countries included in the Global Adult Tobacco Survey, except in Mexico and Poland where age group has no influence, while the trend of tobacco consumption decreases with increasing age in the Russian Federation (Jakovljevic and Milovanovic, 2015), Ukraine and Uruguay. The trend shows a significant reduction in the incidence of tobacco use by increasing the level of education in Bangladesh, Egypt, India, the Philippines and Thailand, Poland, the Russian Federation, China, Ukraine, and Vietnam (Palipudi et al., 2012). Other studies also have shown that tobacco consumption was significantly higher among older, poorer and less educated population. Smoking prevalence also varies depending on the individual and sociocultural characteristics (Rani et al., 2003).

The correlation between tobacco use among men and women of Asian countries, with socio-economic and demographic factors, showed that the inhabitants of rural areas were more likely to smoke. Older men are more likely to smoke in most countries. Also, smokers are more likely to be married men and married women. Smoking is strongly associated with education and with the level of wealth in many Asian countries. Individuals who were educated and wealthier individuals were less likely to smoke. Smoking has been associated with religion (Agrawal et al., 2013; Sreeramareddy et al., 2014).

The trend of reducing the chances of tobacco products use with the increase of wealth existed in results obtained in populations of Bangladesh, India, the Philippines, Thailand, Turkey, Ukraine, Uruguay, and Vietnam (Rancic and Jakovljevic, 2016). However, in several countries wealth and higher level of education did not result in decreased use of tobacco, such as Mexico where tobacco use was actually lower among poor people and in China where the lowest rate of tobacco use was present among both the poorest and the wealthiest (Palipudi et al., 2012; Jakovljevic, 2014). Correlation between smoking and socio-economic status among Chinese smokers has shown that the poorest and uneducated or illiterate people smoked 11% and 14% more than those who earned more or who had higher level of education (Guo and Sa, 2015). And other studies that dealt with the connection of smoking with socio-economic status also demonstrate that cigarette smoking is more prevalent among low educated and poorer people (Nédó and Paulik, 2012).

CONCLUSIVE REMARKS

Social differences in smoking behavior could make the existing social inequalities related to health even worse. Therefore, policies and interventions which promote cessation of smoking should pay more attention to the disadvantages social groups. Policymakers should consider the socio-economic importance of tobacco use in the design, implementation and evaluation of tobacco control interventions.

AUTHOR CONTRIBUTIONS

All authors listed, have made substantial, direct and intellectual contribution to the work, and approved it for publication. DV and SR developed research questions, designed the study, and prepared manuscript for this Data report. NM contributed through data analysis and interpretation.

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OPINION
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Trends and Patterns of Disparities in Oral Cavity and Pharyngeal Cancer in Serbia: Prevalence and Economic Consequences in a Transitional Country

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EPIDEMIOLOGY OF ORAL CAVITY AND PHARYNGEAL CANCERS

Oral cavity and pharyngeal cancers (OCPc) encompass malignancies arising in variety of anatomical subsites and are homogeneous regarding epidemiology, clinical presentation, associated risk factors and treatment modalities (Robinson and Macfarlane, 2003; Conway et al., 2006). Worldwide, they are the sixth most common type of cancer, with an estimated 529,500 new cases and 292,300 deaths globally during 2012, accounting for 3,8% of all cancer cases and 3,6% of cancer deaths (Ferlay et al., 2015; Shield et al., 2017). The regions with the highest incidence of OCPc include South and Southeast Asia (India, Pakistan, Sri Lanka), Eastern and Western Europe (Hungary, Slovakia, France, Portugal), Latin America (Brazil, Uruguay, Puerto Riko) and the Pacific (Papua New Guinea) (Warnakulasuriya, 2009; Chaturvedi et al., 2013; Weatherspoon et al., 2015). OCPc are the eighth most common cancers among the European countries with an incidence of 73,856 new cases and eleventh leading cause of cancer-related mortality with 34,285 death cases in the year 2012 (Ferlay et al., 2013). In the United States (US), an incidence of 41,380 newly diagnosed patients and 7,890 deaths due to OCPc was reported in 2013 (Weatherspoon et al., 2015). The incidence of OCPc has declined in recent decades in most parts of the world, but has increased in the US, United Kingdom, Australia, Canada, Sweden, Denmark and the Netherlands (Chaturvedi et al., 2013). OCPc are about three times more common in men than women, but this ratio is declining mainly due to increased exposure of women to risk factors (Warnakulasuriya et al., 2015). Recent study showed an increase of the incidence of OCPc for Serbian population for both men and women between 1999 and 2010 (Videnović et al., 2016). Age standardized incidence rates for OCPc for the Serbian population in 2012 were 11,2/100,000, which is lower compared to some European countries (Ferlay et al., 2013). The prevalence for men was 3,5 times higher than for woman, similar to trends in other parts of the Europe (Jankovic et al., 2006; Santric-Milicevic et al., 2009; Ferlay et al., 2013).

OCPc RISK FACTORS

The traditional risk factors for OCPc are considered tobacco smoking and alcohol consumption, but strong evidences support the infection with high risk human papillomavirus (HPV) types

16 and 18, as an important causation factor (Marur et al., 2010; Chaturvedi et al., 2011; Radoï and Luce, 2013). Tobacco smoking and alcohol consumption are related to 75% of OPCc (Shield et al., 2017) and believed to have a synergistic effect (Cunningham et al., 2011). Reduction in smoking worldwide has resulted in significant declines in the incidence of oral cavity cancers in anatomical subsites such as lip, gum, floor of the mouth, hard palate, buccal mucosa, and vestibule (Tota et al., 2017). Evaluation by the International Agency for Research in Cancer (IARC) concluded the carcinogenicity of HPV type 16 in the oral cavity, oropharynx (including tonsil cancer, base of tongue cancer and other oropharyngeal cancer sites), and limited evidence for laryngeal cancer (IACR, 2012). HPV infection is accounted for more than 30% of OCPc in Northern and Western Europe (De Martel et al., 2012) and more than 60% in the United States (De Souza et al., 2011), compared to less than 10% in economically undeveloped countries (Chaturvedi et al., 2013). The incidence of HPV-infected OCPc is as much as 64% in Serbia (Kozomara et al., 2005). Currently immunization against the most common HPV types is not obligatory in Serbia, although the immunization against HPV type 16 of both men and women can prevent a large proportion of oropharyngeal cancers (IACR, 2012).

Much has been done in the Serbian legislature after 1999 in regards to preventive anti-smoking activities since Serbia had a reputation of having a very high smoking prevalence (Djikanovic et al., 2011). The Serbian health ministry ratified the World Health Organization (WHO) Framework Convention on Tobacco Control (Ministry of Health, 2007). The Law on Protection of Population from Exposure to Tobacco Smoke was passed in the Republic of Serbia in 2010, determining the measures of restricted use of tobacco products (Official Gazette of RS, 2010). However, the results of the National Health Survey in 2013 revealed that the smoking rate had increased by 3% after the year 2006 (Ministry of Health, 2014). In 2013 34,7% of the population were smokers with higher prevalence for men, but significant increase in the number of daily women smokers had been observed (Ministry of health 2014). Alcohol drinking in Serbia represents socialy acceptable behavior and alcohol use is a part of tradition and culture (Jakovljevic et al., 2013). According to WHO statistics the drinking pattern in Serbia has been scored 3 on a scale of 1–5, where 5 represents the riskiest drinking pattern (Jakovljevic et al., 2013).

THE ECONOMIC BURDEN OF CANCER TREATMENT ON SERBIA'S HEALTH SYSTEM

The Republic of Serbia is a middle-income European country with high unemployment rates and decrease in growth of gross domestic product (GDP) (Santric-Milicevic et al., 2016). The health system in Serbia was based off of the health system of former SFR Yugoslavia, referred to as the Stampar model (Bredenkamp et al., 2011). This system has changed substantially after Yugoslavia's dissolution in the 90's, especially after democratic changes in the 2000 (Jakovljevic and Getzen, 2016; Jakovljevic et al., 2016; Mihailovic et al., 2017). Between 2006 and 2013 health care expenses rose from 9 to 10.4% GDP (The World Bank, 2016). More than half of public health expenditure is spent on salaries while only 3% is spent on capital investments and 6% on preventive health services (Santric-Milicevic et al., 2016).

Cancer reporting is obligatory by law in Serbia since 1986 (Miljuš et al., 2010). The Population Register for Cancer was formed in Serbia in 1970, which originated from the Plan of Statistical Research of Interest for the Republic (Official Gazette of the Republic of Serbia No. 32/69). Cancer reports were collected separately by the two cancer registries of Serbia: the Cancer Registry of Central Serbia and the Cancer Registry of Vojvodina (Mihajlović et al., 2013). Until the year 1998, the quality of data collection from these registries was insufficient. But in 1998 they both became members of IACR and the European Network of Cancer Registries which significantly improved the quality of the data (Miljuš et al., 2010).

In the US the 2008 health expenditures in treatment of malignancies reached 77,4 billion dollars (American Cancer Society, 2013) while EU costs for 2009 were 57 billion euros (Luengo-Fernandez et al., 2013). With the worldwide increase in cancer incidence, as well as developments in diagnostic and treatment procedures, these costs will constantly grow (Radovanovic et al., 2011). The burden of malignant diseases in Serbia is enormous (Jakovljevic et al., 2015). In a nation-wide population study on Serbian cancer incidence during 1999–2009 an alarmingly high incidence and mortality compared to European regions was reported (Mihajlović et al., 2013). A rising cancer incidence may be attributed to military conflict in the region, bombardment with depleted uranium during NATO campaigns, post war syndrome and poor socioeconomic parameters (Mihajlović et al., 2013; Kovacević et al., 2015). According to the last edition of the Statistical Yearbook of the Republic of Serbia, 21,865 people died of malignancies in the 2015 (Statistical Office of the Republic of Serbia, 2016).

In Serbia the diagnosis and treatment costs of cancer are dominated by radiotherapy related direct medical costs (Jakovljevic et al., 2015). Direct medical cancer care costs increased by 30% between 2007 and 2010 with radiotherapy consuming about 54% of all expenditures (Radovanovic et al., 2011). Regarding palliative cancer treatment the highest expenditures were observed for pharmaceutics (42%) (Kovacević et al., 2015). Economic recession and domestic policy constraints affected the affordability and quality of cancer treatment for the Serbian population (Dagovic et al., 2015). Lack of national screening programs, insufficient equipment capacities, poor network facilities across rural regions, late diagnosis and palliative care are the main issues to be solved in order to achieve better clinical outcomes and cost-effectiveness of the health care system (Jakovljević, 2013; Dagovic et al., 2015; Jakovljevic et al., 2015, 2017). Due to the economic recession, Serbia faces a migration of medical professionals (specialists, doctors, nurses), which may have potentially disastrous effects on quality of public health system (Santric-Milicevic et al., 2014, 2015, 2016).

ECONOMICS OF OCPc TREATMENT

Early diagnosis of OCPc is vital to patient survival (Shield et al., 2017). Only one study assessed the effects of oral cavity cancer screening of high-risk groups, and reported that visual oral examination could reduce mortality by 29% (Sankaranarayanan et al., 2005). In many cases OCPc are diagnosed at advanced stages, when management is complex and multidisciplinary, and requires prolonged medical care (Hallenbeak et al., 2015). In the North American and European clinical practice, patients with early stage OCPc receive surgical treatment, patients with localy invasive disease are treated with combined treatment modalities (surgery, if indicated + radiotherapy and chemotherapy) while patients with end-stage metastatic disease usually receive palliative chemotherapy (Gold et al., 2009; Chan et al., 2012). Recontructive surgery, medical prostheses and multidisciplinary rehabilitation, follow up care and surveillance are required (Chan et al., 2012; Wissinger et al., 2014).

The full societal burden of cancer treatment consists of associated direct medical expenditures and indirect costs including reduced work force participation, loss of productivity and premature mortality (Wissinger et al., 2014). The existing data on costs associated with OCPc are available from a limited number of socioeconomic studies, mostly from the US and several from Europe. Summarized data from these studies suggest different pattern of expenses since costs associated with OCPc in the US were greatest for systemic therapy, while in the Europe the highest burden of costs was on surgical treatment (Preuss et al., 2007; Diaz-de-Cerio et al., 2013; Wissinger et al., 2014). In 2010 the direct medical costs of head and neck cancer treatment in the US totaled 3.64 billion dollars, which was slightly higher than indirect costs totaled 3.4 billion dollars (Mariotto et al., 2013). The mean per-patient direct medical costs for treatment of head and neck carcinomas in the US totaled 32,500–48,847 dollars, depending on the stage of disease (Wissinger et al., 2014). A report from Greece found that mean direct costs of treatment of OCPc were 7,450 dollars (Zavras et al., 2002). A similar study in the Netherlands reported direct per-patient costs of OCPc treatment of 22,080 dollars (van Agthoven et al., 2001). The main cost burden in patients with advanced disease is the need for multimodal treatments as well as the need for prolonged hospitalization and medical care (Wissinger et al., 2014). The costs of hospitalization of patients with OCPc in the US ranged approximately 20,000–23,000 dollars in 2012 (Le et al., 2013). Regarding the length of hospitalization, the average length of stay in US hospitals for OCPc patients was 16 days (Ryan and Hochman, 2000), considerably lower than in France (29 days) (Pinsolle et al., 1992), The Netherlands (31 days) (van Agthoven et al., 2001) and Greece (34 days) (Zavras et al., 2002). Regarding surgical treatment and defect reconstruction of OCPc, several studies from Europe, the US and Canada compared total costs within the first year of treatment after oral cavity reconstruction with microvascular flaps and local flaps, and observed minimal cost differences (Smeele et al., 2006; Le et al., 2013; Santamarta et al., 2013).

FUTURE IMPLICATIONS TO OCPc PREVENTION

Although Serbian public health care expenditure is limited due to the recession, slow market recovery since 2013 has resulted with the substantial increase in oncology related public expenditure (Dagovic et al., 2015; Jakovljevic et al., 2015). Currently there are no data on the costs of treatment of OCPc in the Republic of Serbia and there is the need for further research on the budgetary costs. The future national strategies to reduce the prevalence of OCPc should include population health education targeted to reduce exposure to main risk factors: tobacco smoking, alcohol consumption and HPV infection. Promotion and finance of national screening programs, supported by legislure. may be one of the options to reduce cancer treatment costs and obtain more affordable health care.

AUTHOR CONTRIBUTIONS

All six authors designed the research questions and concept of this opinion article. TK and DB acquired selected published data from the public registry European Health for All Data base issued by WHO. All six authors jointly interpreted the findings stated in the article and contributed important intellectual content to the final manuscript. All six authors checked English spelling and grammar.

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OPINION
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Unnecessary Hysterectomy due to Menorrhagia and Disorders of Hemostasis: An Example of Overuse and Excessive Demand for Medical Services

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MENORRHAGIA IN CLINICAL MEDICINE

Excessive menstrual bleeding—menorrhagia is a common gynecologic disorder affecting women of reproductive age. Subjectively, menorrhagia is defined as a complaint of heavy cyclical menstrual bleeding occurring over several consecutive cycles (Rönnerdag and Odlind, 1999). Objectively, it can be defined as heavy menstrual bleeding lasting for more than 7 days or resulting in the loss of more than 80 mL per menstrual cycle (ACOG Committee on Practice Bulletins—Gynecology, American College of Obstetricians and Gynecologists, 2001). An objective evaluation of the existence of menorrhagia is not simple. Alkaline hematin technique is completely objective measure (extracting hemoglobin from sanitary wear to assess blood loss), but it is impractical out of controlled research settings. Widely used alternative is the pictorial blood loss assessment chart (PBAC) and this is semiobjective method takes into account the number and the degree of staining of items of sanitary wear used. PBAC is easier to perform than the alkaline hematin technique, yet yields more objective results than self-reporting (Warner et al., 2004). Data from literature suggested that approximately 10% of reproductive-aged women had objective evidence of menorrhagia, but studies based on self-reported information suggested that approximately 30% of women of reproductive age were afflicted with heavy menstrual bleeding (Dilley et al., 2002; Shapley et al., 2004). According to our research, out of 115 women who self-report these excessive menstrual bleeding only 55% had actually verified menorrhagia by PBAC (Djukic et al., 2013). Menorrhagia can happen due to anatomic (uterine fibroids, endometrial polyps, endometrial hyperplasia, and pregnancy), endocrinologic (thyroid and adrenal gland dysfunction, pituitary tumors, anovulatory cycles, polycystic ovarial syndrome, obesity, and vasculature imbalance), iatrogenic (steroid hormones, chemotherapy agents, medications) and organic (organ dysfunction infection, bleeding disorders) abnormality (Vilos et al., 2001; Albers et al., 2004).

THE ROLE OF BLEEDING DISORDERS

Underlying bleeding disorders only have been recognized during the last two decades as a significant etiopathogenetic factor for menorrhagia formation. The available data from the literature show the frequency of hemostasis disorders in women with menorrhagia in the range of 10–20% (El-Hemaidi et al., 2007), whereas some of the most representative studies by Kadir and associates state the information about 17% of patients (Kadir et al., 1998). The reported prevalence

of von Willebrands Disease (vWD) as the most frequent among them is ranging from 5 to 20% with an overall estimate of 13%, based on a systematic review (Shankar et al., 2004). The considerable proportion of women with menorrhagia is found to have single coagulation factor deficiencies such as factor XI deficiency (1–4%), carriers of hemophilia A and hemophilia B observed in approximately 1–4% of females with menorrhagia and less common deficiencies of factor I, II, V, VII, X, XI, XIII (Dilley et al., 2001; Mannucci et al., 2004; Philipp et al., 2005; Plug et al., 2006).

Previous research has shown that in the population of women who suffer from menorrhagia, the frequency of disorders of hemostasis is 17% (Djukic et al., 2009). Analyzing the incidence of certain disorders of hemostasis in previous research is shown that the most commonly disorder is also VWD, although deficiency of factor IX, then deficiencies of factor FVII, X, and XI (Djukic et al., 2013) (**Figure 1**).

Studies have shown that physicians are not likely to consider a bleeding disorder as a possible cause of menorrhagia. Only 3% of them would refer patients to a specialist and four percent of gynecologists surveyed would consider von Willebrand's disease as a possible diagnosis in women with menorrhagia (Dilley et al., 2002). Anamnestic indicators suggesting an underlying bleeding disorder include menorrhagia since menarche, failed response to conventional management of menorrhagia or family history of a bleeding disorder. In addition, the clinical presentation includes: epistaxis, bleeding of oral cavity or gastrointestinal tract without an obvious anatomic lesion, notable bruising without injury; minor wound bleeding, prolonged or excessive bleeding after dental extraction, unexpected postsurgical bleeding, hemorrhage from ovarian cysts or corpus luteum; hemorrhage requiring blood transfusion; postpartum hemorrhage (especially delayed) (Nicols et al., 2008; Rodeghiero et al., 2009). In a population of women who suffer from heavy menstrual bleeding, disorders of hemostasis are often not recognized. Some studies show that the diagnostic delay from onset of bleeding symptoms can be up to 16 years (Kirtava et al., 2004). As these patients usually do not respond adequately to conventional treatment for menorrhagia, the radical procedures (like a hysterectomy) carry out more often than is necessary. Referral to an attending gynecologist for menorrhagia meant a 43% chance of a hysterectomy (Coulter et al., 1991) and menorrhagia is the major cause for approximately 300,000 hysterectomies per year in the U.S (James et al., 2006). Studies have shown that women with von Willebrand's disease are more likely to undergo a hysterectomy and to have the hysterectomy at a younger age (Kirtava et al., 2003). A randomized comparison of approach with hysterectomy and the levonorgestrel-releasing intrauterine system (IUS) in terms of the quality of life of women with menorrhagia and cost-effectiveness demonstrated that health-related quality of life improved significantly in both the IUS and hysterectomy, but overall costs were about three times higher for the hysterectomy group (Hurskainen et al., 2001). Timely diagnosis and treatment of hemostasis disorders in women with menorrhagia, unnecessary hysterectomy could be avoided. Undiagnosed coagulation abnormalities have effect on women's quality of life. It can cause serious problems such as iron deficiency anemia, complications from surgical procedures, lost work or school time, lifestyle issues, psychological problems (Rae et al., 2013). Anemia is associated with menorrhagia and coagulation abnormalities in women of reproductive age. At least 20 % of women with heavy menstrual bleeding experience anemia (Vercellini et al., 1993). In the local European study of 115 women who reported menorrhagia 53% suffered from anemia (Djukic et al., 2011).

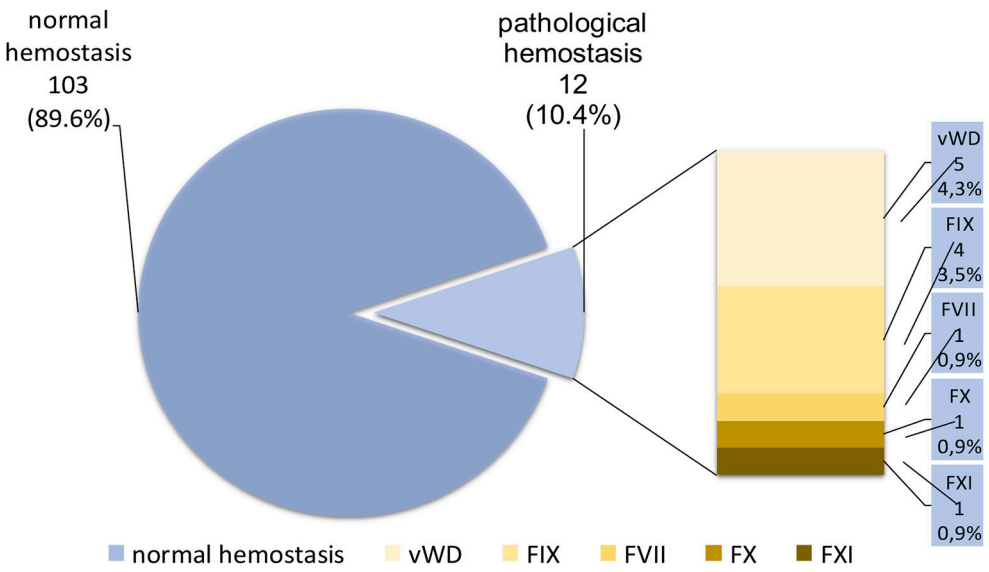

FIGURE 1 | Frequency of coagulation disorders in Serbian women with symptoms of menorrhagia. vWD, von Willebrand disease; FVII, factor VII deficiency VII; FIX, factor IX deficiency; FX, factor X deficiency; FXI, factor XI deficiency.

EXCESSIVE HYSTERECTOMY AND OPPORTUNITY COSTS OF BLEEDING DISORDERS MEDICAL CARE

Disorders of hemostasis, especially the ones seldom recognized (Lukes et al., 2005), have a major impact on health-related quality of life, work impairment and health-care costs. So far published data indicate that this field of clinical medicine accounts for a large share of workload for the national health systems, hospital sector and primary care alike (Fraser et al., 2009). Global Burden of Disease Project reports scale of morbidity, mortality (Wang et al., 2016) and disability attributable to this group of illnesses to a great detail (Vos et al., 2016). Associated workload and economic burden of abnormal uterine bleeding was proved to be significant even in highly effective health sectors. The national health expenditure available and current resource allocation strategy varies greatly with mature Western (Jakovljevic, 2016) and top performing health markets representing different historical legacies (Jakovljevic et al., 2016a). However, regardless of these large geographical diversity, willingness to pay threshold in bleeding disorders remains an issue for public debate in many countries (Eastaugh, 2000). In case of hemophilia and Von Willebrand's illness as the most frequent conditions, thorough studies on cost-effective procedures are available (Miners et al., 1998). Due to bold pharmaceutical innovation in this area a variety of drugs have been evaluated as well (Goudemand, 1999). However, particularly concerning interventions are presented by the surgical procedures that might have been avoided. Once performed, hysterectomia in women of child bearing age, in the Era of low fertility, (Jakovljevic and Laaser, 2015) could mean a life time decision affecting family planning and core life goals (Cloutier-Steele and West, 2003; Sardeshpande, 2014).

Certain lack of awareness of the potential of hemostasis disorders to cause abnormal bleeding is clearly present in the clinical gynecology. Besides there is a substantial need to develop more reliable clinical tools for the objective assessment of excessive menstrual bleeding. These circumstances lead to the underdiagnosed cases and suboptimal treatment of women with bleeding disorders, including unnecessary hysterectomy (Ranson and John, 2002). In the US setting it has already been proven that hysterectomy imposes a significant burden on the national hospital sector (Easterday et al., 1983). Furthermore, it is known that other major gynecological interventions such as cesarean section are greatly overused and the major obstacle to delivering universal health coverage nationwide (Gibbons et al., 2010). It was even since the 1980s that elective hysterectomy was disputed as an exemplary non-necessary surgical intervention in many clinical cases (Travis, 1985). Economic consequences of abnormal uterine bleeding attracted attention in academic research even in more recent years (Liu et al., 2007). Overlooked evidence in clinical interventions makes serious ramifications in terms of excessive consumption of non-necessary medical services and incurred additional costs of care (Palmer et al., 1986). In most situations attending physician is unaware of the existing evidence to guide his/her decision toward far less risky pharmacological treatment of bleeding disorder (Chang et al., 2003). Thus, such excessive surgery falls into the so called "supplier induced demand" phenomenon (Labelle et al., 1994). One of the possible approaches to tackle this inefficiency might be to invest into the capacity building and raise clinicians' consciousness about more cost-effective and less risky procedures (Jakovljevic et al., 2016b).Among other solutions has been proposed an alternative treatment strategy of deploying levonorgestrel-releasing intrauterine system vs. hysterectomy for treatment of menorrhagia (Hurskainen et al., 2001). In risky pregnancies and many other associated conditions there is documented evidence of significant inequality in incremental cost-effectiveness ratios even among the standard gynecological treatments (Jakovljevic et al., 2008). Such inequalities in ICERs measured in a sound methodological framework indicate that clinical physician's should be more acquainted to deal with health economic evidence. History of health economics taught us that even minor niche for improvement in clinical decision making could mean a lot for the social opportunity cost of potentially misleading reasoning (Jakovljevic and Ogura, 2016). This peculiar insight from the gynecology surgical practice gives an excellent hints toward serious and hidden causes of excessive demand for medical services. Opportunity costs of lost opportunity for conventional treatment via pharmacological protocols, here might mean incurring higher costs of medical care in the short run (Jakovljevic et al., 2016c). However, potential for long term savings is obvious. Particularly keeping in mind that population aging is the cornerstone demographic landmark of our time (Jakovljevic and Ogura, 2016). Preserving the fertility choice for young women who might be willing and capable to sustain at least one or one more child in their lifetime is precious. It's not only a blessing for the individual family. It is a blessing for most modern day societies whose demographic dividends have long forgone (Pandey, 2015). Medical decision crossroads where such a deep choices depend on estimate and knowledge of single attending physician should be given far more attention in a foreseeable future.

AUTHOR CONTRIBUTIONS

SD made conception of the work, data collection and interpretation. DL made data collection and interpretation. NJ made data collection. MV made conception of the paper, critical revision of the article and final approval.

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Using New Instruments of Clustering Policy in the Health Care System. The Case of Poland

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The issue of clusters as a form of organization of market entities has recently attracted an increasing attention of health care management theoreticians and practitioners. In our opinion the existing theoretical basis gives a foundation for considering clusters as a source of potential for increasing the effectiveness of health policy and health care organizations. It can be assumed that in case of health care clusters there is a possibility of interregional diffusion of innovation, based on ventures undertaken on the health care market, increasing not only the potential of the entities in the cluster, but also of its surroundings and subcontractors. It is possible to realize the idea of a flexible health care implemented regionally with the use of modern techniques of communication, knowledge transfer and high specialization. Nonetheless, in case of Poland the potential of clustrification remains untapped, being characterized by a limited actions of public and private bodies, marginal role of non-profit sector organizations and limited engagement of R&D sector. This is because a general distrust in the cluster formula, and the lack of relevant knowledge among local officials and health business leaders. For this reason the process of clustrification among health care entities requires external support through the increased efforts to create a system of legal and tax preferences for cluster initiatives and provision of organizational support in terms of know-how, targeted particularly at bodies and individuals, who may act as cluster leaders.

Keywords: economic clusters, health policy, health care organization, regioinal development, Poland

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INTRODUCTION

The issue of clusters as a specific form of organization in the area of economic policy, including health policy, has recently attracted an increasing attention of health care management theoreticians and practitioners. Although the phenomenon of clustering itself was observed as early as the end of the 19th Century (Feser and Luger, 2003), it was the last few decades, when the concepts on how to define a cluster, what are the cluster forms and methods of their scientific investigation, as well as what are the methods of creating and supporting them, started to develop very rapidly. Literature review leads to the conclusion that the functional branches for which the cluster concept has reference, are constantly expanding, covering more and more areas of social and economic life. Based on this trends it is also possible to consider, whether the development of clusters in the health care system could provide an organizational answer for the rising demand for

medical services determined by the inevitable process of demographic change, which Poland and Europe are going to face in the next few decades.

Cluster applied on the health care market is quite a vague matter. The recent results of research on it have developed a theoretical material located in an interdisciplinary context, related to regional policy, entrepreneurship and health sciences. In our opinion this theoretical basis gives a sufficient foundation for considering clusters, along with the collaborative links being its feature, as a source of yet unused potential for increasing the effectiveness of health policy.

WHAT ARE CLUSTERS

One of the first cluster definitions was proposed by M.E. Porter, who defines it as "a geographical proximate group of interconnected companies and associated institutions in a particular field, linked by commonalities and externalities" (Porter, 2000). E. M. Bergman and E. J. Feser define cluster more narrowly as "close ties to certain companies and operators in terms of various aspects of their joint activity" (Bergman and Feser, 1999). These authors however also draw the possibility of defining cluster in a very broad way, as "a group of business enterprises and non-business organizations for whom membership within the group is an important element of each member firm's individual competitiveness" (Bergman and Feser, 1999).

The legal definitions of cluster differ depending on the actual source. In the Polish legislation this issue remains somewhat unclear, even though in the strategic documents clusters are perceived as a preferred form of economic cooperation (Rozporządzenie Ministra Gospodarki z dnia 2 grudnia, 2006; Rozporządzenie Ministra Rozwoju Regionalnego z dnia 7 kwietnia, 2008; Olko et al., 2011; Dzierżanowski, 2012)[1]. The European Commission documents in turn, instead of the cluster concept, used to apply a wider category of "innovative cooperation network" (Regional Clusters in Europe, 2002; W kierunku światowej klasy klastrów w Unii Europejskiej, 2008). In this case clusters are presented as groupings of independent businesses, emerging innovative companies, small, medium and large entities and research organizations that operate in a particular sector and in a particular territorial area. These structures are designed to stimulate innovative activity by promoting intensive contacts, sharing of facilities and exchange of knowledge and experience, in order to facilitate technology transfer, networking and dissemination of information within the organization (Stawicki, 2008).

The geographical concentration of entities in the cluster tend to appear mainly in the highly urbanized areas, where there is a natural tendency to cooperate, arising of the territorial proximity, as well as the density of entities being potential cluster members. Additionally, the specific location of the cluster, as well as the expected results of its emergence, makes the local authorities a natural partner participating in its activity, particularly at the regional level. In such a case, cluster becomes a kind of redefinition of the traditional approaches to the economic policy. The main participant of the competitive market game tends to change—from self-interest-oriented business entity, as assumed in the classic neo-liberal theories, to the regional community represented by its authorities. The role of the administration becomes to initiate and moderate the entire process of cluster creation and provide it with a specific support (Borras and Tsagdis, 2011). At the same time, clusters and the internal rules of these organizations are becoming similar to the concepts of interpersonal interactions and relationships, in social sciences commonly referred to as "social capital" (Vassileva, 2009).

The basic premise for clustering is the commonality of the benefits gained by all cluster participants, but natural beneficiaries are also members of the local community and the local authorities. They may gain purely economic profits, like increased budget revenues, or higher increase of employment. But such benefit may appear also as higher quality and availability of specific services or goods in a given region. In case of the business enterprises, the benefit is based primarily on ensuring the stability of demand for goods and services they offer on the regional market. They may also get better perspectives for market expansion, thereby increasing their competitive advantage outside of the region. Considerably important is also the reduction financial costs, social barriers and administrative procedures related to business activity. For other legal entities possibly participating in clusters (research institutions, NGOs) benefit will be primarily to provide favorable conditions from the point of view of their statutory objectives, and thus ensure the stability of the organization's existence (Stawicki, 2008; Borras and Tsagdis, 2011).

CLUSTERS IN HEALTH CARE

In face of the characteristics of modern economic systems, regional policy (Madej, 1998; Mayer, 1999; Poniatowicz, 1999; Sługocki, 2004; Głowacki, 2005; Waldziński, 2005; Sokołowicz, 2008) can be treated as an interesting area of synthesis of issues concerning cluster-based policy and health policy. The role of the latter one is assuming that companies operating in the area of health, including units involved in provision of health services, and manufacturers of medical or pharmaceutical technologies, can be an important factor improving the regional economic competitiveness. Of significance is also the fact that medical industry is among the branches strongly contributing to the growth of innovative products and technologies available on the market. In other words, modern health care has to be seen as a developing branch of the national economy, which may be a basis for building development-oriented regional strategy with regard to its innovative features and competitive advantage. In light of the technological, demographic, political and economic changes the world is experiencing, further expansion should be expected, beyond the borders of the narrowly defined medicine serving the patient. Obvious is also the mutual relationship between health and economic growth. On the one hand, health is an important factor of economic development, on the other one—economic growth has a significant, positive impact on the

[1]www.mg.gov.pl (accessed 17 April, 2016)

health of the population, affecting the overall level of welfare. Beside of that, due to the compliance of purposes and aspirations, initiatives in the health care market can provide a platform of harmonious cooperation between public and private partners. In such circumstances, clusters seems to appear as a potentially very useful tool to be used also in this sector of activity.

One of the features of health care clusters is their broad spectrum of interests. Actually, any initiative, which may bring positive impact on the improvement or protection of health status of individuals or populations, may be qualified to this group. In case of absence of a clear strategic vision, this wideness might be an obstacle for the development of cluster. Nonetheless, in context of health objectives, such a wide margin of inclusion for potentially positively impacting initiatives, should be perceived as advantage. Businesses of almost any industry can find their own areas of action on the health care market. Scientific institutions can also find a space for developing innovations in an almost unrestricted manner. Finally, public administration is by law required to support the initiatives positively influencing public and individual health on their area of competence.

When understanding the concept of health as a public good, in connection with the metropolitan regionalism and entrepreneurship based on clustered collaboration, a previously mentioned role of social capital as a foundation for mutual projects based on trust, cooperation and constructive competition becomes a key factor (Brodzicki and Szultka, 2002; Sztompka, 2006; Romaniuk, 2011). In view of the concepts of regional policy and cluster-based policy, in connection with the features of health industry, it can be assumed that also in case of health care clusters there is a possibility of interregional diffusion of innovation, based on ventures undertaken on the health care market, increasing not only the potential of the entities in the cluster, but also of its surroundings and subcontractors. It is possible to realize the idea of a flexible health care implemented regionally, with the use of modern techniques of communication, knowledge transfer and high specialization.

These statements are confirmed by the experience of the existing health care clusters in Poland. According to G. Bigaj[2], health care cluster is a platform of understanding and cooperation of all elements of the health care system. The result of its existence and activity should be the elimination of the health care system imperfections. Thanks to the implementation of new technologies, procedures, materials and medicines an improvement should be observed in the sphere of organization of services, service quality, and effectiveness of treatment. Among the objectives of such a cluster, there is a creation of networking between medical institutions which provide—on the principle of complementarity—medical services to an open group of patients. Another aim is also to support providers in relations with the public payer, administration, state's institutions and local self-government units. However, the principal aim of the cluster initiative is a partnership that will provide members with faster and more effective achievement their assumed objectives. Because the medical industry is one of the most cost-intensive, a well-organized cooperation of specialized entities means a greater chance of obtaining the necessary resources. E.g., Medical Cluster of Wielkopolska focuses on three areas: new medical technologies, improving management systems of health care centers, including the computerization of management processes and the functioning of the health system.

Despite such opinions and experiences, in Poland the potential of clustrification currently seems to be untapped. During our study of health care clusters in Poland we found moderate will for participation of public administration units and for-profit organizations, marginal role of non-profit sector organizations and limited engagement of R&D sector. Paradoxically, this is not because the health service is being included in a specific sub-market, which tends to be perceived as less profit oriented subject of public responsibility. As the studies have shown, local governments deciding to get involved in health care cluster initiatives, treat them in a manner analogous to structures operating in other market sectors. At the same time, there is observable higher involvement in such initiatives by the units identifying on their territory the existence of a key medical product (Holecki and Romaniuk, 2016). This observation suggests that local governments start to recognize the potential lying in the use of the cluster formula within the health services market. This also confirms the features of health industry, as an important contributor to the local economic system and its competitiveness, moreover that decision-makers, business collaborators, providers, and sometimes even patients, are willing to consider it in such a way. Thus, medical services can strengthen the competitive advantage of Polish regions, but should be preceded by a thorough diagnosis of the initial state, which in this specific market requires particular precision, political and economic balance of arguments and social consensus.

The limited use of cluster formulas is reflected in the small-scale support to clusters, as well as in the nature of this support, largely limited to declarations only, not a real operations. The reason for this seems to be a general reluctance of possible cluster members to use this formula, arising of distrust, but also lack of relevant knowledge among local officials and health business leaders, disabling them to engage in the development of clusters, even if there is a will to do so.

In Poland the number of health care clusters, even if to apply its broad definition, including organizations active in medicine, pharmacy, medical products supply and public health initiatives, is limited and concentrated in the traditional sectors. The situation is different in West European countries, where the development of medical sciences makes the business areas for health care clusters to constantly evolve and expand the scope of their activity to new areas, such as e-health and m-health. They are using new sub-markets and technologies to stimulate their own economic success, but also to strengthen the economy of the region or country, while ensuring their citizens access to the latest technological achievements. Depending on the specialization, they can associate enterprises from various industries, both small and medium-sized, just entering the market, or having longer experience. Some clusters are composed of hundreds of companies, others are limited to a few or

[2]A leader of the Medical Cluster of Wielkopolska—personal interview.

several entities. In larger countries, such as Germany or France, they are concentrating mainly on regional dimension, often being stimulated by renowned academic centers. There are first examples associating companies from several countries, such as the Brussels Life-Tech Cluster, which consists of over 600 companies from 14 countries. There are also first examples of cooperation between clusters themselves (Kaczmarek and Iltchev, 2015).

Worth noting are the cases of implementation of the clustering model based on the WHO's strategy "Health 2020." An example of this might be a primary health care reform project applied in Hungary, which was referring to the concept of clusters as network of cooperating providers, who tend to expand the catalog of classical health services with a wide spectrum of activities in the area of disease prevention and health promotion (Adany et al., 2013; Jakab, 2013). Among the examples of health care clusters in Poland, there are interesting cases of groupings aimed at development of health services provided internationally, thus providing attempt to implement solutions to increase the competitiveness of Polish health care providers, under the provisions of the EU directive on cross-border health care[3,4].

CONCLUSIONS

The expansion of cluster initiatives stimulated by the economic law, which can be observed in many sectors of modern economies, most probably will appear also in the health sector. In light of recent clustrification experience in this sector, as well as opinions and expectations expressed by health market participants and experts specializing in investigating this sector, it remains an open question, what final form this process is going to take. At least two possible directions of evolution of these organizational solutions should be expected. On the one hand, due to the strong fusion between health care market and public administration, which in the vast majority of developed countries is embarked with the responsibility for ensuring access to health care services to the population, we can expect clustering to become a tool used for increasing the efficiency of this process. On the other hand, it may become just a tool of commercialization of ideas, taking a form analogous to, or only slightly differing from, clusters already existing in other markets. It is worth noting that in the light of the considerations outlined in this article, both of these forms can develop with a strong stimulation on the side of the state's economic and social policy. In both cases, however, slightly different will be the objectives of such stimulation. In the first case the assumed beneficiary of clustrification will be the community living in a given geographical area, and the expected effect of government's stimulus measures will be to improve the efficiency of health services, reduce their costs and increase availability, so in terms of general application—to increase the effectiveness of the impact on public health. Although in this case, similarly to the second one, we have to deal with the combination of commercial and non-commercial entities, bodies directly involved in providing health services, and those engaged rather in development and delivery of new technologies, units from the area of economy, science or social organizations—their advantage will be rather a secondary to the profit generated in the sphere of health system and social life.

In the second case the assumption of public stimulation will be primarily to support the competitiveness of companies operating in the health care market. This may apply to service providers and to companies specializing in developing modern medical technologies, pharmaceuticals, or the broadly recognized know-how. The average receiver of health care benefits also in this case can gain some profit, like the access to services at a higher level of technological advancement, with potentially better therapeutic effectiveness and quality. It will be, however, more a side effect of stimulus measures addressed primarily to the market participants, as well as supporting the economic development of regions, where health care will become one of the elements contributing to the competitiveness of geographically concentrated economic system.

The previous experience with clustrification in health care suggest dominance of the second of described trends. Moreover, in a relatively small scale the observable processes are actually the result of intentional supportive actions taken by the public administration. To a greater extent they are a result of bottom-up initiatives taken by the stakeholders. At the same time health care organizations emphasize the great potential inherent in the clustrification process, while among the obstacles to its dynamization, they indicate mainly the deficit of trust and lack of leaders who would be willing to take on the burden of initiation and ongoing coordination of the development and functioning of the cluster. It is also commonly underlined that the large scope of potential benefits of clustrification may be obtained more in the social sphere, than on the market. In our opinion, in the area of public health policy there is the space for providing the social sphere and the market with the expected coordinative solutions. At the same time it is possible to manage the affected processes in such a way, as to maximize the chances of achieving the desired positive economic effects, and optimizing internal processes taking place within the health system. Thus, in our opinion, health care cluster can be an innovative tool for the harmonization of public interest and the particular interests of a purely economic nature, that in the public debates on health are often situated in an antagonistic position to each other.

The example of Poland proves that the process of clustrification among health care entities requires external support, which should be firstly understood as the activity of public institutions. This is all the more justified, that the formula of public-private symbiosis, organizational and financial co-responsibility, is a favorable solution from the point of view of the expected health outcomes and efficiency. Despite this fact, the case of Polish public administration is that it do not provide enough support for entities willing to take action in health care with the use of economic cluster. Therefore, it

[3]www.pikmed.pl/centrum-informacji-ds-transgranicznej-opieki-zdrowotnej (accessed 10 May, 2016)

[4]http://medycyna.lublin.eu/o-klastrze/wizja-misja-cele/?lang=en (accessed 10 May 2016)

appears advisable to formulate a package of recommendations for state's policy to support clustrification of health care through the increased efforts to create a system of legal and tax preferences for cluster initiatives and provision of organizational support in terms of know-how. This support should be targeted particularly at bodies and individuals, who may act as cluster leaders.

AUTHOR CONTRIBUTIONS

PR and TH delivered the data for the study and outlined the paper's key messages. JW prepared the draft of the paper. TH contributed to the preparation of the final version of the paper and provided new information necessary to revise the paper. PR prepared the final version of the paper.

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