CHALLENGES OF PHARMACOECONOMICS IN GLOBAL HEALTH ARENA

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CHALLENGES OF PHARMACOECONOMICS IN GLOBAL HEALTH ARENA

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The pace of globalization has significantly accelerated since the end of the Cold War Era in 1989. These changes profoundly affected health care systems worldwide. Health policy makers increasingly started facing new harsh challenges in their uneasy task to provide universal health coverage and decent equity of access to medical services. Among the most prominent demand-side issues are extended longevity joined with population aging, rise of non-communicable diseases, and growing patient expectations. Supply-side causes are gains in societal welfare and living standards, technological innovation in medicine and continuing rapid urbanization in developing world regions. Successful insurance-based risk sharing agreements made drug dispensing and medical service provision cheap or virtually free at the point of consumption in most OECD and many middle-income countries. Coupled with massive build-up of workforce capacities and strengthening of primary care and hospital networks, all these factors contributed to the "supplier induced demand" phenomenon.

There is straightforward historical evidence of long-term growth in pharmaceutical and overall health spending both in absolute and GDP% terms worldwide. The accumulated constraints deriving from skyrocketing costs of care were felt in many areas of clinical medicine even among the richest societies. Cardinal examples of expensive and hardly affordable therapeutic areas are orphan drugs indicated to treat rare diseases and targeted biologicals used in autoimmune disorders and cancer. Last but not least, is troubled and frequently denied access to even essential generic pharmaceuticals still taking place in many nations. This appears to be particularly the case among the world's poor and under-served citizens residing in rural and suburban areas of low- and middle-income countries. To a large extent, these difficulties are worsened by lack of evidence-based resource allocation strategies and less sustainable financing strategies.

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EDITORIAL
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Editorial: Challenges of Pharmacoeconomics in Global Health Arena

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Editorial on the Research Topic

Challenges of Pharmacoeconomics in Global Health Arena

The pace of globalization has significantly accelerated since the end of the Cold War Era in 1989. These changes profoundly affected health care systems worldwide (Jakovljevic et al., Jakovljevic et al.). Health policy makers increasingly started facing new harsh challenges in their uneasy task to provide universal health coverage and decent equity of access to medical services. Among the most prominent demand-side issues are extended longevity joined with population aging (1), rise of non-communicable diseases, and growing patient expectations (2). Supply-side causes are gains in societal welfare and living standards, technological innovation in medicine and continuing rapid urbanization in developing world regions (3). Successful insurance-based risk sharing agreements made drug dispensing and medical service provision cheap or virtually free at the point of consumption in most OECD and many middle-income countries. Coupled with massive build-up of workforce capacities and strengthening of primary care and hospital networks, all these factors contributed to the "supplier induced demand" phenomenon (4).

There is straightforward historical evidence of long-term growth in pharmaceutical and overall health spending both in absolute and GDP% terms worldwide (5). The accumulated constraints deriving from skyrocketing costs of care were felt in many areas of clinical medicine even among the richest societies. Cardinal examples of expensive and hardly affordable therapeutic areas are orphan drugs indicated to treat rare diseases and targeted biologicals used in autoimmune disorders and cancer (Kamusheva et al.). Last but not least, is troubled and frequently denied access to even essential generic pharmaceuticals still taking place in many nations (6). This appears to be particularly the case among the world's poor and underserved citizens residing in rural and suburban areas of low- and middle-income countries (3). To a large extent, these difficulties are worsened by lack of evidence-based resource allocation strategies and less sustainable financing strategies (Pejcic).

This Research Topic has successfully attracted a variety of contributions tackling the core challenges of medicines provision and medical care financing across the globe. Its target to reveal some of the hidden underlying causes of uneven access to medicines was achieved to great extent. A total of eleven articles have been published. Exceptional regional diversity covering national health system issues ranging from Papua New Guinea to Brazil, Syria, Denmark, Finland, Bulgaria, Serbia, Bosnia and Herzegovina, Croatia, Macedonia, Montenegro, Slovenia, and South Africa.

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A variety of methodological approaches was exploited in these articles inclusive of epidemiological research, perspectives, literature reviews, commentaries, and ultimately two systematic reviews. Large part of these contributions focused on sustainability of antibiotics supply in hospitals (Zwane et al.) and clinical and economics consequences of irresponsible prescribing and dispensing (Horvat et al.). Probably the most prominent example, given the civil war related circumstances is the contribution coming from Syria, describing how one of the most developed pharmaceutical industries in MENA/Eastern Mediterranean region came to drug shortages of essential medicines (Jakovljevic et al.).

Japanese research was conducted on malaria diagnostics in pediatric South-East Asian populations (Tsukahara et al.). The Bulgarian group wrote an excellent review on the role of ethical and legal considerations in biometric data usage (Deliversky and Deliverska). Another piece coming from Balkan academic centers dealt with prescribing policies on pharmaceuticals and their affordability among chronic patients suffering from NCDs (Pekez-Pavlisko et al.). Probably the two most ambitious pieces were the two systematic reviews. The first one compiled the evidence published in the Brazilian academic, industry and governmental sectors output in interdisciplinary studies surrounding health economics (Decimoni et al.) while the second one, compiled by one of the Topic editors, did a bibliographic synthesis of global health economics publishing output in quantitative terms (Jakovljevic and Pejcic). Given the entire scale of contributions by solicited and unsolicited research groups worldwide, Editors believe that the Research Topic has lived up to its goal and achieved expectations filling some knowledge gaps in the science of pharmacoeconomics.

AUTHOR CONTRIBUTIONS

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

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PERSPECTIVE
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Antibiotic Resistance in Syria: A Local Problem Turns Into a Global Threat

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Pharmaceutical sector of Syrian Arab Republic before the war was characterized by bold and successful development since the late 1980s. With the beginning of war in the country back in March 2011, momentum has changed significantly. Traumatism, communicable diseases related to morbidity and mortality as well as wound infections became particularly hot public health concern. This relates not only to the direct victims of military conflict but also to the displaced civilians, refugees, and ordinary citizens alike. Evolving legislative framework in Syria since 1980s tolerated dispensing of antibiotics without appropriate prescription. Such practice led to spreading of antibiotic resistance among the local bacteria frequently causing both community-acquired and nosocomial infections. Laboratory findings of resistant bacteria strains among the Syrian refugees in some European countries serve as evidence of concern spreading far beyond Middle East. Practice of self-diagnosis and self-medication with antibiotics by patients themselves and restraint to pharmacist advice is widespread. A number of recommendations is presented to stakeholders to compact antibiotic resistance after the peace is established in the country. The successful implementation of such recommendations is the way to preserve shrinking golden reserve of highly potent antibiotics as it is the last defense line against resistant bacterial strains causing severe life—threatening infections.

Keywords: Syria, pharmaceuticals, market, antibiotics, resistance, bacteria, civil war, crisis

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HUMANITARIAN CRISIS, WAR, AND PHARMACEUTICAL MARKET—LEGACY OF SYRIA

Pharmaceutical markets worldwide exhibit great diversity in terms of prescription and dispensing patterns and value-based turn over (1). Their dynamics is grounded in the legacy of health care system establishment. Traditional medical services provision and financing differ profoundly from one global region to another. Few core examples of such diversity are major historical systems ranging from British Beveridge (2) to Soviet Semashko (3) and from German Bismarck (4) to Chinese contemporary health system (5) war.

Middle East presents a distinctively different region of the Old World (6). Ninety year old historical records on practice of pharmacy in Syria describe it as a former Ottoman province under French mandate. Its humble market presence of seldom drugs recognized in official clinical medicine of post WWI era was following Turkish traditions largely (7). The aim of this article is to review the current state of antibiotic use in Syria and clarify the main reasons behind the widespread irrational use of antibiotics in order to suggest venues of interventions.

In Syria, the main source of health financing comes from the government's budget presented by the Ministry of Health and other ministries such as the Ministry of Higher Education, the Ministry of Defense, and the Ministry of Local Administration (8). Public health services in places such as health centers and hospitals have long been offered free of charge. However, since 1998, patients have had to pay little charges to get access to certain health services in some public hospitals (9). Although inexpensive, people more often utilize these facilities in certain medical conditions, such as complicated surgeries, hemodialysis, cancer chemotherapy, and blood disorders.

Public health services in Syria are commonly of insufficient quantity and quality (State planning organization, 2006). Hence, patients have to visit private clinics, where they make out-of-pocket payments. Those payments slightly increased from 59.6% in 2000 to 61% in 2008 (10). No national insurance system that covers all population exists in Syria. Some small-scale health insurance schemes offered limited coverage to individuals in certain public companies, ministries and professional associations (11). Since 2004, private insurance companies have provided limited services to individuals (8). The high out-of-pocket spending and the absence of a national health insurance system drove patients to pharmacists to dispense medicines.

Before the current war began in 2011, Syria was recognized among the Arab League nations for its strong domestic pharmaceutical industry (12). Back in 1988, it had sufficient supply of educated clinical physicians. Occasional drug shortages and lack of access to vital medicines were recognized as the core weakness of the national health system (13). Since the late 1980s until the late 2000s, governmental supported this sector to cover almost 90% of national needs compared to only 6% in the beginning (14). Notable $150 million valuable annual exports were achieved toward few dozen of Organization of Islamic Conference (OIC) countries. Local labor market, heavily dominated by women consisted of over 17,000 employees and even 54 local pharmaceutical factories (14).

Coming back to contemporary momentum, we witness a disastrous war inside the Syrian Arab Republic as a consequence of complex chain of events following the Arab Spring colored revolutions (15). As in several similar previous large conflict areas such as Somalia, Afghanistan, the Democratic Republic of Congo and Haiti, health care provision, and outcomes are greatly affected (16). Relief in severely disrupted countries is achieved largely by multilateral donor agencies such as the Red Cross (17), WHO Division of Emergency and Humanitarian Action, Red Crescent (18) and many others (19). With the intent to provide more equitable and just outreach of essential drugs supplies toward most vulnerable citizens, some of the UN agencies such as WHO even created guidelines for distribution of donation medicines aimed to cover drug shortages (20). Probably, the most notable example of health system crisis in the surrounding Middle Eastern nations are reports coming from Iraq described as early as of 2003 (21).

Syria is no exception to similar vulnerabilities. Threatened supplies of essential medicines is currently the case even far outside major refugee migration routes (22) and war torn areas of the country. Major multilateral agencies such as the Médecins Sans Frontières (MSF) have claimed serious degree of disrupted access to basic health care for the ordinary citizens. Official WHO estimate was that Syria needed a total of $900 million worth of essential medicines and supplies in a single year following March 2013. However, keeping in mind the international financial climate at that time and the stage of the war, major donors only partially covered the urgent needs. Consequences were particularly striking in some clinical areas such as diabetes, cancer care, appropriate blood storage and testing facilities necessary for safe transfusions in surgery (22).

CONCERNING GROWTH OF ANTIBIOTIC RESISTANCE IN SYRIA

If we think about the nature of modern urban warfare, we could notice a long term trend that infantry weaponry is actually being made with the purpose to make wounds instead of killing at the first place. This trend in military equipment manufacturing is purely related to industrial and strategic reasons (23). This sad truth had profound and disastrous consequences both for the combatants (military personnel) of all fractions and civilians in Syria. The huge frequency and scale of traumatism impose a burden of appropriate blood transfusion provision and need to cure pyogenic wound infections. Bacterial causes are primarily aerobic Streptococcus, Staphylococcus species, and anaerobic Clostridium bacteria, notorious for causing gas gangrene.

Here we face another core issue even when common broad-spectrum antibiotics are at disposal of major hospitals and day care centers throughout the country. Antibiotic resistance presents an alarming threat to antimicrobial therapy. This occurring public health concern extends far beyond Syria toward other Middle Eastern neighborhood countries and the European countries alongside major refugee evacuation routes (24). The roots of this problem are inherited in the Syrian health system. The epidemiological burden of infections morbidity and mortality continues to grow further (25) as documented in the framework of Global Burden of Disease Project (26). Workload for the local and international health workforce and costs of care are largely attributable to traumatism, community-born and nosocomial bacterial infections arising from neglected chronic conditions (27). These refer to poverty and absence of decent medical care and access to medicines as indirect consequences of war. Contributions to release the suffering and medical expenditure are paid by Middle Eastern and high-income donor countries worldwide, given the wide spread of Syrian refugee crisis (28). The evidence clearly suggests that together with

migration of patients with infections, bacterial resistance also moves (29). This study looks into the evidence compiled from samples collected in Syria, Jordan, and Europe and the reasons behind this problem (30).

A study on the Syrian antibiotic resistance performed by Omran and Askar at Al-Mouwasat University Hospital (31) demonstrated a decline in the bacterial resistance against the antibiotics that were included in the study in comparison with earlier studies carried out at the same hospital (30). Antibiotic resistance may develop in weeks, months, or over a period of years. The increase in travel from Syria to different parts of the world due to the War indicates that the antibiotic resistant microbes can be transported within hours or days to other locations. A report from a charitable hospital in a neighboring country, Jordan, has documented cases of clinical failure to the first-line choice for prophylaxis and treatment of skin and soft-tissue infections (narrow-spectrum cephalosporin) (32).

In 2016, 48 Syrian migrants arrived in Italy. Upon their arrival, they received a physical examination and were subject to microbiological surveillance by blood, rectal, pharyngeal, and nasal swabs collection. Swabs were delivered and examined in local Italian clinical pathology and microbiology laboratory. Pathological analysis showed that all the 48 migrants were negative for HBV, HCV, and HIV infections. However, a large number of unusual gram-negative bacteria species were isolated and among the isolates, different strains resistant to antibiotics were found (33). European centers (for healthcare of asylum seekers) also reported multi-drug resistant (MDR) pathogens among wounded adult patients and refugees from Syria. In Germany, among refugees from Syria in 2016, the rate of colonization with gram-negative MDR pathogens was 60% (34).

In Syria, patients are frequently self-diagnosed and self-medicated, or they seek the advice of their local pharmacists (35) with prevalence rate of 57% (36). Over-the-counter sales of antibiotics have been reported in many countries of the Middle East; the prevalence rate of antibiotic self-medication ranged from 19 to 82% (37). Pharmacists, who have to be acquainted with adverse effects of antibiotics misuse, provide antibiotics over the counter without prescription fearing that their customers would go elsewhere (35). The supply of an antibiotic from a pharmacy without a prescription usually involves a consultation with a pharmacist. In previously published study, one out four participated pharmacists in Syria considers him/herself qualified to give the right medicine (38). Also, they reviled that among chosen pharmacies, 13.8% of pharmacies are working without a pharmacist. This fact is obviously leading to providing misinformation about drugs and selling antibiotics according to popular demand (39).The result of this action is that citizens acquire antibiotic without proper diagnosis and are at higher risk of developing antibiotic resistance.

It is very easy to purchase antibiotics in Syria without prescription (35). A cross-sectional study carried out on pharmacists in the capital, Damascus, found that 87% of them sold antibiotics without prescription, 10% accepted with prescription, and only 3% refused to give antibiotics without prescription (38). Pharmacists included in this study treated recurrent simple infection with common antibiotic, such as amoxicillin, with or without clauvalenate or cephalexin. A similar study conducted in Aleppo also showed that the overall prevalence of antibiotic drug dispensing without prescription was 85.5% (39).

Over long time, in a loose regulatory setting, physicians have frequently mistakenly prescribed antibiotics as a cure to diverse communicable diseases, such as flu and common cold. It is well-known that viruses are the origin of these diseases, therefore antibiotics are ineffective (40–42). Antibiotic sensitivity patterns are rarely checked. Doctors prescribe antibiotic as soon as possible in a fake attempt to save the patient's time and money. They sometimes even prescribe high doses of wide spectrum antibiotic to show patient families their ability to improve the clinical outcomes in a short time. Tendency of physicians to ignore good clinical practice guidelines is to a lesser extent evident even in high-income European, Asian, and North American clinical and academic milieu (36). However, in the Middle East, it has far more concerning extent (43).

Patients, on the other hand, who may not be aware of the side effects of such antibiotic treatment, may misuse their prescribed antibiotic by stopping the course of treatment too early, when the painful symptoms begin to relieve (44). They may also reuse the same antibiotic drug when they have similar symptoms after a period of time. This sort of poor patient compliance has been documented across a variety of low and middle-income countries even in full social peace and welfare living (37, 45).

In 2010, a cross-sectional study was carried out on 430 randomly selected adult residents of Kalamoon in Syria using standardized questionnaire. The study found that 85% had taken antibiotic medicines in the past 4 weeks and 34% were not aware of the adverse effects of antibiotics. Only 43% (out of the 85%) were prescribed the antibiotic by a physician to treat the condition, while 57% used an old prescription or took someone else's advice. This clearly indicates that the laws that control purchasing of antibiotics are ignored (46).

It is well-known that Syria still has the largest number of pharmaceutical companies compared to most other Arab countries. Although this branch of the economy suffered heavily due to military actions, domestic companies, despite war conditions, are capable to provide antibiotics at reasonable prices. Although antibiotics are not cheap, they are affordable to many middle-income households and patients.

Syria has a national-level committee designed to address antibiotic treatment related issues, including resistance. However, it has insufficient funding, resources, and leadership and thus it cannot play a significant role in controlling prescription, dispensing, and sale patterns. Moreover, Syria does not have a national policy restricting the availability of antibiotic medicines without a prescription (47).

In Syria, three national authorities deal with antibiotic resistance: The Central Infection Prevention and Control Committee, The Directorate of Drug Affairs, and The Department of Infection Control in Hospitals' Directorates. Despite of the presence of those national bodies, the WHO officer reported that the priority given to antimicrobial resistance had been declining, due to the current war. Syria has also national laboratories with the ability to identify resistant

bacteria; however, these laboratories do not produce reports or have a monitoring or reporting system for antibiotic resistance. Moreover, Syria does not participate in the regional infection control network (47).

The Ministry of Health in Syria, three decades ago, passed a law (Number 2/T, dated 12/1/1988) that determined drugs that could be sold to people without a medical prescription and antibiotics were not included in the list of drugs [Syrian Syndicate for Pharmacists—Laws and orders that coordinate pharmacy career in Syria]. Damascus, Syrian Syndicate for Pharmacists, 1994 [In Arabic]). Another law (Number 2/T, dated 23/1/1992) prevented pharmacists from reselling prescribed antibiotic to the same individual without the permission of a physician and prevented physicians from prescribing an antibiotic more than twice to treat the same infection for the same individual (Syrian Syndicate for Pharmacists, 1994). However, those regulations are not clearly stated or strictly enforced (48).

LEARNING FROM THE SYRIAN'S EXPERIENCE

Despite the global interest of the consequences of AMR, there is no sense of urgency about the current AMR status in Syria. Antimicrobial resistanceis not anymore purely a national concern. It turns to be an international issue with financial consequences. Hence, efforts should be coordinated in a Syrian national strategic plan to control the development of AMR. This can be done through reactivating the role of existed national committee and imposing more restrictions on dispensing antibiotics without prescriptions. Any savings made from the reinforcement of prevention and control activities are cost-effective and financial deficit should not be a barrier.

The establishment of antimicrobial surveillance system in Syria will be a good start. This surveillance system could benefit from the instructions of European Antimicrobial Resistance Surveillance Network (EARS-Net) reporting protocol (49) similar to the one suggested in Italy (50). The aim of such system would be to produce a reliable data on the sales of antibiotics from pharmacies as well as the development of AMR from laboratories. Accumulated data can be made publicly available on the Ministry of Health website with regular periodic updates to track and monitor the progress of AMR.

Given that the high level of AMR is the result of purchasing antibiotics without prescription (35, 38), it is necessary to increase the awareness of current and possibly future pharmacists of the negative consequences of AMR. Educational programs among community pharmacists and pharmacy students may help enhance the rational use of antibiotics with similar programs been suggested in other countries (51). Similar awareness programs among physicians may also address this concern. The second reason for the widespread irrational use of antibiotics is the soft enforcement of legislations regarding the illegal dispensing of antibiotics. Strong enforcement of those legislations includes imposing fines on the inappropriate dispensing as seen in the Republic of Srpska (52) or temporarily suspending pharmacists' licenses, which may reduce the illegal selling of antibiotics. Another action could be taken by the Ministry of Higher Education through designing teaching modules, where pharmacy students are taught to be health educators, and incorporate respecting legislations in their code of Ethics. Syrian Syndicate of Pharmacists should also play a role in promoting FIP and WHO guidelines of dispensing antibiotics through continuous education to pharmacists especially those located in mid and low educated areas (53, 54). In 2017, WHO reported that three pharmacy graduates, in collaboration with Syrian Syndicate of Pharmacists, started a campaign to inform pharmacists of their role in preventing antibiotic resistance (55). They reached over 400 pharmacies in Damascus in addition to healthcare centers and hospitals. This may be a promising strategy to reduce antibiotic resistance.

We also recommend activating the role of the national committee for the rational use of antibiotics to play its expected role as a national coordinating body responsible for enhancing the prudent use of antibiotics, similar to other countries (56, 57). Stakeholders can also reduce irrational antibiotic use by expanding health insurance coverage; this will encourage patients to visit physicians, rather than pharmacists. Hence, only physicians can make decision whether it is necessary to take antibiotics.

The negative economic impact of AMR involves increasing mortality rate and permanently reducing the size of population and prolonging the periods of sickness and, consequently that could reduce the labor workforce efficiency. A study by Taylor estimates the GDP loss due to AMR in the MENA countries (including Syria) to range between USD 2 billions and 159 billions per year over 40 years (58). Such large costs impose additional burden to the already exhausted Syrian economy recovering from the costly crisis (59). The implementation of the above mentioned recommendations shall contribute toward building up Syrian welfare state and a decently efficient and cost-effective health system once again in the near future.

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MJa, SA, MJu, and SM all contributed equally to the acquisition of published evidence, selection, and screening of evidence for its validity and methodological quality. All three authors have revised and contributed significantly to final manuscript for important intellectual content fulfilling all ICMJE conditions for authorship.

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Comparison of Health Service Utilization for Febrile Children Before and After Introduction of Malaria Rapid Diagnostic Tests and Artemisinin-Based Combination Therapy in Rural Papua New Guinea

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Background: In Papua New Guinea (PNG), a malaria treatment policy using rapid diagnostic tests (RDTs) plus artemisinin-based combination therapy (ACT) was widely introduced to rural communities in 2012. The objectives of the study were to evaluate the effect of this RDT/ACT introduction to a rural PNG population on health service utilization and to compare factors associated with health service utilization before and after the RDT/ACT introduction.

Methods: Household surveys with structured questionnaires were conducted before and after the introduction of RDT/ACT in a catchment area of a health center in East Sepik Province, PNG. We interviewed caregivers with children less than 15 years of age and collected data on fever episodes in the preceding 2 weeks. Using propensity score matching, febrile children before the introduction of RDT/ACT were matched to febrile children after the introduction. Then, the adjusted difference in the proportion of health service utilization [i.e., the average treatment effect (ATE) of the introduction of RDT/ACT on health service utilization] was estimated. We also employed a multilevel Poisson regression model to investigate factors influencing the use of health services.

Results: Of 4,690 children, 911 (19%) were reported to have a fever episode. The unadjusted proportion of health service utilization was 51.7 and 57.2% before and after the RDT/ACT introduction, respectively. After matching, no significant difference in the health service utilization was observed before and after the introduction of RDT/ACT (ATE: 0.063, 95% confidence interval −0.024 to 0.150). Multilevel regression analysis showed that the consistent factors associated with a higher utilization of health services were severe illness and being female.

Conclusion: The utilization of health services was not significantly different before and after the introduction of RDT/ACT. Villagers may have neither sufficient informations on the new protocol nor high acceptance of RDT/ACT. The observed gender bias in health service utilization could be due to female caregivers' preferences toward girls.

Keywords: antimalarials, delivery of health care, health service needs and demand, treatment-seeking behavior, sex factors

INTRODUCTION

Despite the recent progress of investments in global malaria control, an estimated 212 million malaria cases and 429,000 malaria deaths still occurred in 2015 worldwide (1). Accurate diagnosis and prompt treatment with appropriate antimalarial drugs are critical for reducing the malaria burden. Because of the widespread resistance of *Plasmodium falciparum* malaria parasite species to chloroquine and sulphadoxine/pyrimethamine (SP), the World Health Organization (WHO) has recommended quality-assured artemisinin-based combination therapy (ACT) for uncomplicated *falciparum* malaria since 2005 (2).

Parasite-based diagnosis is desirable before use of ACT because over-prescription of ACT, which is much more expensive than using conventional drugs, is a great threat to cost-effective intervention. Moreover, parasitological diagnosis can reduce the risk of adverse drug reactions as well as unnecessary drug pressure to malaria parasites. In most remote rural health facilities in malaria-endemic regions, however, microscopic diagnosis is limited, and malaria diagnosis has traditionally relied much on the history of fever and symptom-based diagnosis. Rapid diagnosis test (RDT) for malaria, therefore, enables accurate diagnosis in rural settings because it is easy to use, not time-consuming, and does not require electricity unlike microscopic examination (3). Consequently, in 2010, WHO changed the policy from clinical diagnosis to parasitological diagnosis, with either microscopy or RDT for all suspected malaria cases prior to treatment (4). Parasitological confirmation of malaria before treatment has been mandatory since 2015 in the latest guidelines for treatment of malaria (5).

Many studies have evaluated the impact of the introduction of RDT/ACT from health provider perspectives: reduction in antimalarial prescriptions (6–10); reduced hospital stays and prescription of antibiotics (11) and improved availability of antimalarial drugs (12). On the other hand, comparative studies of patient treatment-seeking behavior before and after the introduction of RDT/ACT have been quite few, although investigations of changes in health demand will be essential in evaluating the effectiveness of the newly introduced policy. A community-based study in Tanzania reported no significant change in health facility attendance for child fever before and after the introduction of RDT/ACT (13). In that study, however, health facility utilization for febrile children was exceptionally high (>75%) in the baseline survey partly because of a long-term social campaign at the site. Consequently, little information is available about the impact of introducing RDT/ACT on health service utilization in routine health service settings in malaria-endemic areas.

Papua New Guinea (PNG) remains a high-risk country for malaria in the Asia Pacific region. The number of malaria cases per 1,000 population was estimated to be 118 in 2015 (1). In 2011, the PNG government introduced a new protocol recommending ACT as the first-line malaria treatment together with parasite-based diagnosis with either RDT or microscopy as a result of widespread chloroquine resistance (14). By the end of the year 2012, malaria diagnosis using RDT and ACT treatment became available at the community level, including all remote/rural health facilities.

In the present study, we assessed the impact of the introduction of RDT/ACT on health demand in a rural PNG population. If patients rationally decide to maximize their utility and recognize the benefit of accurate RDT diagnosis and efficacious ACT, health demand for RDT/ACT will increase after the introduction of RDT/ACT. To prove this, we aimed to evaluate the effect of the introduction on health facility utilization to adjust for covariates using propensity score matching. Further, we investigated factors associated with health facility utilization before and after the introduction of RDT/ACT.

MATERIALS AND METHODS

Study Area and Antimalarial Drug Supply in the Area

We conducted the study in a malaria-endemic lowland coastal area within the catchment area of a major health facility (i.e., a health center) located approximately 56 km from Wewak, the provincial capital of East Sepik Province, PNG. Malaria transmission in the study area is all-year round, and malaria is a leading cause of health facility visits. Prior to introduction of the RDT/ACT protocol, malaria was diagnosed clinically without support of microscopy at the health facility, with the antimalarial drug treatment regimen consisting of chloroquine plus SP for adults and amodiaquine plus SP for children.

Rapid diagnostic test/ACT was introduced to the formal health facilities in Wewak District in December 2011. Other than the health center, five aid posts were operated in the study site and the surrounding areas. Health center staff occasionally visited communities for a mobile clinic. There were a general hospital and two clinics in Wewak town; however, residents of the study site rarely used those facilities for malaria treatment (15). In 2007, each community assigned a village health volunteer (VHV) who

Abbreviations: ACT, artemisinin-based combination therapy; ATE, average treatment effect; ATET, average treatment effect on the treated; CI, confidence interval; GPS, global positioning system; PNG, Papua New Guinea; PR, prevalence ratio; RDT, rapid diagnostic test; SP, sulphadoxine/pyrimethamine; VHV, village health volunteer; WHO, World Health Organization.

clinically diagnosed malaria and provided SP plus chloroquine or amodiaquine after completion of a 1-month initial training. VHVs were allowed to use RDT/ACT after retraining in August 2012.

Data Collection

A baseline cross-sectional survey among 20 communities was undertaken in February 2011 and February 2012. All caregivers with children aged less than 5 years were included as target interviewees. Trained field assistants interviewed caregivers to collect data on the fever episodes of their children, treatment choices, and caregiver and patient characteristics in the 2 weeks preceding the interview. If a caregiver had children aged 5–14 years, information on these children was also collected. The caregivers were primarily mothers; if not mothers, the caregivers included adult household members who mainly cared for the children, such as fathers, aunts, and grandmothers. We also obtained information on the characteristics of the health facility from direct observation or interviews with health workers. The detailed procedures of the baseline survey have been described elsewhere (15).

In February–March, 2015, a follow-up cross-sectional survey was conducted in 23 communities. The target population included all children aged less than 15 years. The same information as that in the baseline survey was collected. In addition, caregivers were asked about their knowledge of health facility locations and the experience of malaria treatment visits at health facilities in the preceding year.

Outcome and Covariates

The outcome variable was whether caregivers of a febrile child initially chose health providers who were able to provide diagnosis and treatment in accordance with the national protocol in case of malaria (i.e., hospital, health center, aid post, clinic, mobile clinic, or VHV = 1; traditional health practitioner, pharmacy, general shop, neighbor, or self-care = 0). Covariates were selected based on our previous study (15) as follows: household's asset index, patient's gender, patient's age, severity of the illness as perceived by the caregiver, the caregiver's education, direct cost for utilization of the nearest health facility to patient's house, distance from patient's house to the nearest health facility, and drug availability at the nearest health facility.

In general, there was no user fee for VHV, but VHVs were allowed to charge a small amount. The observed maximum fee was PNG Kina 1 (USD 0.48 in 2011) in 2011 and 2012 and Kina 2 in 2015. In contrast, the outpatient fee for a child at formal health facilities was PNG Kina 1 (USD 0.48 in 2011) before November 2011 and Kina 2 for age <6 years and Kina 3 for age between 6 and 14 years after November 2011. This fee included the examination, a prescription, drugs, and revisit costs. The nearest health facilities for the patients were located within walking distance from their houses; thus, medical costs were equivalent to direct costs. The locations of houses and health facilities was recorded with global positioning system devices and direct distance from the house to the health-care facility was calculated using a digital map of the area (PASCO Satellite Ortho, PASCO Corporation, Tokyo, Japan) and Quantum GIS 2.14.1. To estimate asset index, seven dummy variables were selected: own mobile phone, own radio or stereo, own house with tin roof, own house with western-style wall, own generator, own rainwater tank for drinking, and own car or outboard motorboat (15). Assets were used as a proxy variable for long-term economic status by constructing a linear index of asset ownership and housing characteristics using principle component analysis (16).

Statistical Analysis

Propensity score was estimated using a logistic regression adjusted with the covariates described above, which were possible determinants of utilization of health facilities. The vector of the covariates was defined as $\boldsymbol{X}$. Binary outcome $Y = 1$ denoted utilization of health facilities and $Y = 0$ denoted otherwise. Treatment dummy variable Z was assigned 1 for a treated individual, that is, a febrile child after the introduction of RDT/ACT, and 0 for a comparison individual, that is, a febrile child before the introduction of RDT/ACT. Propensity score of individual i was given as

$$\Pr(Z = 1 \mid \boldsymbol{X} = \boldsymbol{X}_i) = \frac{\exp(\boldsymbol{X}_i'\boldsymbol{\beta})}{1 + \exp(\boldsymbol{X}_i'\boldsymbol{\beta})}.$$

Each individual i had potential outcomes, Y_{1i} if $Z = 1$, and Y_{0i} if $Z = 0$; however, only one of Y_{1i} and Y_{0i} was observed in the study setting. Propensity score matching enabled us to estimate the missing potential outcome for each individual. We applied a full matching method: a treated individual was matched to one or more comparison individuals, with replacement, and a comparison individual was matched to one or more treated individuals with replacement. Nearest-neighbor matching was adopted within a caliper of 0.2 of the SD of the logit of the propensity score (17). We adjusted the standardized difference after matching to achieve balance of covariate (18); thereafter, average treatment effect (ATE) and average treatment effect on the treated (ATET) were estimated. Stata SE14.2 command *teffects psmatch* (StataCorp, TX, USA) was applied for the analysis. ATE and ATET were defined as:

$$\mathrm{ATE} = E[Y_{1i} - Y_{0i}],$$

$$\mathrm{ATET} = E[Y_{1i} - Y_{0i} \mid Z = 1].$$

To investigate factors associated with health facility utilization, a two-level random-intercept Poisson regression model with a robust variance estimator was applied to the pooled data (19). Individual level was determined as level one and village level was applied as level two. The same variables as the covariates used for propensity score matching plus the treatment dummy variable were included in the vector of the explanatory variables $\boldsymbol{V}$. Random intercept of village j was defined as u_j. The probability of the outcome Y selected by the individual i living in the village j was represented as

$$\Pr(Y_{ij} = y \mid \boldsymbol{V}_{ij}, u_j) = \frac{\exp(-\mu_{ij}) \times \mu_{ij}^{y}}{y!}, \; y = 0,1,$$

where $\mu_{ij} = \exp(\boldsymbol{V}_{ij}'\boldsymbol{\beta} + u_j)$. We estimated adjusted prevalence ratio (PR) and confidence interval (CI) using Stata SE14.2

command *mepoisson*. The threshold for significance was set at $p < 0.05$ (two-tailed).

Ethical Clearance

Ethical clearance for the study was obtained from the Medical Research Advisory Committee of the PNG National Department of Health (No. 09.26; No. 14.22) and the Tokyo Women's Medical University Ethical Committee (No. 1744). This study was conducted in accordance with the Declaration of Helsinki and the recommendations of those committees with written informed consent from all participants.

RESULTS

Descriptive Statistics

The participation proportion of the target households was 87% (736/851) in the baseline survey and 96% (1062/1103) in the survey after the introduction of RDT/ACT. A total of 4,690 children belonging to 2,143 caregivers participated in the study, and 911 (19%) fever episodes were reported in the preceding 2 weeks. Unadjusted (i.e., prematching) descriptive statistics of comparison (before the introduction of RDT/ACT) and treated (after the introduction of RDT/ACT) groups are presented in **Table 1**. The proportion of health service utilization increased from 52% before the introduction of RDT/ACT to 57% after the introduction, but the increase was not significant. The distributions of availability of antimalarial drugs at the nearest health facility, direct cost of the nearest facility, age of patients, and illness severity perceived by caregivers were significantly different between the comparison and treated groups.

In 2015, about 3 years after the introduction of RDT/ACT, 99% (1165/1171) of caregivers knew the location of at least one health facility and 70% (815/1171) had visited a health facility to seek malaria diagnosis and/or treatment for their child in the preceding year.

TABLE 1 | Descriptive statistics.

	Comparison group (*N* = 418)		Treated group (*N* = 493)		
Variables	***n***	**%**	***n***	**%**	***p*-Value**
Health facility utilization					
Yes	216	51.7	282	57.2	0.094
No	202	48.3	209	42.4	
Missing	0	0.0	2	0.4	
Drug availability: yes	281	67.2	403	81.7	<0.001
Direct cost (PNG Kina[a])	0[b]	0–1[c]	0[b]	0–1[c]	<0.001
Distance (km)	0.70[b]	0.26–1.18[c]	0.84[b]	0.21–1.61[c]	0.493
Age of patient (years)	4[b]	2–5[c]	5[b]	3–9[c]	<0.001
Gender of patient: male	215	51.4	257	52.1	0.834
Illness severity					
Mild	233	55.7	227	46.0	<0.001
Moderate	113	27.0	181	36.7	
Severe	40	9.6	85	17.2	
Missing	32	7.7	0	0.0	
Education of caretaker (years)	6[b]	6–8[c]	6[b]	6–8[c]	0.953
Missing	23	5.5	0	0.0	
Asset index	−0.312[b]	−0.91–0.58[c]	−0.312[b]	−0.91–0.33[c]	0.805
Missing	5	1.2	8	1.6	
Number of villages	20		22[d]		

To compare the difference of variables between the comparison [before the introduction of rapid diagnostic test (RDT)/artemisinin-based combination therapy (ACT)] and treated (after the introduction of RDT/ACT) groups, chi square test was used for categorical variables and Wilcoxson rank-sum test was used for continuous variables.

[a]PNG Kina 1 = USD 0.48 in 2011 (average exchange rate calculated by the World Bank).

[b]Median.

[c]Interquartile range.

[d]Of 23 villages studied, no fever episode was reported in a village.

Estimation of ATE Using Propensity Score Matching

We excluded 7.5% (68/911) of episodes due to at least one missing value of the covariates used for matching. Consequently, 360 children from the comparison group and 483 from the treated group were included for calculating the propensity score. Although the standardized difference with respect to the gender of patients slightly exceeded 10%, the covariate balance after matching was improved (**Table 2**). After matching, the adjusted difference of the proportion of health service utilization after the introduction of RDT/ACT compared with the baseline proportion was positive but not statistically significant [ATE: 0.063, 95% CI −0.024 to 0.150, $p = 0.153$; ATET: 0.057, 95% CI −0.047 to 0.161, $p = 0.283$].

Factors Associated With Health-Care Utilization Using Regression Models

In line with the results of propensity score matching, the effect of the introduction of RDT/ACT on the utilization of health-care facilities was not significant using the multilevel Poisson regression model (PR, 1.07; 95% CI, 0.92–1.24) (**Table 3**, Model 1). Moderate- and severe-febrile patients were approximately 30 and 50% more likely, respectively, to use health facilities than mild-febrile patients (moderate: PR, 1.31; 95% CI, 1.11–1.56; severe: PR, 1.50; 95% CI, 1.22–1.87), whereas being male was inversely associated with health service utilization (PR, 0.85;

TABLE 2 | Standardized differences of covariates.

	Standardized differences	
Covariates	**Unmatched**	**Matched**
Antimalarial drug availability: yes	0.325	0.008
Direct cost (PNG Kina[a])	−0.235	−0.088
Distance (km)	0.092	−0.017
Age of patient (years)	0.582	−0.065
Gender of patient: male	−0.019	0.102
Illness severity: moderate	0.182	−0.005
Illness severity: severe	0.203	0.048
Education of caretaker (years)	−0.058	0.040
Asset index	−0.023	−0.043

[a]PNG Kina 1 = USD 0.48 in 2011.

TABLE 3 | Estimation results of multilevel Poisson model.

	Model 1: pooled data		
Fix variables	**Prevalence ratio**	**95% Confidence interval**	***p*-Value**
Treatment dummy (comparison = 0/treated = 1)	1.07	0.92–1.24	0.38
Drug availability (no = 0/yes = 1)	1.02	0.83–1.25	0.84
Direct cost (PNG Kina[a])	0.99	0.83–1.18	0.90
Distance (km)	0.88	0.84–0.93	<0.001
Age of patient (years)	0.99	0.97–1.00	0.16
Gender of patient (female = 0/male = 1)	0.85	0.78–0.93	<0.001
Illness severity: moderate	1.31	1.11–1.56	0.002
Illness severity: severe	1.51	1.22–1.87	<0.001
Education of caretaker (years)	1.02	0.99–1.05	0.24
Asset index	1.00	0.93–1.07	0.98
Intercept	0.51	0.38–0.70	<0.001
Random variable			
Village (variance of intercept)	0.01	0.00–0.10	
Number of individuals	843		
Number of villages	24		

	Model 2: comparison group			Model 3: treated group		
Fix variables	**Prevalence ratio (PR)**	**95% confidence interval (CI)**	***p*-Value**	**PR**	**95% CI**	***p*-Value**
Treatment dummy (comparison = 0/treated = 1)						
Drug availability (no = 0/yes = 1)	0.98	0.68–1.42	0.92	0.93	0.74–1.18	0.57
Direct cost (PNG Kina[a])	1.24	0.90–1.71	0.19	0.91	0.78–1.06	0.21
Distance (km)	0.83	0.72–0.95	0.007	0.90	0.82–1.00	0.050
Age of patient (years)	0.98	0.95–1.01	0.11	0.99	0.98–1.01	0.42
Gender of patient (female = 0/male = 1)	0.86	0.76–0.98	0.020	0.83	0.71–0.97	0.022
Illness severity: moderate	1.32	1.06–1.64	0.013	1.32	1.07–1.62	0.009
Illness severity: severe	1.57	1.20–2.05	0.001	1.50	1.19–1.91	0.001
Education of caretaker (years)	1.03	0.97–1.09	0.30	1.02	0.99–1.05	0.25
Asset index	0.98	0.88–1.09	0.68	1.00	0.92–1.10	0.93
Intercept	0.49	0.32–0.75	0.001	0.59	0.43–0.81	0.001
Random variable						
Village (variance of intercept)	<0.001			<0.001		
Number of individuals	360			483		
Number of villages	20			22[b]		

The data collected before and after the introduction of rapid diagnostic test/artemisinin-based combination therapy were defined as comparison and treated groups, respectively. Adjusted PR and 95% CI for fix variables and variance of intercept for a random variable are shown.

[a]*PNG Kina 1 = USD 0.48 in 2011.*

[b]*Of 23 villages studied, no fever episode was reported in a village.*

95% CI, 0.78–0.93) (**Table 3**, Model 1). The effect of illness severity as well as gender of patient on health service utilization was nearly consistent before and after the introduction of RDT/ACT (**Table 3**, Models 2 and 3). Distance to the nearest health facility was inversely associated with health service utilization in the pooled data (PR, 0.88; 95% CI, 0.84–0.93); however, the association was not significant after the introduction of RDT/ACT (**Table 3**, Models 1 and 3).

DISCUSSION

We have shown that (a) the introduction of RDT and ACT did not significantly affect the utilization of health facilities offering such services and (b) illness severity and gender of patient were consistent determinants of health service utilization before and after the introduction of RDT/ACT.

As a theoretical framework of access to health care, physical accessibility to health facilities and availability of good health services, financial affordability, and perceived acceptability of health services by patients are considered indispensable dimensions of health-care access (20, 21). We showed no significant effect of RDT/ACT on health service utilization with adjustments for availability, accessibility, and affordability of health-care facilities as well as patient-related individual characteristics using propensity score matching. If caregivers suspecting child malaria show a higher acceptance of RDT/ACT than of the conventional protocol, a higher utilization of health-care facilities is expected to be observed.

Incomplete information on RDT/ACT may have influenced the decision-making of caregivers. There was no active promotion of the introduction of the new protocol in PNG. Health workers informally noticed the policy change to the general public at their visits to formal health facilities. In the study area, almost all caregivers knew the location of health facilities, and a substantial proportion of them had a recent experience of malaria diagnosis and/or treatment. However, this does not mean that they had heard of the benefit and necessity of the introduction of RDT/ACT from health professionals. To increase the demand for

utilization of RDT/ACT, active promotion of its importance to villagers through mass media and/or short message service may be helpful (22, 23).

Although villagers have information about the new protocol, rational decision-making is a different aspect. Several studies in African countries showed trust and positive acceptance by villagers of RDT performed by village community workers (24–26). In contrast, qualitative studies indicated that those who are familiar with conventional drugs had a negative acceptance of ACT in rural communities (27, 28). Some people in the study area may prefer chloroquine that was withdrawn from public health-care facilities. It was possible for them to get the drug at pharmacies and general shops and use it as self-medication, although it was not common to get over-the-counter drugs in the private sector (15). Investigation of villagers' stated preferences among conventional and newly introduced protocols will be useful in formulating health promotion strategies. The management of over-the-counter drugs also needs to be considered.

The magnitude of the effect of perceived illness severity on access to health-care facilities was consistently the largest before and after the introduction of RDT/ACT, suggesting that this variable was a primary and reliable determinant of decision-making for health-care utilization. Encouragement of health facility utilization by caregivers even for their perceived mild fever in children may increase the overall use of health facilities. Systematic reviews reported that caregiver assessment of fever in children by palpation was relatively accurate in excluding fever and that its specificity was low (29, 30). Thus, a higher number of negative malaria test cases would be expected with a higher utilization proportion for perceived fever episodes. Training for VHVs on integrated fever management, including treatment for negative malaria test cases, should be required (31).

Economists have argued gender bias of parental care as unequal allocation of parental investment to maximize one's own utility. Thomas (32) proposed the "like father, like son; like mother, like daughter" hypothesis. In the resource-limited condition, parents may make unequal allocations of resources among children. If men and women have socially different tasks, mothers may invest more in daughters and fathers in sons due to expectations of future returns to the investments in the form of help for their tasks from children of the same gender as them. If there is a conflicting interest between the father and mother about investment in a child, whether father or mother has the power to make a decision should be considered as another key determinant influencing actual behavior.

The observed gender bias of utilization of health-care facilities for febrile children may be a girl preference by female caregivers. In the study area, the division of labor based on gender and cooperation of labor between household members for food production from sago palm (*Metroxylin sagu*), the staple food of the area, were reported (33). The result was in accordance with the economic hypothesis mentioned above. However, recent analysis in 57 low- and middle-income countries reported that the proportion of utilization of health facilities for common illness of children was similar for boys and girls (34). In only two countries (Haiti and Uganda), females were more likely to be taken to health facilities, although the result from PNG was not included in the study. Because female bias in caregiver health-care-seeking behavior seemed rare (34), caution should be exercised with application of the "like father, like son; like mother, like daughter" hypothesis. Female vulnerability due to lower general health status in PNG could be a reason for the observed gender bias in health-care facility utilization (15).

Our study includes several limitations. First, propensity score matching can reduce selection bias in estimating treatment effects due to observed differences between the treatment and comparison groups, but our estimation is subject to biases from unobserved covariates. In particular, we were not able to remove the influence of an unobserved time change between 2011 and 2015 because policy change was simultaneously introduced in the study area. The global trend in treatment seeking for formal health facilities was estimated to show a 0.93 percentage point increase per year during the last 20 years (34). If this was the case in the study area, the trend increase is estimated to show a 3.7 percentage point increase before and after the introduction of RDT/ACT. Considering the magnitude of estimated ATE, a 6.3% point increase, there may be little risk of bias in the main findings because the difference of health service utilization before and after the introduction of RDT/ACT is expected to be smaller. Second, the external validity of the study was limited because our study population was limited to a catchment area of a health center in rural PNG. The proportion of health service utilization may be relatively high partly because over-the-counter use was not common in the study area. This may influence the results. Third, all information related to individual characteristics was based on caregiver reports. To minimize recall bias, we focused on fever episodes in the 2-week preceding reports.

In conclusion, we performed a propensity score matching analysis with a rural PNG population before and after the introduction of RDT/ACT to evaluate the effect of the policy change on the utilization of health facilities. The estimated ATE was not significant. The result was consistent with that of a conventional multilevel Poisson regression model. Further, we compared the factors associated with health service utilization before and after the introduction of the new malaria treatment policy. Illness severity and gender of patient were consistent determinants. Continued research in the same area will be needed to increase the internal validity of the study findings.

ETHICS STATEMENT

Ethical clearance for the study was obtained from the Medical Research Advisory Committee of the Papua New Guinea National Department of Health (No. 09.26; No. 14.22) and the Tokyo Women's Medical University Ethical Committee (No. 1744). This study was conducted in accordance with the Declaration of Helsinki and the recommendations of those committees with written informed consent from all participants.

AUTHOR CONTRIBUTIONS

TT conceived the study, designed the study, conducted the data collection, analyzed and interpreted the data, wrote the first draft of the manuscript, and completed the final version. TS designed

the study and interpreted the data. TF and FH collected and interpreted the data. All authors critically revised the draft and approved the final version.

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Cold War Legacy in Public and Private Health Spending in Europe

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Cold War Era (1946–1991) was marked by the presence of two distinctively different economic systems, namely the free-market (The Western ones) and central-planned (The Eastern ones) economies. The main goal of this study refers to the exploration of development pathways of Public and Private Health Expenditure in all of the countries of the European WHO Region. Based on the availability of fully comparable data from the National Health Accounts system, we adopted the 1995–2014 time horizon. All countries were divided into two groups: those defined in 1989 as free market economies and those defined as centrally-planned economies. We observed six major health expenditures: Total Health Expenditure (% of GDP), Total Health Expenditure (PPP unit), General government expenditure on health (PPP), Private expenditure on health (PPP), Social security funds (PPP) and Out-of-pocket expenditure (PPP). All of the numerical values used refer exclusively to per capita health spending. In a time-window from the middle of the 1990s towards recent years, total health expenditure was rising fast in both groups of countries. Expenditure on health % of GDP in both group of countries increased over time with the increase in the Free-market economies seen to be more rapid. The steeper level of total expenditure on health for the Free-market as of 1989 market economies, is due mainly to a steep increase in both the government and private expenditure on health relative to spending by centrally-planned economies as of the same date, with the out-of-pocket expenditure and the social security funds in the same market economies category following the same steepness. Variety of governments were leading Eastern European countries into their transitional health care reforms. We may confirm clear presence of obvious divergent upward trends in total governmental and private health expenditures between these two groups of countries over the past two decades. The degree of challenge to the fiscal sustainability of these health systems will have to be judged for each single nation, in line with its own local circumstances and perspectives.

Keywords: public health, private health, health spending, cold war, Europe

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INTRODUCTION

Evolution of health care associated expenditure in Europe (1), like elsewhere, was closely related to the geopolitical and economic realities on the continent (2). Cold War Era lasting approximately from 1946–1991 was marked by the presence of two distinctively different economic systems, namely the free-market and central-planned economies. These two patterns of governance had also profoundly different views over the societal role of health care (3).

The Western ones, led by the USA, were so called free-market economies and their dominant social theory ultimately leading to the rise of neoliberal capitalism. In health care, a variety of models were deployed but Beveridge and Bismarck models of health care financing and provision were the most broadly accepted (4). It is very important to emphasize that the return on investment in health care and the role of population health in societal economic productivity were well understood very early on by the prominent Western health economists (5). This knowledge was later on successfully introduced into the social policy. The level of medical technology and innovation, with few exceptions among some disciplines, tended to be higher compared to the East. However major weaknesses of these systems were rather significant, with social inequities in terms of access to medical care and affordability. These inequities, in some leading Western health systems (6), became even deeper with the accelerated globalization (7) that followed after the end of the Cold War.

The Eastern ones, led by the USSR, were presented by centrally-planned socialist economies that were rooted in Marxist social theory. The Soviet Semashko model of health care financing and provision prevailed in these countries. To its great historical credit, it is recognized to be the first one to globally deliver universal health coverage back in the early 1930s at the level of medical technology of that time. Even the poorest citizens had the right to state-funded basic medical care (8). After WWII, the famous Five-year plans led to rapid industrialization in USSR and some of its client states. This ultimately established USSR as the second ranked economy globally (9) for the most of Cold War Era duration (10). It is important to notice that both health care and education were regarded as purely consumption branches of the overall economy (11). They were assigned limited resources unlike some industrial priority areas believed to be far more productive in bringing budgetary revenues (12). This causal link between population health and social economic productivity was not well understood, and in reality not even exploited. Medical technology development and pace of innovation, with limited exceptions in some cutting-edge disciplines [psychiatry (13), orthopedic (14) and eye surgery (15), cosmic (16), aeronautic and alternative medicine (17) to mention a few (18)] were lagging behind vis-à-vis the West (19). However the social justice system in the East was exceptionally efficient (20). Poverty was almost eradicated and social inequalities in terms of access to state-funded health care were far lower compared to the Western ones (21). The scale of corruption and informal payments within the health system at that time were controlled and rather low (22). These countries became heavily industrialized, characterized by massive rural-urban migration and morbidity and mortality structures were similar to the West (23). Although the pool of maternal mortality was liquidated (24) and early childhood survival (25) improved rapidly in early post-WWII decades (26), overall life expectancy was lagging significantly behind the top performing free market economies (27).

METHODS

The main goal of this study refers to the exploration of development pathways of Public and Private Health Expenditure in all of the countries of the European WHO Region following their different starting points back in time at the end of the Cold War Era (28). Back in 1991 free-market economies continued evolving their traditions further and accelerated globalization was one of the main changes affecting health policy challenges. Unlike them, since 1991 Central and Eastern European centrally planned socialist economies underwent profound and complex socioeconomic and health care reforms. Their aim was to convert old socialist into a new capitalism grounded economic system (29). At the same time, mostly less efficient, massive, hospital, curative-oriented health systems had to be changed into the lighter and less costly ones based on preventive medicine (30) and outpatient care (31). These processes of social change became broadly known as the "Eastern European Transition" (32). In some countries of the region, they came almost to an end in 2017, while in others they continued with less or more significant changes of health policy and financing traditions. It should be noted that some countries of this region among the Commonwealth of Independent Nations (CIS) led by Russian Federation, after the early attempts in 1990s (33), have willingly abandoned such transition and adopted their own distinctive model of development, based on Semashko traditions (34).

Based on the availability of fully comparable data from the National Health Accounts system (35) introduced by WHO, we adopted the 1995–2014 time horizon. After thorough consideration of several public registries issued by the UN, OECD, World Bank, EuroStat and other multilateral agencies, we decided that the Global Health Expenditure Database will be our sole source of data for this study (36). We took the end of the Cold War as a point in time when initially divergent economic models began to converge in certain number of countries. What we wanted to show is that even today, after two and a half decades of "transition," countries eastern from the Iron Curtain still in many core indicators of health spending are closer to their Semashko root than to the Western Bismarck/Beveridge model like in the pharmaceutical spending for example the studies of Álvarez-Gálvez,and Jaime-Castillo in 2018 (37). Although, divergency began in 1917 after the Revolution, during the Westfallen peace in between two world wars most of Central Europe was still capitalist.

The initial set of observed variables comprised of ten different health spending indicators: Public funds, Rest of the world

funds / External resources, Total expenditure on health, General government expenditure on health, Ministry of Health, Social security funds, Private expenditure on health, Private insurance, Out-of-pocket expenditure and Non-profit institutions serving households (e.g., NGOs). However, after a pilot extraction of data was done, we noticed significant gaps in both chronology and geographical coverage. These could not be addressed with any valid statistical missing data handling strategy. Therefore, we shortlisted the final count to the six major health expenditures, all of which were broadly presented and available: Total Health Expenditure (% of GDP), Total Health Expenditure (PPP unit), General government expenditure on health (PPP), Private expenditure on health (PPP), Social security funds (PPP), and Out-of-pocket expenditure (PPP). All of the numerical values used refer exclusively to per capita health spending in order to eliminate the bias arising from any nation's population size.

Using the premise of this observation, all countries were divided into two groups: those defined in 1989 as free market economies and those defined as centrally-planned economies. With the exception of Eastern Germany after reunification, data on all other UN recognized countries were accessible regardless of the changes of borders and statehoods in Central and Eastern Europe (38). A clear list of countries in both groups can be found in **Table 1** below. Moreover, **Table 2** below, shows the data for each individual country within both groups.

TABLE 1 | Division of European countries based on their economic system at the end of Cold War Era back in 1989.

Free market economies as of 1989	Centrally planned economies as of 1989
Andorra	Albania
Austria	Armenia
Belgium	Azerbaijan
Cyprus	Belarus
Denmark	Bosnia and Herzegovina
Finland	Bulgaria
France	Croatia
Germany	Czech Republic
Greece	Estonia
Iceland	Georgia
Ireland	Hungary
Israel	Kazakhstan
Italy	Kyrgyzstan
Luxembourg	Latvia
Malta	Lithuania
Monaco	Montenegro
Netherlands	Poland
Norway	Republic of Moldova
Portugal	Romania
San Marino	Russian Federation
Spain	Serbia
Sweden	Slovakia
Switzerland	Slovenia
Turkey	Tajikistan
United Kingdom of Great Britain and Northern Ireland	The former Yugoslav Republic of Macedonia
	Turkmenistan
	Ukraine
	Uzbekistan

STATISTICAL ANALYSIS

We then conducted a comparative statistical analysis on two time cross sections, comparing these two groups of countries for the period 1995–2014. Another part of the analysis refers to comparison of the time trend between the groups. For the first case, the Mann-Whitney U Test was applied and in another case we decided for the Wilcoxson's test, because our data did not fulfill parametric conditions for a normal (Gauss') distribution. We checked this fact with the Shapiro-Wilk test.

STUDY LIMITATIONS

This study presents a retrospectively designed research on aggregate national level data. Such data are being reported by the national authorities, such as governments and ministries of health to the respective UN and WHO offices. Authors take data as guaranteed by the national governments and checked by WHO European Office and are not capable of checking reliability, consistency of such reporting or the internal accounting systems which may slightly vary from country to country. This way of tracking and reporting financial flows within the nation's health system have been made as much consistent as possible through the lengthy process of WHO initiated introduction of the National Health Accounts in the early 1990s (39). It assumed mandatory staff trainings and capacity building by the health insurance funds' and ministry of health officials exactly for the purpose to make these follow the unique patterns and indicator definitions that have been adopted during the establishment of the NHA system by all the representatives of all the country members of the United Nations.

Other possible limitations refer to the fact that this is a purely health economic observation. While conducting this study, we were focused on the different dimensions of health expenditures of given European nations while using only six core indicators and only two units of measurement (THE as % of GDP and PPP) out of many currency units available in a given database (40). If we had opted to observe country group parities in nominal dollar terms, landscape might have looked quite different (41). However, we followed the ground health economics theory that says that purchasing power parity allows the best possible comparison among the nations with significantly different levels of income/industrial development (42). Likewise, observation of total health expenditure expressed as percentage point share of gross domestic product was selected, because according to broadly accepted economic theory, this indicator is the only one allowing us transnational comparisons among inherently different economic systems (43).

Based on data we worked with, there is no evidence for definite conclusions on effectiveness and performance of these national health systems in terms of their public health output. We did not use, nor consider data such as longevity, morbidity, mortality, utilization of medical services or medicines or any

TABLE 2 | The data for each individual country within both groups.

Median (95% confidence intervals)	Total expenditure on health (% of GDP)	Total expenditure on health in current PPP per capita	General government expenditure on health in current PPP per capita	Private expenditure on health in current PPP per capita	Out of pocket expenditure in current PPP per capita	Social security funds in current PPP per capita
FREE MARKET ECONOMIES AS OF 1989 (1995–2014)						
Andorra	6.1 (6.0–7.3)	2259.7 (2146.2–3028.5)	1587.4 (1507.4–2293.1)	717.9 (627.0–747.2)	519.7 (444.9–538.3)	1222.6 (1170.5–1712.5)
Austria	10.4 (10.2–10.7)	3517.7 (3203.0–4011.7)	2605.8 (2394.2–3019.4)	912.0 (807.4–993.7)	613.9 (514.8–658.5)	1516.6 (1382.2–1712.2)
Belgium	9.2 (8.7–9.6)	2949.7 (2601.4–3406.7)	2262.7 (1977.4–2616.1)	706.8 (622.6–792.0)	559.1 (503.6–633.7)	1931.4 (1686.7–2238.2)
Cyprus	6.3 (6.0–6.8)	1555.4 (1340.1–1828.9)	671.8 (567.9–811.9)	889.8 (769.5–1015.4)	727.5 (691.1–883.0)	–
Denmark	9.7 (9.2–10.2)	3188.3 (2899.9–3815.4)	2690.1 (2438.0–3235.2)	498.2 (461.7–580.5)	450.6 (417.0–515.9)	–
Finland	8.2 (8.0–8.6)	2525.2 (2220.0–2911.2)	1857.5 (1626.0–2167.9)	667.6 (593.8–743.6)	512.1 (457.5–561.7)	373.2 (312.6–413.9)
France	10.5 (10.3–10.8)	3159.9 (2885.6–3597.1)	2462.9 (2266.6–2799.4)	697.0 (615.3–785.5)	221.9 (205.7–251.7)	2357.3 (2149.4–2661.6)
Germany	10.4 (10.2–10.7)	3283.7 (3076.4–3891.5)	2504.8 (2404.6–2993.1)	780.1 (670.5–899.6)	458.0 (381.4–517.2)	2190.9 (2095.2–2640.2)
Greece	8.7 (8.5–9.1)	2096.9 (1837.3–2343.5)	1266.4 (1090.0–1475.4)	810.5 (734.2–878.5)	710.1 (648.0–784.5)	642.5 (494.4–791.9)
Iceland	8.9 (8.7–9.2)	3338.7 (2842.2–3357.9)	2728.0 (2323.4–2735.0)	600.0 (517.5–624.2)	550.8 (486.5–577.8)	910.9 (780.2–937.6)
Ireland	7.2 (6.9–7.8)	2901.8 (2306.3–3204.3)	2208.6 (1685.3–2303.6)	693.1 (609.6–912.1)	451.0 (362.6–525.1)	14.1 (11.4–16.7)
Israel	7.4 (7.4–7.5)	1871.6 (1785.1–2074.6)	1174.6 (1131.1–1292.9)	678.9 (620.2–764.8)	512.7 (472.9–549.9)	826.4 (818.5–939.3)
Italy	8.5 (8.1–8.8)	2520.5 (2290.7–2836.1)	1913.7 (1690.4–2140.3)	608.9 (598.7–697.4)	538.5 (533.4–607.1)	2.3 (2.4–5.3)
Luxembourg	7.3 (6.7–7.5)	5420.5 (4171.4–5656.7)	4600.2 (3618.7–4831.3)	778.2 (544.5–830.2)	573.3 (415.6–599.5)	3662.8 (2938.5–3936.9)
Malta	8.2 (7.4–8.6)	1906.0 (1574.7–2206.7)	1284.2 (1057.5–1471.8)	621.8 (514.9–737.3)	536.6 (461.9–663.2)	–
Monaco	3.7 (3.5–3.9)	4269.9 (3625.2–4836.9)	3762.8 (3194.6–4266.0)	507.1 (429.8–571.7)	298.9 (253.8–338.6)	3707.6 (3140.8–4204.8)
Netherlands	8.9 (8.4–9.6)	3302.9 (2908.8–3996.6)	2236.5 (2131.6–3269.4)	673.1 (673.4–831.0)	237.0 (210.7–247.0)	2069.1 (1966.3–2981.0)
Norway	9.1 (8.6–9.2)	4204.1 (3556.6–4835.9)	3512.6 (2976.2–4080.2)	691.6 (579.4–755.9)	658.6 (551.7–716.1)	–
Portugal	9.5 (8.8–9.6)	2101.7 (1752.4–2301.8)	1472.6 (1179.9–1550.9)	629.1 (569.7–753.6)	459.2 (408.6–558.8)	–
San Marino	4.7 (4.5–5.2)	2700.7 (2626.2–3017.3)	2468.7 (2382.9–2780.1)	234.8 (227.3–253.1)	213.2 (206.4–229.8)	2468.7 (2382.9–2780.1)
Spain	8.1 (7.8–8.6)	2162.7 (1884.8–2506.1)	1562.0 (1363.9–1827.6)	600.8 (519.1–680.3)	463.8 (418.1–542.1)	134.4 (120.2–143.7)
Sweden	9.1 (8.8–10.0)	2964.9 (2696.4–3702.8)	2409.5 (2241.6–3079.7)	555.5 (450.3–627.5)	481.2 (404.2–550.7)	–
Switzerland	10.5 (10.3–10.9)	3988.9 (3723.2–4839.1)	2350.7 (2184.8–3026.8)	1638.2 (1530.6–1797.0)	1233.7 (1130.5–1361.8)	–
Turkey	5.3 (4.5–5.4)	587.1 (505.3–757.6)	407.6 (361.1–568.0)	169.2 (139.7–194.1)	125.6 (107.0–141.4)	244.8 (206.4–359.6)
United Kingdom of Great Britain and Northern Ireland	8.1 (7.6–8.6)	2653.1 (2189.4–2860.8)	2150.1 (1780.8–2348.2)	504.6 (403.6–514.8)	259.8 (226.8-279.2)	–

(Continued)

TABLE 2 | Continued

Median (95% confidence intervals)	Total expenditure on health (% of GDP)	Total expenditure on health in current PPP per capita	General government expenditure on health in current PPP per capita	Private expenditure on health in current PPP per capita	Out of pocket expenditure in current PPP per capita	Social security funds in current PPP per capita
CENTRALLY PLANNED ECONOMIES AS OF 1989 (1995–2014)						
Albania	6.1 (6.0–6.5)	371.1 (329.8–448.8)	160.2 (128.8–204.0)	211.0 (200.6–245.3)	197.8 (196.2–240.0)	45.9 (49.1–123.1)
Armenia	5.3 (4.8–5.5)	233.8 (179.0–255.1)	73.0 (61.3–104.6)	140.8 (115.7–152.5)	134.1 (110.3–145.0)	–
Azerbaijan	5.4 (5.2–6.1)	492.0 (347.0–628.5)	59.0 (63.0–125.7)	429.8 (282.6–504.1)	384.4 (246.9–450.0)	–
Belarus	6.2 (5.9–6.4)	614.3 (491.2–726.8)	453.1 (355.5–511.2)	161.2 (132.7–218.6)	114.7 (96.0–178.3)	–
Bosnia and Herzegovina	8.7 (8.3–9.1)	536.3 (441.6–683.7)	306.9 (267.0–458.3)	229.3 (172.1–227.9)	229.3 (170.8–224.4)	290.8 (253.9–429.7)
Bulgaria	6.8 (6.1–7.0)	686.8 (561.6–881.3)	417.6 (339.7–500.7)	268.9 (221.4–381.1)	261.3 (216.9–371.1)	–
Croatia	7.2 (6.9–7.5)	1047.0 (949.7–1324.8)	876.1 (801.2–1110.3)	166.0 (145.8–217.2)	157.2 (131.1–175.7)	790.3 (724.6–967.8)
Czech Republic	6.8 (6.7–7.1)	1434.2 (1262.5–1672.8)	1265.0 (1109.9–1430.8)	169.2 (151.7–242.9)	151.0 (142.9–223.9)	1134.3 (994.7–1298.2)
Estonia	5.8 (5.5–6.0)	786.8 (725.3–1121.9)	599.1 (573.9–879.9)	184.7 (144.1–234.3)	164.0 (132.6–221.5)	–
Georgia	8.3 (7.5–8.6)	328.6 (277.0–448.9)	57.1 (48.0–85.0)	271.5 (228.1–364.8)	253.3 (202.2–301.5)	30.1 (25.7–54.5)
Hungary	7.5 (7.3–7.7)	1381.0 (1087.6–1455.6)	955.5 (769.6–980.1)	416.7 (316.8–476.8)	346.7 (266.0–379.4)	787.8 (639.0–817.2)
Kazakhstan	4.1 (3.9–4.3)	512.0 (435.9–670.7)	291.7 (254.1–382.3)	206.3 (179.9–290.3)	203.4 (177.4–286.7)	–
Kyrgyzstan	5.9 (5.7–6.3)	120.0 (109.8–155.5)	49.0 (52.0–82.7)	70.3 (57.2–73.4)	63.3 (52.1–66.4)	–
Latvia	6.2 (6.1–6.4)	569.2 (475.7–701.0)	323.5 (278.1–424.9)	245.7 (193.7–270.5)	231.6 (185.2–256.8)	–
Lithuania	6.3 (6.1–6.5)	816.7 (749.2–1165.1)	587.1 (533.7–811.2)	257.6 (210.2–341.2)	253.7 (202.2–332.0)	468.1 (400.3–664.4)
Montenegro	7.4 (7.0–7.7)	684.0 (601.1–778.6)	485.9 (407.1–504.0)	188.6 (189.7–278.9)	188.6 (189.7–278.9)	455.0 (390.6–473.5)
Poland	6.2 (6.0–6.4)	831.8 (770.9–1134.8)	573.5 (543.5–800.9)	257.6 (226.3–332.0)	225.3 (201.5–273.2)	–
Republic of Moldova	9.8 (8.7–10.3)	247.7 (225.5–355.9)	117.1 (113.4–173.9)	130.5 (111.3–182.8)	105.7 (91.1–150.5)	–
Romania	5.3 (4.5–5.2)	502.4 (421.7–716.1)	390.0 (336.4–574.5)	108.1 (84.5–141.6)	105.2 (83.0–138.2)	–
Russian Federation	5.9 (5.8–6.5)	573.3 (616.8–1101.4)	349.0 (371.1–616.8)	224.3 (244.8–485.5)	184.7 (203.4–444.8)	142.4 (144.0–266.0)
Serbia	8.5 (7.7–9.1)	719.6 (586.1–949.1)	484.4 (378.6–594.5)	235.1 (206.2–353.0)	206.7 (185.1–328.2)	446.2 (350.9–553.6)
Slovakia	7.1 (6.4–7.5)	1101.0 (966.7–1543.1)	815.8 (754.9–1107.9)	285.2 (209.2–437.8)	230.6 (172.8–341.9)	709.8 (696.2–1004.3)
Slovenia	8.5 (8.2–8.8)	1942.4 (1662.8–2177.5)	1423.9 (1228.8–1593.4)	520.7 (433.4–584.8)	233.5 (196.0–260.4)	1303.8 (1128.5–1447.9)
Tajikistan	5.2 (4.5–5.6)	81.0 (62.2–106.7)	15.4 (15.6–28.6)	65.6 (46.3–78.4)	63.6 (43.7–71.2)	–
The former Yugoslav Republic of Macedonia	8.1 (7.4–8.4)	638.5 (578.2–694.5)	378.2 (353.9–442.3)	240.6 (220.9–255.5)	240.6 (220.9–255.5)	365.1 (337.8–412.3)

(Continued)

TABLE 2 | Continued

Median (95% confidence intervals)	Total expenditure on health (% of GDP)	Total expenditure on health in current PPP per capita	General government expenditure on health in current PPP per capita	Private expenditure on health in current PPP per capita	Out of pocket expenditure in current PPP per capita	Social security funds in current PPP per capita
Turkmenistan	3.1 (2.6–3.5)	172.3 (164.0–210.7)	118.1 (105.6–137.4)	62.1 (55.7–75.9)	62.1 (55.7–75.9)	–
Ukraine	6.7 (6.5–7.0)	410.2 (342.2–486.1)	242.1 (197.5–275.2)	168.1 (143.1–212.5)	156.0 (132.1–198.0)	–
Uzbekistan	5.7 (5.6–6.1)	133.4 (142.7–215.7)	61.5 (66.6–104.0)	74.1 (75.4–112.4)	69.7 (73.0–106.6)	–

Sources: World Health Organization-Global Health Estimates-Database (WHO GHE DB).

other similar indicators (44), as these were beyond the scope of this paper. Therefore, conclusions of this study are limited to health spending dynamics and its evolution over the long period of time without any referral to the success rates of individual systems or their cost-effectiveness / resource allocation efficiency (45).

RESULTS

This study has revealed a set of findings, which were not previously observed to a deeper extent in published evidence (46). In a time-window from the middle of the 1990s toward recent years, total health expenditure was rising fast in both groups of countries. While it almost quadrupled among former socialist countries, in a group of EU15 and few other similar nations, this growth was even more concerning. It began from four times higher starting point around $1,600 PPP on average within the group and reached a value of almost $4,200 PPP in only two decades.

The graphs below illustrate linear regression models of Total Health Expenditure % of GDP as a function of time (years). In general, the models for both the centrally-planned economies and the market-based economies fit the data well. The regression line for free-market economies has a steeper gradient than the one for centrally-planned economies. This is suggestive of accelerated rising costs over time in the former.

Figure 1 shows that total expenditure on health % of GDP in both group of countries increased over time with the increase in the Free-market economies seen to be more rapid. In fact, we can observe some form of similarity in the patterns of both lines. Moreover, the "wave" pattern in both lines seem to be identical for particular years. The level of total expenditure on health in free market economies, starts at a higher level, compared to the centrally planned countries and increases at a faster rate over the time period studied. This is suggestive of both types of economies being subjected to the same types of economic pressures and possibly to the strength of the prevailing global economy. Despite this, the free-market economies' spending remains steeper than the centrally-planned ones.

The steeper level of total expenditure on health for the Free-market as of 1989 market economies, is due mainly to a steep increase in both the government and private expenditure on health relative to spending by centrally-planned economies as of the same date, with the out-of-pocket expenditure and the social security funds in the same market economies category following the same steepness.

Moreover, a widening of the gap in expenditure between the two types of economies over time can be noted. Which seems to result from a relatively stable low level of social security funds in the centrally planned group over the years.

Although, the interest was to study the aggregate, results have also been evaluated and studied at an individual country level. When one compares the averages over the periods within the two figures in **Figure 2** it is still clear that the levels within the "Free Market" economies is overall higher in comparison to the "Centrally Planned" economies. Moreover, when observing the outliers, Luxembourg, Monaco, Norway and Switzerland in one group of countries and Czech Republic, Hungary, and Slovenia in the other group, the range of variation across countries is also much larger in the "Free Market" economic group which seems to indicate much more variation within this group of countries over the years under study.

One can also note, from **Figure 2**, that there is little fluctuation in the private expenditure and the out-of-pocket variables being considered. This implies that variation arises mainly from differences in general government expenditure.

DISCUSSION

Since 1960s, it became apparent first in the US health system that average costs of medical care are rising faster than average monthly income of ordinary citizen. At the macroeconomic level, over time it became visible that this growth was almost twice faster compared to economic growth or gross domestic product disposable within a nation (47). Vast body of literature has identified as some of the major drivers of such growth: blossoming of non-communicable prosperity diseases (48), population aging (49), innovation in medicine (50) and pharmaceuticals in particular (51), excessive utilization of hospital diagnostic imaging (52), underutilization of primary care (53), and preventive measures and inefficient management (54) among others. This issue of financial sustainability of national health care systems became prominent in Western literature (55). Accordingly, to meet these challenges health economics as an

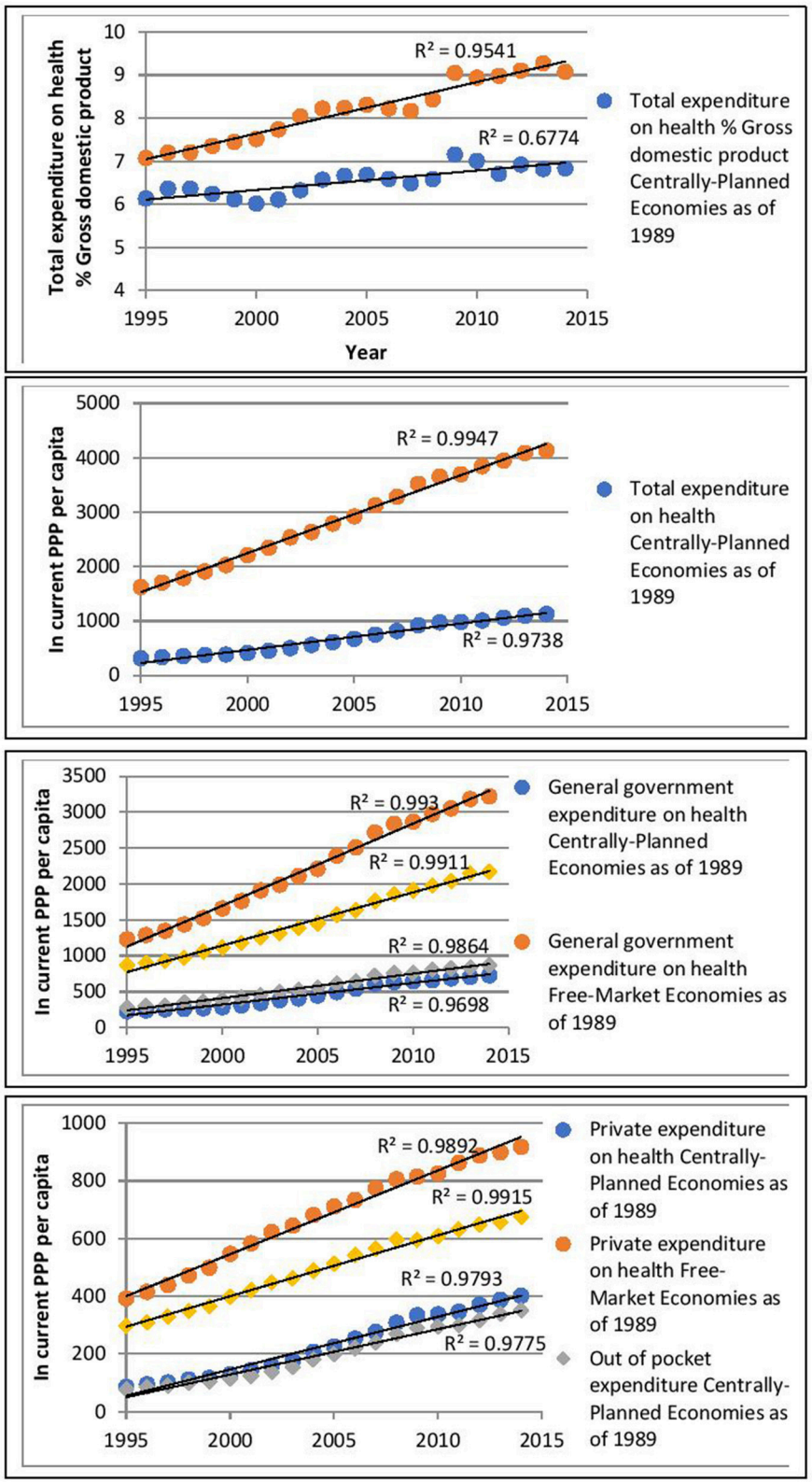

FIGURE 1 | Long term upward trends of health expenditure data extrapolated on the entire group of countries as pondered average of annual values.

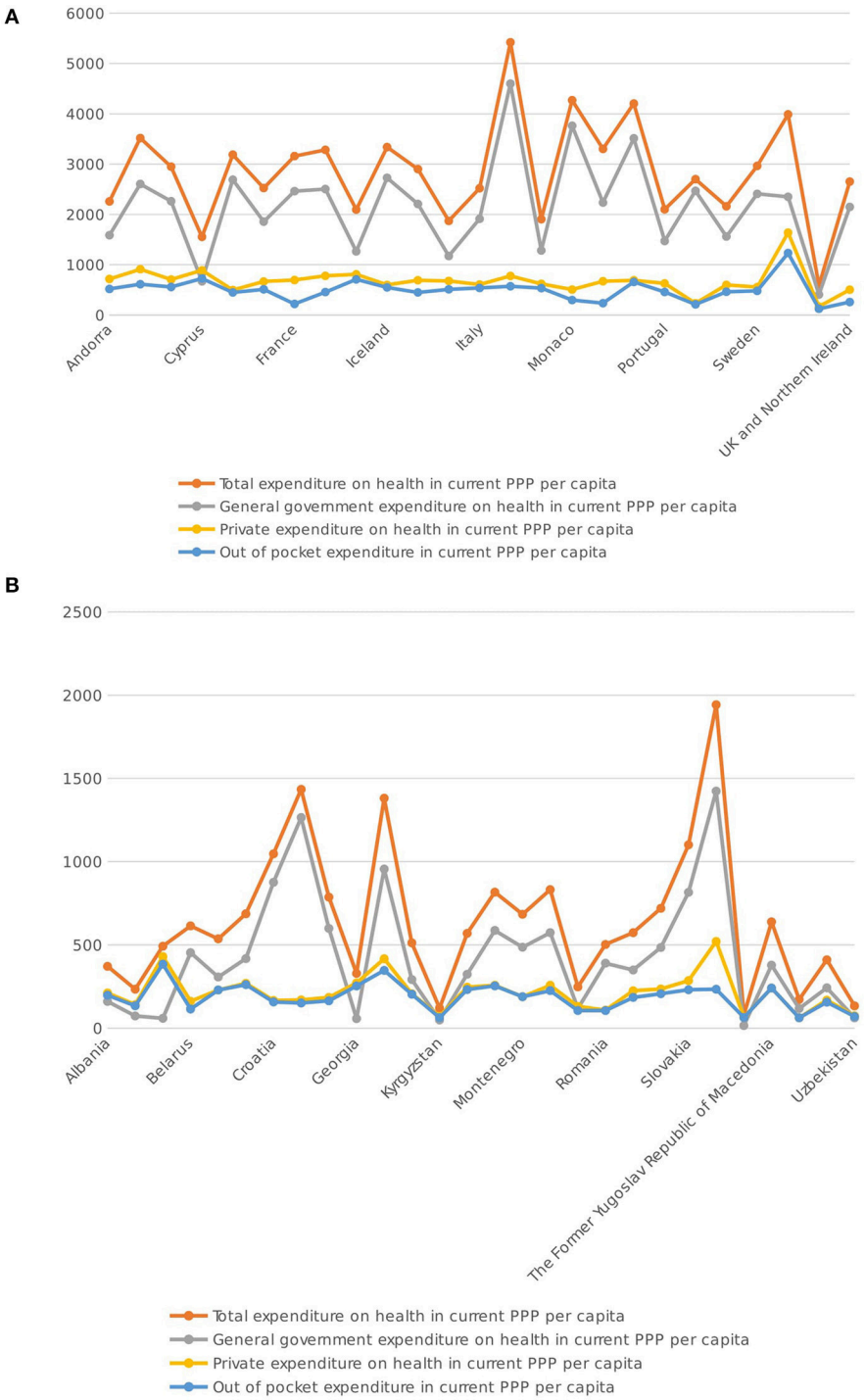

FIGURE 2 | (A) Free Market Economy Indicator comparisons Source: World Health Organization- Global Health Estimates - Database (WHO GHE DB). **(B)** Centrally Planned Market Economy Indicator comparisons Source: World Health Organization- Global Health Estimates - Database (WHO GHE DB).

interdisciplinary science emerged from American traditions in academic economics (56, 57).

On the other hand, during the Cold War Era, socialist countries controlled these health care costs at an unrealistic level by several ways (58). One of them was a negotiation process between one central state-owned health insurance fund as a major purchasing authority for health services and a large tertiary care hospitals as a core provider of such services. They used to be paid based on the performance such as total duration of hospital admissions, number of surgical procedures performed

or outpatient physician examinations (59). However, due to the fact that these funds tended to generate debt in most countries and ongoing fiscal deficits, these services were not covered in total value, but just as a dominant share of such costs. For the rest, hospitals themselves had to generate revenues by a variety of ways but mostly by charging the difference as patient/citizen participation fees (60).

All of these weaknesses became more prominent after the beginning of socioeconomic transition (61) in Eastern Europe since 1991 (62). As these countries moved from the state controlled model toward market controlled mechanisms, a large degree of vulnerability occurred both for the citizens in need (63) and the health system itself (32). This all worsened to a large extent due to the Russian Federation's economic recession reaching its worst-ever level in 1998. This phenomenon dragged the entire region and central Asia into an ensuing economic crisis. This was followed by a notorious mortality crisis in Russia (64) and neighboring nations. Eventually, the situation rapidly improved in the early 2000s (65).

Difficulties experienced by the variety of national health systems in this region are closely explained in the published literature (66). Some authors even went as far as declaring some countries to be "winners" and others "losers" of transition (66). This in our opinion is exaggerated because, almost 30 years after, health policy observations, taught us that each single nation succeeded to adapt in its own way (67). Health coverage (68), accessibility and affordability of services and ultimately core population health outcomes such as longevity, all improved visibly in Eastern Europe (44).

It should be noted that countries created from former Yugoslav Republics present a rather distinct case (68). The former, Yugoslavia, geopolitically outside the Iron Curtain, was by far the richest socialist country. It deployed the system of health care provision and financing, which presented a mixture of Soviet Semashko and Bismarck traditions (69). Its community health outcomes were mostly outperforming other similar nations. After the civil wars of its dissolution in 1990s ended, most countries of the region entered this transition and health care reforms with approximately one decade delay (70). Their public health indictors today slightly lag behind Poland (71), Hungary (72) or Czech Republic (73). However, keeping in mind contemporary health spending disparity in favor of eastern EU members as of 2004, their health systems perform quite satisfactory (74).

Over the years the differences in both the levels of total expenditure on health (in PPP per capita terms) and the proportion of total health expenditure as a % of GDP across the two sets of market economies has increased. Both sets of market economies have recorded significant increases over the years within both components of interest. However the increasing variation between the two sets of countries is clearly noticeable. Indeed, at a more disaggregated level, both general government expenditure on health and private expenditure on health within free market economies reflect the significant increases recorded over the years. The developments within the expenditure on the social security funds component over the years also reflect the above considerations. Whilst recognizing that there might be divergences in behavior over time for such components, within the specific countries which make up each of the two groups under study, the general observations mentioned above apply for most of the particular countries in question.

CONCLUSION

Variety of governments were leading Eastern European countries into their transitional health care reforms. This process was followed by difficult years of poverty, rising socioeconomic inequalities (75) and system inefficiencies to provide equitable and affordable medical care to the citizens (76). The ground assumption of the authorities at some point in time was that former socialist countries should converge with their Western counterparts both in terms of health spending and outcomes. We may witness that these goals have been met only to some extent (77). Long term trends even depict clear divergent trends in some health expenditure indicators. Similar phenomenon has already been described in pharmaceutical spending in previous findings (78). Judgment of allocative or technical efficiency of such financial policies is beyond this research. Although, we may say that historical free-market societies appear to be rising their ability to invest faster in health care (79), based on the data observed, we are unable to estimate the degree of success in public health indicators in particular nations. However, we may confirm clear presence of obvious divergent upward trends in total governmental and private health expenditures between these two groups of countries over the past two decades. The degree of challenge to the fiscal sustainability of these health systems will have to be judged for each single nation, in line with its own local circumstances and perspectives (80).

AUTHOR CONTRIBUTIONS

MJ and SB jointly designed the study and defined research questions. NR did most of the data mining and extraction, purification of files for missing data and artifacts and statistical analysis. CC and SG contributed to the tables, figures creation, and interpretation of data. SG structured, coordinated and uploaded the final revised paper. MJ and KG contributed in the initial discussion. MJ drafted the working version manuscript but all authors contributed to the final version to the extent of important intellectual content.

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A Comparative Cost Analysis of Antibiotic Treatment for Community Acquired Pneumonia (CAP) in Adult Inpatients at Piggs Peak Government Hospital in Swaziland

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Background: Of the different types of pneumonia, community acquired pneumonia (CAP), has been identified as the leading cause of infectious morbidity and mortality in the western and developing countries. To eradicate the bacterial cause of CAP, medical doctors) often tend to prescribe a differing cocktail of medicine which may be costly for the health care system.

Aim: To analyze the cost of oral and/or intravenous antibiotic medicine use in different treatment approaches for treating CAP in adult inpatients from the health care system perspective.

Settings: This study was undertaken at Piggs Peak Government Hospital, a 220 bed tertiary hospital located in the rural northern Hhohho region of Swaziland.

Method: Seventy-one ($n = 71$) medical records of adult patients, hospitalized and diagnosed with CAP at Piggs Peak Government Hospital from July 2014 to June 2015, were retrieved and entered into the database once confirmed as having met the selection criteria. Only direct antibiotic medicine(s) costs were considered. The total cost per treatment option was calculated by multipling the unit cost of the medicine by the administration frequency and the length of hospital stay. The Kruskal-Wallis test was used to compare the cost difference between more than two treatment options.

Results: Medical doctors at Piggs Peak Government Hosptial use a range of antibiotics to treat community acquire pneumonia. Furthermore, doctors prefer using dual antibiotics combination as first line treatment of CAP in adult inpatients. The cost of treating community acquire pneumonia at the hospital ranged from ZAR 70.98 to ZAR 467.60 per adult inpatient admitted into care. A statistically significant difference in the cost of the different treatment approaches used for treating CAP was noted.

Conclusion: This cost-exploratory study has highlighted a significant difference in the monetary cost of the differing approaches used for treating CAP at the hospital. It is evident therefore that the use of different treatment approaches in treating CAP significantly influences the cost of CAP treatment. There is therefore need for cost minimization measure to be put in place at the facility.

Keywords: CAP, pneumonia, cost, antibiotics, treatment

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INTRODUCTION

Community-acquired pneumonia (CAP) is the leading cause of infectious morbidity and mortality in the western and developing countries, with the African continent carrying a substantial burden of CAP. Around 30% of the estimated 430 million LRTIs episodes reported in Africa each year are CAP (1). It is one of the most serious infectious diseases, accounting for a considerable number of hospital admissions and increased rates of serious complications.

Although an important cause of mortality and morbidity worldwide, emerging data is available on specific incidences for etiologies of acute respiratory such as CAP in children and adults in the African continent (2, 3). The 2015 Global burden of disease (GBD) study reported over 290 million cases of LRTIs worldwide, a 6.8% increase from the 2005 LRTIs incidence (4). This according to Corrêa et al. (5) accounts for 4.9% of all deaths in the world (5). Cupurdija (6) further estimated that 4–6 million of CAP cases occur in the United States annually, of which approximately 20–25 % required hospitalization (6). A study by Cajetan and Chukwuka (7) in Nigeria that reviewed 160 inpatient cases of CAP showed an 11.9% hospital mortality rate whereas a similar study in Ethiopia (1) showed 11% comparable mortality among admitted patients with CAP.

Most cases a diagnosis of CAP is made on clinical grounds and patients are often initiated on empirical antibiotic treatment before the results of laboratory tests are seen (4) or worst, if they are not done at all. Medical doctors in such instances tend to prescribe a differing cocktail of medicine in order to eradicate pneumonia (5). Many factors may contribute to the rationale behind these differing approaches. These differing treatment options though may not improve outcome of patients and may hence impact negatively on the health care cost (6).

In low income hospital settings like Swaziland where overuse and/or inappropriate use of medicines (including antibiotics), and where empirical treatment is widely practiced, this may precipitate in both patients and the health care system spending excessively on pharmaceuticals and wasting financial resource (7).

For the 2013/14 financial year, Central Medical Stores (CMS) data reflects that the government of Swaziland spent over 1 million South African Rands (equivalent to $108500) to procure essential antibiotics alone. According to B Mhlanga (Personal Communication, October 2015) of this, approximately 39% (ZAR 387 000) was calculated to have been issued for use at Piggs Government Hospital, a 220 bed region hospital located in the northern Hhhohho region of Swaziland.

To curb this inappropriate or over usage of antibiotics or drugs in general the World Health Organization (WHO) from time to time publishes a core list of minimum medicine needed for a basic health-care system (8). Listing the most efficacious, safe and cost–effective medicines for priority conditions like CAP. In the treatment of mild to moderate CAP, WHO recommends the use of amoxicillin, amoxicillin + clavulanic acid, ampicillin, or benzylpenicillin as first choice treatment. Cephalosporines, Cefotaxime and ceftriaxone, together with clarithromycin, and/or gentamicin is recommended for treatment of severe or complicated CAP in adults (9).

A study that analyses the cost of the use of antimicrobial medicine for CAP has not been done in Swaziland. As a result, it is hence difficult to determine whether the different treatment strategies employed in the treatment of CAP improve patient outcomes or they are an unnecessary burden on the country's healthcare system. The lack of such economic analyses makes it difficult to make improvements in CAP treatment strategies in the country.

This study was hence designed to determine and compare the cost associated with antimicrobial medicine used in treating CAP in adult inpatients at Piggs Peak Government Hospital. The cost comparison shall guide decision makers, medical practitioners, pharmacists and help to improve the national guidelines for the treatment of CAP in Swaziland. It shall also guide medicines budgeting both at hospital and national government level.

With no such study previously done in the country, this research hopes to form basis for later cost comparison studies in the Kingdom. It is further hoped that such study will be replicated in other hospitals in Swaziland, for different diseases and across different age groups in the Southern African Developing Countries.

METHODS

Study Design

This study was undertaken at Piggs Peak government hospital a health care facility located in the rural northern Hhohho region of Swaziland. Piggs Peak government hospital is a tertiary government referral hospital with a total bed capacity of 220. This was a retrospective study that assessed the treatment of CAP in adult male and female patients between the age of 18 and 65 years who were admitted at the hospital between July 2014 and June 2015. Retrospective patient information that was contained in the admission sheet, bed head, continuation form, nurses note, doctors' notes, treatment sheet and discharge summary of a complete patient file was retrieved and captured using a questionnaire.

Study Sample

Sample size was based on the number of adult patients admitted and diagnosed with CAP over a specific period. Medical records of adult patients hospitalized in the male and female wards were retrieved and all patients diagnosed with CAP were selected and entered into the database once confirmed to having met the selection criteria. Seventy-one suitable patient records were identified and sampled from this site.

After data collection patients were classified into treatment groups based on initial antimicrobial regimen prescribed and administered. Only antimicrobials administered within the first 36 h after hospital arrival was considered in the classification of patients into the treatment options. Costs of any subsequent treatment(s) were included based on the initial treatment classification.

Inclusion and Exclusion Criteria

Eligible patients were adults 18 years or older admitted into care with a diagnosis of CAP between 1 July 2014 and 31 June 2015. Patients with the Human immunodeficiency Virus

(HIV), pregnant or nursing woman, children, patients with active tuberculosis and patients with chronic kidney failure were considered ineligible and excluded from the study sample.

Analysis for CAP was limited by excluding patients who were in the hospital 14 days prior to admission for CAP. Only the first of patient's multiple hospitalisations for CAP was included for analysis. Cases of death or discharge within 24 h after admission were also excluded. Confidentiality was maintained throughout the study.

Data Collection

Data was collected over a period of three (3) months. A data collections tool was developed by the researcher to collect information on patient demographics, diagnosis, antibiotics prescribed, treatment duration, date of admission and discharge.

Continuous, categorical and nominal types of data were collected for the different variables that were examined. The hospital number instead of patient name was used for purposes of confidentiality. The date of admission and discharge were used to calculate length of hospital stay.

Cost Calculations

The study only considered antibiotic medicine costs used in the treatment of CAP. The 2014/2015 fiscal year central medical stores tender medicine cost prices were used when calculating the relevant cost of antibiotic treatment for the specific treatment duration. The quantification of costs considered for the study were medical costs associated with antibiotics used.

Statistical Analysis

For each of the study objectives data was analyzed and presented as shown in the Results section of this paper. For statistical analysis, the 2015 version of the Statistical Package for Social Science (SPSS) was used.

The total cost was calculated using information extracted from the patient's medical file. The Kruskal-Wallis test was used to compare the cost difference between more than two treatment options. Results of the different analysis and comparisons were analyzed and are presented in the Results section.

Ethical Considerations

The protocol of this study was reviewed and given full ethics approval by the Biomedical Research Ethics Committee (BREC), an ethics committee registered with the South African National Health Research Ethics Council (REC-290408-009) and in country (Swaziland) by the Swaziland Research and Ethics Council (SEC). To ensure confidentiality of information source(s), patient hospital numbers rather than names were used for patient identification.

RESULTS

Patient Demographics

A total of 71 ($n = 71$) patient records were identified and reviewed in this study. Forty-four (44%) percent of patients admitted with a diagnosis of CAP were male, and most of the patients were between 21 and 50 years. SPSS analysis shows the average age for this study sample to be 43 years.

Table 1 below shows that on average a person admitted with CAP will spend approximately 8 days at the hospital admitted. Furthermore, whilst hospitalized, patients are put on intravenous antibiotics for an average of 4 days.

Antibiotic Treatment Options for CAP

Table 2 illustrated the various treatment options used to treat CAP by medical doctors at Piggs Peak Government Hospital. Fifteen treatment options were identified. The treatment options identified show that practitioners at PPGH use either a single or a combination of antibiotic when treating CAP. Furthermore, medical doctors at the hospital use either single or double medicine combinations in treating CAP at the hospital.

Amoxicillin, ceftriaxone and benzyl penicillin are amongst the widely used antibiotics in the treatment of CAP. These it has been identified are used either alone or in combination with another antibiotic medicine.

The results show that the most preferred antibiotic combination for CAP treatment at Piggs Peak hospital is a combination of benzylpenicillin and gentamycin. Of the 71 identified case of CAP between July 2014 and June 2015, a majority (33.8%) of patients were treated with benzylpenicillin and gentamycin, 14.1% and 15.5% were each treated with

TABLE 1 | Study patient demographics.

		Patient age		Age (years)	Days on treatment	Days hospitalized
		Female	Male			
N	Valid	40	31	71	71	71
	Mean	36	50	43	4.01	8.10
	Median	33	51	43	3.50	7.00

TABLE 2 | Antibiotic treatment for CAP.

Medicine treatment option	No. Patient(s) $N = 71$
Benzylpenicillin + Gentamycin	24
Ceftriaxone + Genatmycin	11
Amoxicillin + Gentamycin	10
Ceftriaxone only	7
Benzylpenicillin only	6
Amoxicillin only	4
Amoxicillin + Gentamycin + Ceftriaxone	1
Benzylpenicillin + Gentamycin+ Ciprofloxacin	1
Benzylpenicillin + Amoxicillin + Gentamycin	1
Ciprofloxacin only	1
Ceftriaxone + Chloraphenicol + Gentamycin	1
ceftriaxone + Chloraphenicol	1
Benzylpenicillin + Chloramphenicol	1
Benzylpenicillin + Ceftriaxone	1
Amoxi-Clavulanic Acid + Gentamycin + Benzylpenicillin	1

a combination of either amoxicillin and gentamycin and ceftriaxone and gentamycin, respectively.

A small fraction (8.5%) of patients was treated with benzylpenicillin, which is the standard recommended treatment specified in the national standard treatment guidelines for treatment of CAP. Other single medicine regimes that were identified included amoxicillin (5.6), ciprofloxacin (1.4%) or ceftriaxone (9.9%).

Cost of Treatment Options

The Shapiro-Wilk test of normality in distribution of cost of treatment in this population sample was not normal. The Shapiro-Wilk test for normal data gave a $p > 0.001$, hence the assumption of normality was rejected. Therefore, non parametric statistical tests were used.

The unit cost of medicines was obtained from medicine records kept at the Central Medical Stores. The total cost of each antibiotic medicine treatment administered was calculated using the unit dose cost multiplied by the dosing frequency and the number of days the patient was hospitalized and put on antibiotic treatment.

The median cost of treating CAP at the hospital was found to be ZAR 113.58 and the mean cost was calculated at ZAR 145.06. It is further established that it is more costly to use multiple antibiotic medicine therapy than single antibiotic therapy.

Treatment Option Cost Analysis

The Dunn's test on cost of medicine treatment by age group showed that there is no significant difference in the cost of treatment by age group ($p = 0.7$). The two-sample Wilcoxon rank-sum (Mann-Whitney) test showed that there is no difference in the cost of treatment by gender ($p = 0.9$).

The Kruskal-Wallis test was used to compare the differing cost of CAP treatment options. A p-value ($p < 0.001$) from this test suggests that the cost differs by category of treatment. To determine where this difference in treatment cost lay, the Dunn's pairwise comparison test was used.

Table 3 shows where the differences in treatment option cost lies. For example **Table 3** shows that cost of treatment with Amoxicillin plus Gentamycin differs from that of treatment option benzylpenicillin + plus gentamycin. Furthermore, treatment with benzylpenicillin only and ceftriaxone + gentamycin options differs from treatment with benzylpenicillin + gentamycin and benzylpenicillin only option.

The Swaziland Standard Treatment Guidelines (STG, 2015) recommends the use of benzyl penicillin 5 mu four times a day for 5 days for treatment of hospitalized CAP cases. This in monetary value translates to ZAR 79.80. This cost was calculated based on unit antibiotic medicine cost, the standard recommended dosing frequency and duration of treatment duration.

The difference between actual and standard antibiotic medicine cost in USD was calculated at three different percentiles and is shown in **Table 3** herein.

The difference between actual and standard was significantly different from 0 when using Wilcoxon signed-rank test for: treatment option with amoxicillin + gentamycin (Prob > |z| = 0.0050) and treatment option with ceftriaxone + gentamycin (Prob > |z| = 0.0033). These had actual cost significantly greater than standard treatment.

TABLE 3 | Cost comparison analysis.

Treatment cost	*N*	p50	p25	p75
Amoxicillin plus gentamycin				
Actual cost	10	241.41	171.53	345
Std cost	10	79.8	79.8	79.8
Diff	10	161.61	91.73	265.2
Benzylpenicillin plus genatmycin				
Actual cost	24	48.88	40.7	87.4
Std cost	24	79.8	79.8	79.8
Diff	24	−30.92	−39.1	7.6
Ceftriaxone plus genatmycin				
Actual cost	11	200.45	172.5	272.92
Std cost	11	79.8	79.8	79.8
Diff	11	120.65	92.7	193.12
Benzylpenicillin only				
Actual cost	6	35.91	27.93	39.9
Std cost	6	79.8	79.8	79.8
Diff	6	−43.89	−51.87	-39.9
Amoxicillin only				
Actual cost	4	155.25	115	272.94
Std cost	4	79.8	79.8	79.8
Diff	4	75.45	35.2	193.14
Ceftriaxone only				
Actual cost	7	100.2	100.2	267.2
Std cost	7	79.8	79.8	79.8
Diff	7	20.4	20.4	187.4
Other				
Actual cost	9	140.9	95.47	206.05
Std cost	9	79.8	79.8	79.8
Diff	9	61.1	15.67	126.25

Actual cost, cost of the treatment option used; Std cost, cost of standard treatment (benzylpenicillin only); Difference, difference between actual and standard antibiotic medicine cost.

The Kruskal-Wallis test used to compare more than two treatment options showed a $p < 0.001$ suggesting that cost differed by treatment option. To determine where this difference in cost lay, the Dunn's pair-wise comparison test was used. **Table 4** shows this pair-wise comparison and where the differences in cost lay.

Table 4 shows that (i) Treatment with amoxicillin+gentamycin differed significantly from treatment with benzylpenicillin+gentamycin ($p = 0.0004$) and benzylpenicillin only ($p = 0.0003$). (ii)Treatment ceftriaxone+gentamycin differed from treatment benzylpenicillin+gentamycin ($p = 0.0004$) and benzylpenicillin only ($p = 0.0004$).

DISCUSSION

This study considered only level 1 costs i.e., price of antibiotic medicines used in treating CAP at a tertiary hospital.

TABLE 4 | Dunn's Pair-wise Comparison of cost of medicine treatment.

	Amoxicillin + Gentamycin	Benzylpenicillin + Genatmycin	Ceftriaxone + Genatmycin	Benzylpenicillin	Amoxicillin	Ceftriaxone
Benzylpenicillin+Gentamycin	4.1046					
	0.0004					
Ceftriaxone+Genatmycin	0.1250	−4.0930				
	1.0000	**0.0004**				
Benzylpenicillin only	4.1824	1.3471	4.1479			
	0.0003	0.85587	0.0004			
Amoxicillin only	0.5959	−2.2078	0.5102	−2.799		
	0.9989	0.2504	0.9995	0.0523		
Ceftriaxone only	1.3248	−2.0767	1.2372	−2.708	0.4791	
	0.8701	0.3304	0.9093	0.0686	0.9997	
other	1.6184	−2.0500	1.5329	−2.6870	0.6507	0.1801
	0.6798	0.3482	0.7430	0.0730	0.9981	1.0000

P-values of significance are highlghted in bold.

The study has identified sixteen different antibiotic cocktails used by medical doctors when treating CAP in adult inpatients at Piggs Peak Government Hospital, the rationale of which still needs to be explored.

Amongst the antibiotic medicines recommended in the treatment of CAP, the WHO Essential Medicines List (9) of 2017, states amoxicillin, ceftriaxone, gentamicin, benzylpenicillin and amoxicillin-clavulanic as recommended molecules. It is worth noting that of the identified treatment cocktails for CAP at PPGH 99% of the cases were treated using these WHO recommended medicine either alone or in combination.

Of the identified antibiotic treatment options in this study, 27% consisted of a single antibiotic and 73% was either a combination of 2 or three antibiotics. In contrast to this, Sow in his study of comparing clinical features and outcome in Africa (Republic of Guinea) and Europe (France) highlighted a large number (90%) of cases in Guinea (Africa) (10) where CAP was being successfully treated using a single antibiotic- penicillin. This may seem to suggest that doctors at the hospital believe use of multiple antibiotics is superior over a single antibiotic option.

In the combined medicine therapy treatment options identified at facility the majority, 33% of the CAP cases were treated with a combination of injectable benzylpenicillin and gentamycin, and 15.5% were treated with a combination of ceftriaxone plus gentamycin. Both these antibiotic medicines are recommended in the latest WHO Essential Medicines List (9) for the treatment of CAP. From the analysis it is not clear whether the choice of medicine is linked to age, gender or severity of disease.

The cost of treating CAP using amoxicillin plus gentamycin differed from treating using benzylpenicillin plus gentamycin or the benzylpenicillin only option. Furthermore, the cost of treating CAP with ceftriaxone plus gentamycin differed from benzylpenicillin plus Gentamycin and the benzylpenicillin only option.

When comparing treatment cost by gender or age, it was found that there was no difference in the cost of treatment by age (p-0.7) or by gender ($p = 0.9$).

CONCLUSION

This cost comparison analysis has shown that age or gender did not influence the cost of antibiotic medicine treatment, but the choice of antibiotic(s) used had an influence on the treatment cost. The study has highlighted a significant difference in the monetary cost of the differing approaches used for treating CAP at PPGH.

Treatment with (i) dual therapy -amoxicillin plus gentamycin and (ii) ceftriaxone plus gentamycin cost significantly greater when compared with the recommended standard treatment of benzylpenicillin. No significant difference in cost between the standard treatment (benzylpenicillin) and (i). benzylpenicillin plus gentamycin, (ii) amoxicillin only, and 3. ceftriaxone only treatment options was noted.

Treatment as per empirical treatment recommended in the national CAP treatment guidelines therefore cost less than the identified antibiotic used by doctors at the hospital. The rationale behind the differing antibiotic medicine choices when treating CAP needs to be explored and cost minimization measures put in place in order to contain medicine costs at the facility.

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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An Overview of the Reimbursement Decision-Making Processes in Bulgaria As a Reference Country for the Middle-Income European Countries

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Background: Policy makers face a lot of challenges in the process of drug reimbursement decision-making, especially in the context of entering the market of more and more innovative medicinal products (MPs). The aim of the current study is to make an overview of the reimbursement system development and to evaluate the access of innovative medicines, which have entered the EU-market in the period 2015–2017, in Bulgaria as reference example for middle-income European country.

Methods: A literature and a legislative systematic review regarding the Bulgarian reimbursement system as well as a defining the number of available innovative reimbursed MPs in 2017 in Bulgaria was made.

Results: The reimbursement legislation in Bulgaria is quite unstable due to constant changes, which have been made, especially in the recent years. Despite this fact, the reimbursement process in Bulgaria is in accordance with the Transparency Directive. Bulgarian patients have a relatively delayed access to innovative medicines as only 5% of centrally authorized MPs in 2017 are available in the positive drug list (PDL), 16% of all in 2016 and 18%—in 2015. This could be explained by the long procedure for their appraisal in Bulgaria: the first step is issuing an opinion by the HTA Committee, followed by negotiation of discounts between the marketing authorization holder and the National Health Insurance Fund and making a final decision by the National Council on Prices and Reimbursement (NCPR) for the inclusion into the PDL.

Conclusion: Optimization of the procedure for issuing reimbursement status for innovative MPs is needed, such as improvements in the process of conducting HTA reports and their appraisal, incorporation of adequate systems for following the effectiveness and safety of MPs in the real-world conditions, value-based pricing implementation, and increasing the financial control over the health insurance system.

Keywords: reimbursement, Bulgaria, low and middle-income Balkan countries, innovative medicines, access, affordability, positive drug list

INTRODUCTION

The policy makers are constantly facing the challenge to find the balance between the increased patients' needs of innovative, high costly medicines and limited financial resources (1). The scarce resources and the increasing patients' needs define the need for implementation of strict pharmacoeconomic evaluations for the purposes of making the right decision.

A lot of issues still exist, notably in the middle and upper-middle-income European countries (2). The economic situation in these countries is critical and there is an emergency need of more efficient reallocation of the resources especially in the pharmaceutical sector. Their health-care systems are not as stable as they should be due to a lot of reforms which have been made in the recent years (2). Rancic et al. concluded that the total health expenditures showed significant growth in the period 1995–2012 probably due to population aging (3). Pharmaceutical expenditures are a significant part of total health-care expenditures. For example, in Bulgaria the pharmaceutical expenditures increase every year, which leads to the annual budget deficit for National Health Insurance Fund (NHIF) (4). Therefore, more precise cost-containment measures should be applied as well as optimization of HTA usage in order to get better value for money (2, 5). Implementation of effective working generic policy and entering the market of biosimilar products are also possible measures (2). As Jakovljevic et al. highlighted there are some factors such as demographic crisis which could not be overcome and which is a main pharmaceutical expenditures driver in the next years (2, 6–8). Moreover, Bulgaria as the EU Member State with the lowest income per capita [only 47% of the EU average (9)] faces many challenges in ensuring the most innovative medicines for its citizens.

The aim of the current study is to make an overview of the reimbursement system development and to evaluate the access of innovative medicines, which have entered the EU-market in the period 2015–2017, in Bulgaria as reference example for middle-income European country.

MATERIALS AND METHODS

The first part of the study was a literature and a legislative systematic review regarding the implemented reimbursement system in Bulgaria for the period 2000–2017. A search was made in the official websites of Bulgarian institutions such as Ministry of Health, NHIF, National Council on Prices and Reimbursement of Medicinal Products (MPs), National Centre for Public Health and Analyses, and Bulgarian Drug Agency in order to identify the latest legislative documents and guidelines for conducting of administrative pricing and reimbursement procedures.

The second part of the study included a search of all MPs (MPs) which received marketing authorization through the centralized procedure for the period 2015–2017. A comparison of the generated list of these MPs by the website of the European Medicines Agency (EMA) and the current Bulgarian Positive Drug List (PDL) was made. Therefore, the availability of the newest medicines in Bulgaria was analyzed.

The third part of the study presents a systematic and analytical review of the identified issues in the reimbursement process in Bulgaria on the basis of the authors' point of view and officially published scientific studies.

RESULTS

Reimbursement Legislation in Bulgaria

The Health Insurance Act (1998) introduced the mandatory health insurance in Bulgaria (**Figure 1**) (10). According to this law NHIF was founded in 1999 as an independent public institution (11). The NHIF reimburse MPs, medical devices, dietetic foods, foods for special purposes for treatment of obligatory health insured Bulgarian citizens, as well as for hospitalized patients. For the inclusion of the medicines in the reimbursement lists a methodological approach has been developed and published in 2000, in which several crucial points were stated:

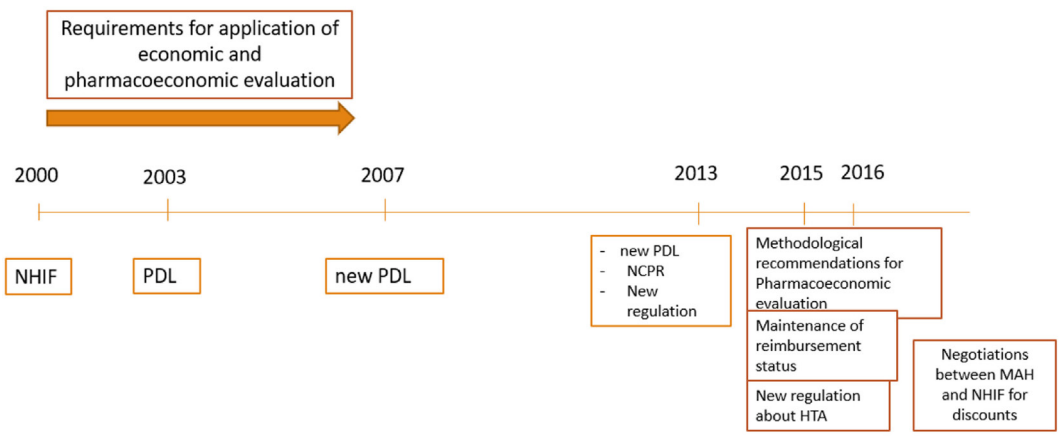

FIGURE 1 | Regulatory development of reimbursement procedures in Bulgaria.

1. economic analysis should precede the pharmacoeconomic analysis;
2. economic analysis includes directs costs, due to product application; market share, prices; additional costs etc.;
3. pharmacoeconomic analysis is a comparison of the costs and consequences of the product application and its competitors (12).

The Council Decree 81 in 2003 stipulates the criteria, conditions and procedures for including MPs in the Bulgarian PDL. Three groups of MPs in PDL were defined:

A new MPs without a medicinal alternative in the clinical practice (new mechanism of action, new ATC code);
B new medicines for which there is a therapeutic alternative with pharmacotherapeutic advantages (group A and B are innovative products);
C MPs with a medicinal alternative in the clinical practice (generics).

A fixed percent of the reimbursement for each MP is defined (100, 75, 50, and 25%) on the basis of its importance for disease therapy and severity of the disease.

In 2007 after the Bulgarian accession to the EU new Regulation was issued and the structure of PDL was changed: ANNEX 1: for fully or partly reimbursed medicines paid by the NHIF; ANNEX 2: medicines paid by the hospital budgets; ANNEX 3: medicines paid by the Ministry of Health budget according to Health Insurance Law; ANNEX 4: medicines for the therapy of rare diseases, HIV, and prophylactics of infections. There were no particular recommendations or guidelines for the development and presentation of the pharmacoeconomic analysis.

The pricing and reimbursement decision process were merged and delegated to one institution in 2013. The National Council on Prices and Reimbursement (NCPR) was established as responsible body for inclusion and exclusion of MPs in the PDL (PDL) and for maintenance of their reimbursement status (13). The PDL was changed and there are now three main annexes and the time for decision was shortened (60 days). All innovative medicines should receive a positive opinion by the Health Technology Assessment Committee since 2015 before issuing the final decision by the Council (14, 15).

Pharmacoeconomic and HTA dossiers are prepared following the officially published methodological guidelines. Science-based efficacy, safety, and pharmacoeconomic evidence should be presented in the dossier. Schematic explanation of the reimbursement procedure is shown on **Figure 2**.

A number of discounts are possible and their level should be negotiated between the Marketing authorization holder (MAH) and the NHIF (16):

1. mandatory discount for reimbursement of Single Source Products (new INNs) (>10%);
2. mandatory discount for new INN and combinations—there is no particular percentage;
3. managed entry agreement—MAH should provide additional discount when the agreed annual expenditures of the MP for each relevant year is exceeded (if the forecast values exceeded to 10% then the discount is not lower than 25%; if the forecast values exceeded to 10–15% the discount is not lower than 50%; if the forecast values exceeded to 15–25 per cent then the discount is not lower than 75%; if the forecast values exceeded 25% then the discount is not lower than 90%);
4. growth discount—MAH should pay back 20% of the relevant rate of growth, when the total growth is higher than 3% from the negotiated (for e.g., the expected expenditures are 100 million BGN, but the real expenditures are 110 mill BGN then the

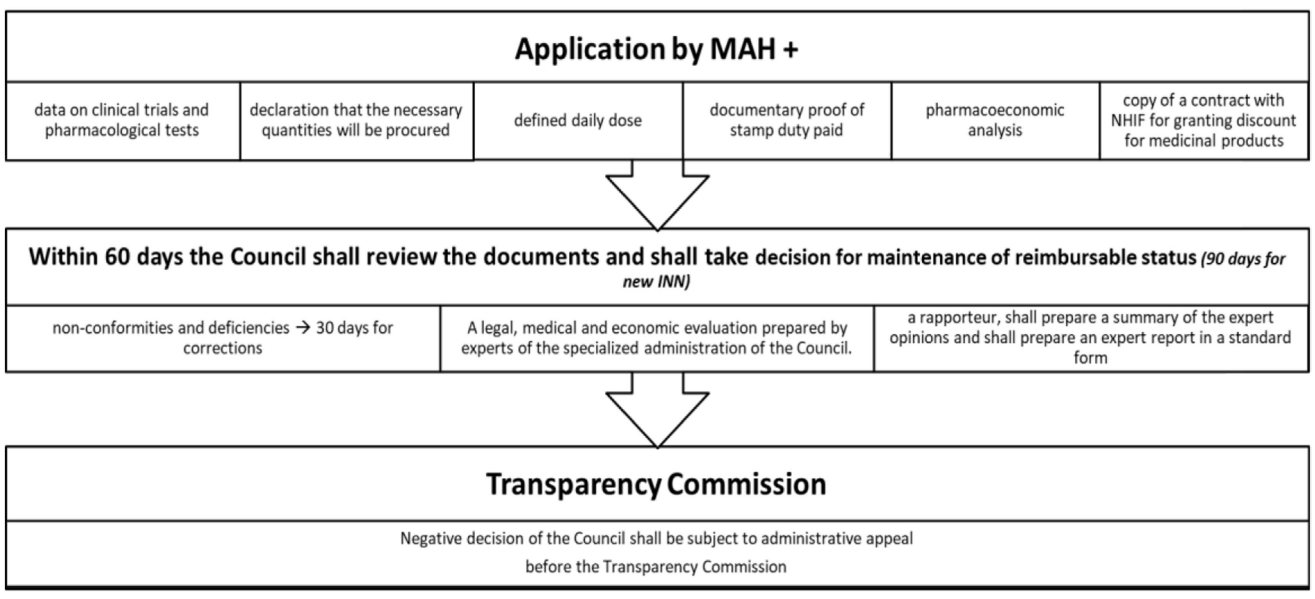

FIGURE 2 | Procedure for inclusion of MPs in PDL. Abbreviations: MPs, medicinal products; PDL, positive drug list.

MAH should pay back 20% of 10 million BGN). Exchange rate is 1 BGN = 0.51 Euro;
5. voluntary discounts—for multiple source products; every MAH could provide voluntary additional discounts.

Access and Affordability to Innovative MPs in Bulgaria

Bulgarian patients have a relatively delayed access to innovative medicines. The percentage of innovative MPs included in the Bulgarian PDL is far below 20%. The number of the newest medicines authorized through the centralized procedure by the EMA in 2017, is 83. Only three of them are reimbursed in Bulgaria and one has received a positive opinion by the HTA Committee. Logically, the number of reimbursed innovative MPs in Bulgaria, which entered the EU-market in 2015 and 2016, is higher than the following year: 18 and 16%, respectively (**Figure 3**). Some innovative products even do not apply for reimbursement and only register prices for non-reimbursable marketing.

Despite the limited number of reimbursed innovative medicines, very important and promising therapies such as those for Hepatitis C, HIV, multiple myeloma, oncological conditions, etc. are ensured for all Bulgarian patients for whom there is no other option (**Table 1**).

MPs Reimbursement Issues in Bulgaria As an Example for Middle-Income EU Country

The financial limitations of low and middle-income countries are the main drivers for cost-containment measures introduction. In the context of medical and pharmaceutical development, the requirements to the NHIF are increasing. Therefore, more precise and regular financial control mechanisms should be implemented. Another serious problem in these countries is the lack of expertise and the limited local epidemiological data for the purposes of preparing a valuable pharmacoeconomic/HTA dossier. Some of the issues regarding the reimbursement process in Bulgaria and the possible solutions are highlighted in **Table 2**.

DISCUSSION

The reimbursement policy in Bulgaria could be characterized by implementation of lots of rules for the inclusion of medicines into the PDL and a clear process of reimbursement performed by the National Council on Prices and Reimbursement (19). Despite the necessity of their further improvement, the available pharmacoeconomic and HTA guidelines give the possibility to the policy decision maker to step on a scientific basis in order to make the best possible reimbursement decision. Some problems such as lack of mechanisms for gathering effectiveness data from real-world studies, the periodic legislative changes and the lack of enough experts in the area could be highlighted. Further improvement in the legislative framework is needed in order to cope with the increasing reimbursement expenditures. Collaboration with other European countries could be useful in order to find the best solutions for the reimbursement practice in Bulgaria (20, 21). The process of development and improvement of reimbursement policy is slower, but it could ensure more options for providing innovative medicines to the population (22, 23) as it is the case in other Balkan countries such as Greece (2, 24), Croatia (25), Bosna and Herzegovina, and Republic of Serbia (26). Several crucial changes are proposed in Polish reimbursement system. One of these changes aims to create an innovative reimbursement budget, which will provide

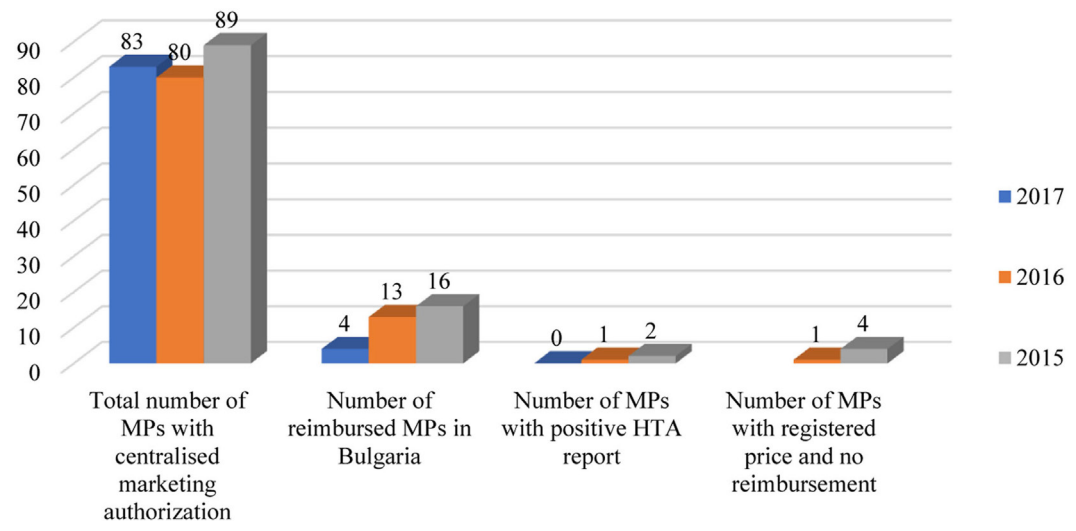

FIGURE 3 | Reimbursement status of MPs in Bulgaria authorized through centralized procedure in the EU. Abbreviations: MA, marketing authorization; MPs, medicinal products; HTA, health technology assessment.

TABLE 1 | Medicinal products with centralized marketing authorization, which are available in Bulgaria.

Active Substance	ATC code	Authorization date	Indication/ICD	Condition Approval/ Exceptional Circumstance/ Orphan/Generic/Biosimilar	Reimbursement status in Bulgaria, Year
Blinatumomab	L01XC	23/11/2015	ICD C91.0 Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukemia (ALL)	Conditional approval; Orphan	Positive HTA; 01.2017
Cobimetinib hemifumarate	L01XE38	20/11/2015	In combination with vemurafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation		Price registration; not reimbursed
Efmoroctocog alfa	B02BD02	19/11/2015	ICD: D66 Treatment and prophylaxis of bleeding in patients with hemophilia A		Reimbursed, 2017
Elvitegravir/cobicistat/ emtricitabine/tenofovir alafenamide	J05AR	19/11/2015	Treatment of adults and adolescents infected with human immunodeficiency virus 1 (HIV-1) without any known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir		Price registration; not reimbursed
Sacubitril/valsartan	C09DX04	19/11/2015	ICD: I50.0; I50.1 For treatment of symptomatic chronic heart failure with reduced ejection fraction		Reimbursed, 2016
Carfilzomib	L01XX45	19/11/2015	ICD: C90.0 Multiple myeloma	Orphan	Reimbursed, 2017
Aripiprazole	N05AX12	16/11/2015	ICD: F20.0, F20.1, F20.5, F20.6, F30.0, F30.1, F31.0, F31.1, F31.2, F31.7 Schizophrenia; moderate to severe manic episodes in Bipolar I Disorder; prevention of a new manic episode	Generic	Reimbursed, 2016
Pemetrexed disodium hemipentahydrate	L01BA04	18/09/2015	Malignant pleural mesothelioma	Generic	Reimbursed, 2017
Pregabalin	N03AX16	28/08/2015	ICD: G40.6, G40.7 Epilepsy; generalized anxiety disorder	Generic	Reimbursed, 2016
Aripiprazole	N05AX12	20/08/2015	ICD: F20.0, F20.1, F20.5, F20.6, F30.0, F30.1, F31.0, F31.1, F31.2, F31.7 Schizophrenia in adults and in adolescents aged 15 years and older. Moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode	Generic	Reimbursed, 2016
Bortezomib	L01XX32	20/07/2015	ICD: C90.0, C90.1, C90.2 Progressive multiple myeloma	Generic	Reimbursed, 2016
Evolocumab	C10	17/07/2015	ICD: E78.0 Hypercholesterolemia and mixed dyslipidaemia		Reimbursed, 2016
Nivolumab	L01XC	19/06/2015	ICD: C43.0, C43.1, C43.2, C43.3, C43.4, C43.5, C43.6, C43.7, C43.8, C43.9 Advanced (unresectable or metastatic) melanoma Non-small cell lung cancer (NSCLC) Renal cell carcinoma (RCC) Classical hodgkin lymphoma (cHL) Squamous cell cancer of the head and neck (SCCHN) Urothelial carcinoma		Reimbursed, 2018
Edoxaban tosylate	B01	19/06/2015	ICD: I26.0, I48, I69.3, I69.4, I80.1, I80.2 Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors		Reimbursed, 2017
Empagliflozin/ metformin	A10BD20	27/05/2015	ICD: E11.2, E11.3, E11.4, E11.5, E11.9 Type 2 diabetes mellitus		Reimbursed, 2016
Netupitant/ palonosetron hydrochloride	A04AA	27/05/2015	Prevention of acute and delayed nausea and vomiting		Positive HTA; 08.2017

(*Continued*)

TABLE 1 | Continued

Active Substance	ATC code	Authorization date	Indication/ICD	Condition Approval/ Exceptional Circumstance/ Orphan/Generic/Biosimilar	Reimbursement status in Bulgaria, Year
Ceritinib	L01XE	06/05/2015	Anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC)		price registration; not reimbursed
Bupropion hydrochloride/ naltrexone hydrochloride	A08AA	26/03/2015	Management of weight in adult patients (18 years)		price registration; not reimbursed
Secukinumab	L04AC10	15/01/2015	ICD: L40.0, M07.1, M07.2, M07.3, M45.0, M45.1, M45.2, M45.3, M45.4, M45.5, M45.6, M45.7, M45.8 Moderate to severe plaque psoriasis Psoriatic arthritis Ankylosing spondylitis		Reimbursed, 2016
Dasabuvir sodium	J05AX16	15/01/2015	ICD: B18.2, K74.0, K74.6 Treatment of chronic hepatitis C (CHC) in adults For hepatitis C virus (HCV) genotype specific activity		Reimbursed, 2015
Nintedanib	L01XE	15/01/2015	ICD: J84.1 Idiopathic pulmonary fibrosis (IPF)		Reimbursed, 2018
Ombitasvir/ paritaprevir/ritonavir		15/01/2015	ICD: B18.2, K74.0, K74.6 Chronic hepatitis C (CHC) in adults For hepatitis C virus (HCV) genotype specific activity		Reimbursed, 2015
Pemetrexed diacid monohydrate	L01BA04	18/01/2016	Malignant pleural mesothelioma Non-small cell lung cancer		Reimbursed, 2016
Osimertinib mesylate	L01XE	02/02/2016	ICD: C34.0, C34.1, C34.2, C34.3, C34.8, C34.9 Locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small-cell lung cancer (NSCLC)		Reimbursed, 2018
Tenofovir disoproxil	J05AF07	08/12/2016	ICD: B18.1, K74.0, K74.6 HIV-1 infection Hepatitis B infection	Generic	Reimbursed, 2017
Venetoclax	L01XX52	05/12/2016	ICD: C91.1 Chronic lymphocytic leukemia (CLL) in the presence of 17p deletion or TP53 mutation	Conditional approval/orphan	Reimbursed, 2018
Etelcalcetide hydrochloride	H05BX04	11/11/2016	Secondary hyperparathyroidism (SHPT) in adult patients with chronic kidney disease (CKD) on hemodialysis therapy		Reimbursed, 2017
Palbociclib	L01XE33	09/11/2016	ICD: C50.0, C50.1, C50.2, C50.3, C50.4, C50.5, C50.6, C50.8, C50.9 Hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer		Reimbursed, 2018
Tenofovir disoproxil phosphate	J05AF07	15/09/2016	ICD: B18.1, K74.0, K74.6 HIV-1 infection Hepatitis B infection	Generic	Reimbursed, 2017
Salmeterol xinafoate/ fluticasone propionate	R03AK06	18/08/2016	ICD: J44.8, J45.0, J45.1 Asthma Chronic obstructive pulmonary disease (COPD)		Reimbursed, 2017
Elbasvir/grazoprevir	J05A	22/07/2016	ICD: B18.2, K74.0, K74.6 Chronic hepatitis C (CHC) in adults		Reimbursed, 2016
Emtricitabine/rilpivirine hydrochloride/ tenofovir alafenamide	J05AR19	21/06/2016	Human immunodeficiency virus 1 (HIV-1)		Positive HTA; 08.2017
Sacubitril/valsartan	C09DX04	26/05/2016	ICD: I50.0, I50.1 Symptomatic chronic heart failure with reduced ejection fraction		Reimbursed, 2016
Trifluridine/tipiracil hydrochloride	L01BC	25/04/2016	Metastatic colorectal cancer (CRC)		price registration; not reimbursed

(*Continued*)

TABLE 1 | Continued

Active Substance	ATC code	Authorization date	Indication/ICD	Condition Approval/ Exceptional Circumstance/ Orphan/Generic/Biosimilar	Reimbursement status in Bulgaria, Year
Emtricitabine/tenofovir alafenamide	J05AR17	21/04/2016	ICD: B20.0, B20.1, B20.2, B20.3, B20.4, B20.5, B20.6, B20.7, B20.8, B20.9, B21.0, B21.2, B21.3, B21.7, B21.8, B21.9, B22.0, B22.1, B22.2, B22.7, B23.0, B23.1, B23.2, B23.8, B24, Z21 Human immunodeficiency virus type 1 (HIV-1)		Reimbursed, 2017
Amlodipine besilate/ valsartan	C09DB01	22/03/2016	ICD: I10, I11.0, I11.9, I12.0, I12.9, I13.0, I13.1, I13.2 Essential hypertension	Generic	Reimbursed, 2017
Octocog alfa	B02BD02	18/02/2016	ICD: D66 Treatment and prophylaxis of bleeding in patients with hemophilia A (congenital factor VIII deficiency)		Reimbursed, 2017
Rituximab	L01XC02	13/07/2017	ICD: C82.0, C82.1, C82.2, C82.7, C82.9, C83.2, C83.3, C83.9, C91.1, M31.3, M31.9 Non-Hodgkins lymphoma (NHL) Follicular lymphoma patients CD20 positive diffuse large B cell non-Hodgkins lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy Granulomatosis with polyangiitis and microscopic polyangiitis Induction of remission in adult patients with severe, active granulomatosis with polyangiitis (Wegeners) (GPA) and microscopic polyangiitis (MPA)	Biosimilar	Reimbursed, 2017
Edoxaban tosylate	B01AF03	20/04/2017	ICD: I26.0, I48, I69.3, I69.4, I80.1, I80.2 Prevention of stroke and systemic embolism Deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults		Reimbursed, 2017
Tofacitinib citrate	L04AA29	22/03/2017	ICD: M05.0, M05.1, M05.3, M05.8 Moderate to severe active rheumatoid arthritis (RA)		Reimbursed, 2018
Darunavir	J05AE10	04/01/2017	Human immunodeficiency virus (HIV-1) infection	Generic	Reimbursed, 2017

ATC code, Anatomical Therapeutic Chemical Classification System; ICD, International Classification of Diseases.

funding for reimbursement of innovative products developed by manufacturers with research and development activities with considerable impact on the Polish economy (27). Therefore, the patient access in Poland to innovative therapies could be significantly improved.

Our study confirms that the patient access to innovative medicines from the moment of their marketing authorization is delayed. The number of reimbursed innovative medicines as a percent of the centrally authorized by EMA is far below 20% which confirms some extent of limitations in the patient access. Similar results are presented by Inotai et al. for the patient access to original biologics and biosimilar in Central and Eastern European countries (CEE countries). The authors explain the results with the current implemented biosimilar policies in these countries (28), which means that some improvement in the local legislation is needed. Significant variations exist in uptake of biosimilars in Europe, which could be overcome with implementation of specific procedures and measures (29). While Western Balkan countries has proved through the years that are capable to ensure reimbursed medicines for patients with non-communicable diseases with some exceptions (30), there is still gaps in the knowledge about the patients access to innovative medicines in these countries. Study published in 2017 highlighted the large disparities in access to innovative therapy for metastatic melanoma among the European countries mostly in the Eastern European region (31). The Romanian HTA system implements criteria focused more on the costs and, therefore, it raises a barrier for the innovative medicines in the country (32).

The regulatory bodies especially in CEE countries are pressured in order to ensure new medicines (orphan MPs, innovative biological products, etc.) for severe life-threatening conditions with no available alternative (33). The budget constraints are inevitable, especially in the low- and middle-income countries. The policy makers are trying to balance in the context of deficit resources adopting various approaches. Performance based managed entry agreements for pharmaceuticals is a possible option which is partly applied in Bulgaria. Reassessment of treatments after their inclusion in the reimbursement lists gives a guarantee for collecting of more valuable evidence for effectiveness and cost-effectiveness of the new medicine (34). So, the public fund will be able to stop financing technologies with no proven value in the post reimbursement period. The crucial evidence, which should be taken into account when a reimbursement decision is made, is whether the new medicine brings additional benefits for those patients with no available alternative (23).

TABLE 2 | Reimbursement issues in low and middle-income countries and possible solutions.

Reimbursement process issues	Possible solutions
Financial restrictions (limited budgets)	– Improvement of the collection of health contributions; – Better financial control and monitoring of pharmaceutical expenditures (17); – Improved application of the economic evaluations for the purposes of more efficient reallocation of the resources; – Differentiation of separate budgets for specific group of medicines [for e.g., orphan medicinal products (MPs)].
Lack of expertise (18)	– Providing of educational programs and continuing education for the government employees; – International collaboration.
Improvement in pharmacoeconomic guideline/ HTA guideline	– Taking into consideration the latest pharmacoeconomic studies and their implementation into the practice; – Differentiation of the discount levels for both cost and results; – Definition of separate ICER thresholds regarding the type of evaluated MP; – Implementation of multicriteria decision analysis for some specific groups of MPs.
Lack of systems for tracking and assessment of the effectiveness of the MPs	– Dialog between the information technology companies, pharmaceutical industry and health-care policy makers for creation of a unified common information system; – Development and maintenance of patients registries; – Involvement of non-profit patient organization in the HTA process.

Strength of the current study is that it represents the development of Bulgarian reimbursement legislation since its formation in 2000 to these days. This review could be used for the purposes of making more valuable and evidence based decisions for further reforms in the system. As an example of a middle-income Balkan country, the case with Bulgarian reimbursement system could be used as a model for other Balkan countries, which are economically similar to Bulgaria and which are characterized with similar pricing and reimbursement requirements (35). To the best of our knowledge, this is the first study, which makes an attempt to present the access of Bulgarian patients to reimbursed innovative therapies, which received marketing authorization through the centralized procedure in the EU, and to give some recommendations for improvement of the reimbursement decision about these medicines. Further studies could focus more on the real financial burden of the innovative therapies.

CONCLUSION

Optimization of the procedure for issuing reimbursement status for innovative MPs is needed especially in the Balkan countries, where lots of issues exist. Improvements in the process of conducting HTA reports and their appraisal, incorporation of adequate systems for following the effectiveness and safety of MPs in the real-world conditions, value-based pricing implementation and increasing the financial control over the health insurance system could be some of the possible solutions. It is crucial the level of expertise in these countries to be enhanced through accreditation of shared master Health Technology Assessment programs. Shared experience among Balkan countries could provide additional valuable information regarding economic evaluation and appropriate reimbursement mechanisms for innovative medicines.

AUTHOR CONTRIBUTIONS

All the authors have provided valuable contributions to the manuscript.

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Medicine Availability and Prescribing Policy for Non-Communicable Diseases in the Western Balkan Countries

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Background: During the transition processes, the Western Balkan countries were affected by conflicts and transition-related changes. Life expectancy in these countries is lower, while the mortality from non-communicable diseases (NCDs) is higher in comparison with western and northern parts of Europe. The primary aim of this study was to analyze the treatment possibilities for the most common NCDs in the Western Balkan countries. The secondary aim was to understand and compare the policies regarding prescribing-related competencies of family physicians.

Methods: In June and July 2017, a document analysis was performed of national positive medicines lists, strategic documents, and clinical guidelines for the treatment of the most frequent NCDs; arterial hypertension, diabetes, hyperlipidemia, asthma, and chronic obstructive pulmonary disease (COPD). All text phrases that referred to medicines prescribing were extracted and sorted into following domains: medicine availability, prescribing policy, and medication prescribing-related competencies.

Results: Possibilities for treatment of arterial hypertension, diabetes, hyperlipidemia, asthma, and COPD vary across the Western Balkan countries. This variance is reflected in the number of registered medicines, number of parallels, and number of different combinations, as well as restrictions placed on family physicians in prescribing insulin, inhaled corticosteroids, statins and angiotensin II receptor blockers (ARBs), without consultant's recommendation.

Conclusion: Western Balkan countries are capable of providing essential medicines for the treatment of NCDs, with full or partial reimbursement. There are some exceptions, related to statins, newer generation of oral antidiabetic agents and some of the antihypertensive combinations. Prescribing-related competences of family physicians are limited. However, this practice is not compliant to the practices of family medicine, its principles and primary care structures, and may potentially result in increased healthcare financial ramifications to both the system and patients due to frequent referrals to the specialists.

Keywords: family medicine, Western Balkan, chronic non-communicable diseases, prescribing policy, prescribingrelated competencies

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INTRODUCTION

After the adoption of the Declaration in Alma Ata in 1978, great efforts have been made worldwide regarding the improvement of living conditions (water, electricity, roadways, and other infrastructure), development of primary health care, and vaccination of children (1). All the aforementioned has led to a decline in mortality rate in countries of all levels of development as well as increased life expectancy. Longer lifespan, urbanization, and lifestyle changes result in an increase in morbidity and mortality from non-communicable diseases (NCDs).

According to World Health Organization (WHO) data, of the 57 million global deaths in 2008, 36 million (63%) were due to NCDs, mainly cardiovascular diseases, diabetes, cancer, and chronic respiratory diseases. As the impact of NCDs increases, and as population's age, annual NCD deaths are projected to continue to rise worldwide, and the greatest increase is expected to be seen in low- and middle-income regions (2).

While popular belief presumes that NCDs afflict mostly high-income populations, evidence shows a very different story. Nearly 80% of NCD deaths occur in low-and middle-income countries and NCDs are the most common causes of death in most countries, except in Africa. With this in mind, First Global Ministerial Conference on Healthy Lifestyles and Noncommunicable Diseases Control in Moscow (2011) resulted in Moscow Declaration Preamble (3), followed by a session of the United Nations General Assembly (4), which adopted a number of conclusions of vital importance for primary health care such as to include prevention and control of NCDs among priorities in national health strategies and plans; to revitalize primary health care and promote access to cost-effective interventions for NCDs, including access to essential medicines and technologies and to mobilize additional resources and support innovative approaches to financing essential NCDs health-care interventions within primary health care.

For many decades, Eastern and Southern Europe have had lower life expectancy than the rest of Europe. This was particularly noticeable during the transition processes; however, the countries of the Western Balkan were affected not only by transition related changes but also by conflicts. Hence, besides poverty, transition and conflict have also weakened the health indicators of the Western Balkan countries (5–8). Such conditions were sustained by inadequate or practically non-existent health care reform which did not adapt to the new trends of globalization. A major problem for all newly established countries is decision-making within the health sector that is not based on evidence.

Prior to the disintegration of Yugoslavia, primary health care was at a very high level owing to the work of Andrija Štampar and Ante Vuletić. The latter, at the beginning of the 1960s, introduced the specialty of family medicine which served as a model for the UK, Canada, and other countries. Unfortunately, since 1995, in the Western Balkan countries, family medicine has not had satisfactory position (9–11).

Considering that, along with NCD prevention, both diagnostics and treatment are of utmost importance, the role of regulatory agencies and insurance funds in health policy became vital. Each of the Western Balkan countries has its particular list of medications prescribed by the national insurance fund. Furthermore, each country has regulatory agencies for placing and controlling prescribed medications. Given that some of the countries are small and do not have sufficient capacities, problem with medication control arises after they are placed on the market, especially in Bosnia and Herzegovina and Montenegro (12).

Last but not least, as early as Barbara Starfield's work was brought to light, it was evident that a well-organized primary health care resulted in better health indicators and lower expenditure (13, 14). In countries that have allowed the progress of family medicine and competences of family physicians, there is a decrease in referral to secondary health care and more comprehensive health care. This is particularly important in the treatment of NCDs since the teamwork of a family physician and other health-care professionals is not only favorable for the treatment of patients but also for primary and secondary prevention of both NCDs and infectious diseases, as well as of consequences caused by violence and accidents.

The underlying principle of well-performing primary health care system is to ensure access to essential medicines for treatment of NCDs; however, availability of medicines is not sufficient to provide continuous care required for patients. Very little is know about prescribing policy for NCDs in Western Balkan countries, which share legacy of the former Yugoslavia in management and financing patterns of health care system. Through document analysis, we aimed to analyze the treatment possibilities for the most common NCDs in countries of the Western Balkan. The questions that guided our research were: to what extent essential medicines from WHO list are included into positive medicines lists of these countries and what is the policy regarding prescribing-related competencies of family physicians.

MATERIALS AND METHODS

Setting

The qualitative exploratory study on prescribing policy was conducted by analyzing documents of Health Insurance Funds from Bosnia and Herzegovina (BiH), Croatia, Macedonia, Montenegro, Serbia, and Slovenia. The basic functions of the Health Insurance Funds are to manage the system finances (compulsory health insurance is the main source health care) and provide legal and managerial support to insure with regard to health and health care. According to the legislative requirements, fund develops and maintains database related to health-care activity and insurance coverage. Insurance coverage includes public or private sectors employees, the retired people, the disabled, and the students, while stateless persons and social care recipients are subsidized by the state budget for the uninsured. All patients have the same rights, regardless of the insurance payment level required. Within the financing of health care, the medications listed in positive medicines list are included. Medications appearing on the list are divided into several separate categories, with specific coverage rate, such as reduced, normal, or preferential reimbursement rate provided for each category. The revision is carried out every few years or more frequently, depending on health expenditure level or public needs. The lists are seen as

national documents; therefore, we included them into document analysis to gain a deeper understanding of the prescribing policy and develop empirical knowledge (15).

Design

To cover the knowledge utilization of the documents, six criteria were formulated (16), while four-step process was performed for conceptualizing the document analysis (17). Additions to a knowledge base were the information derived from Model List of Essential Medicines, provided by the World Health Organization (WHO) (18) for all countries. The essential medicines were defined as medicines with safety, effectiveness, availability, and rational use (19). The focuses of research were three domains: medicine availability, prescribing policy, and medication prescribing-related competencies of family physicians regarding treatment of most common NCDs. Medicine availability included essential medicines for the treatment of the most common NCDs: arterial hypertension, hyperlipidemia, diabetes, asthma, and chronic obstructive pulmonary disease (COPD) as well as management of pain at the end of life. Second domain involved analysis of legislative criteria and policy tools that have been used in controlling pharmaceutical spending. Medication prescribing competency framework is defined as a collection of competencies central to effective, rational, and safe prescribing, based on the judgment and ability to make decision rationally for the benefit of patients (20). The analysis covered angiotensin-converting enzyme (ACE) inhibitors, beta blockers, ARBs, oral hypolipidemic agents, oral hypoglycemic agents, Insulin, opiods, and proton pump inhibitors (PPIs).

Procedures

A set of positive medicines lists and strategic documents were retrieved through internet searches in June and July 2017. Due to the political divisions in BiH into two entities (The Republic of Srpska and Federation of Bosnia and Herzegovina) and canton levels (10 cantons in Federation, each with different legislation), the research included lists of the Republic of Srpska (RS) and two Federal cantons, Sarajevo, and Herzegovina Neretva. In the RS, authority over health care system is centralized with administration, financing and decision-making policy held by Ministry of Health and Social Welfare, while in Federation of BiH health care system administration is decentralized with each of 10 cantonal ministries having responsibilities for provision and financing of health care at all levels (Federal Ministry of health has limited role that ensures compliance with entity policy regulations). We also retrieved national clinical guidelines for the treatment of the chronic diseases in research focus and clinical practice guidelines of official professional associations (e.g., European Society of Cardiology). All documents were made available at the research sites. A document browser was used to interactively specify queries on the data. To prove the documents' authenticity, the content of each document has been examined.

Analysis

Credibility, accuracy, and representativeness of the selected information were determined. The first author (Tanja Pekez-Pavlisko) skimmed (superficially examined) and then systematically red retrieved documents. All text phrases that referred to medicines prescribing were extracted and sorted into following domains: medicine availability, prescribing policy, and medication prescribing-related competencies.

The meaningful and relevant data were identified during first-pass review and separated from the non pertinent text. Selected data were re-reviewed and themes construction was performed. Parallel, co-authors (Maja Racic and Srebrenka Kusmuk) individually analyzed documents. The results were compared and the doubts concerning the inclusion or position of data were discussed. The final results represent consensus between all researchers.

RESULTS

Medicines availability varied widely, while the prescribing policy and prescribing policy tools often were not corroborated by scientific approach and national as well as international guidelines.

Possibilities of treatment of arterial hypertension vary across the Western Balkan countries. This variance is reflected in the number of registered medication, number of parallels, and number of different combinations, as well as restrictions placed on family physicians in prescribing certain medication without referral to a clinical specialist. **Table 1** demonstrates the number of categorized medication on insurance lists per country.

Croatian and Slovenian medication lists contain several additional combinations, ACE inhibitors, diuretics, calcium channel blockers, beta blockers, and statins, the display of which would decrease the transparency of basic therapeutic groups of medicine for treatment of hypertension.

Furosemide and hydrochlorothiazide are on the positive medicine list in all countries, whereas spirinolactone is not on the list only in Montenegro. Regarding diuretics, there are no restrictions set on their prescriptions for family physicians, except for torasemide, restricted in the Sarajevo and Herzegovina Neretva cantons. In Sarajevo canton, this medication can be prescribed by certified family physicians, while in Herzegovina Neretva Canton, recommendation of a clinical consultant is requested.

The following beta blockers: atenolol, bisoprolol, propranolol, metoprolol, metoprolol succinate, and nebivolol were found to be on positive lists of all countries (**Figure 1**). Prescribing-related restrictions for beta blockers in family practice are presented in **Table 2**.

Situation with multiple registered products of various companies is similar in the area of ACE inhibitors and ARB as well as their combination with diuretics. In **Table 3**, only medicines with most parallels are shown. Lisinopril and hydrochlorothiazide are charged additionally in the RS, as well as other combinations with hydrochlorothiazide (ramipril, irbesartan). ARB inhibitors and its combinations are additionally charged in Serbia and in Croatia for several brand medicines only. ACE inhibitors do not meet criteria for prescribing restrictions in family practice, while there are several restrictions for ARBs (**Table 4**).

TABLE 1 | Number of medicines for treatment of hypertension according to groups, countries, and cantons.

	Bosnia and Hercegovina (Herzegovina Neretva Canton)	Bosnia and Hercegovina (The Republic of Srpska)	Bosnia and Hercegovina (Sarajevo Canton)	Montenegro	Croatia	Former Republic of Yugoslavia Macedonia	Slovenia	Serbia
Diuretics	5	6	5	2	5	4	5	7
Beta blockers	1	4	6	3	6	4	7	6
Angiotensin-converting enzyme (ACE) inhibitors	7	8	6	7	8	2	8	10
Angiotensin II receptor blockers (ARB) inhibitors	1	2	1	5	6	1	5	3
Ca channel blockers	3	6	3	3	8	3	7	6
Combination ACE inhibitors + diuretics	4	6	4	7	7	0	6	7
Combinations ARB inhibitors + diuretics	0	1	2	1	5	1	3	2
Combinations ACE inhibitors + Ca channel blockers	0	1	1	0	3	0	2	2

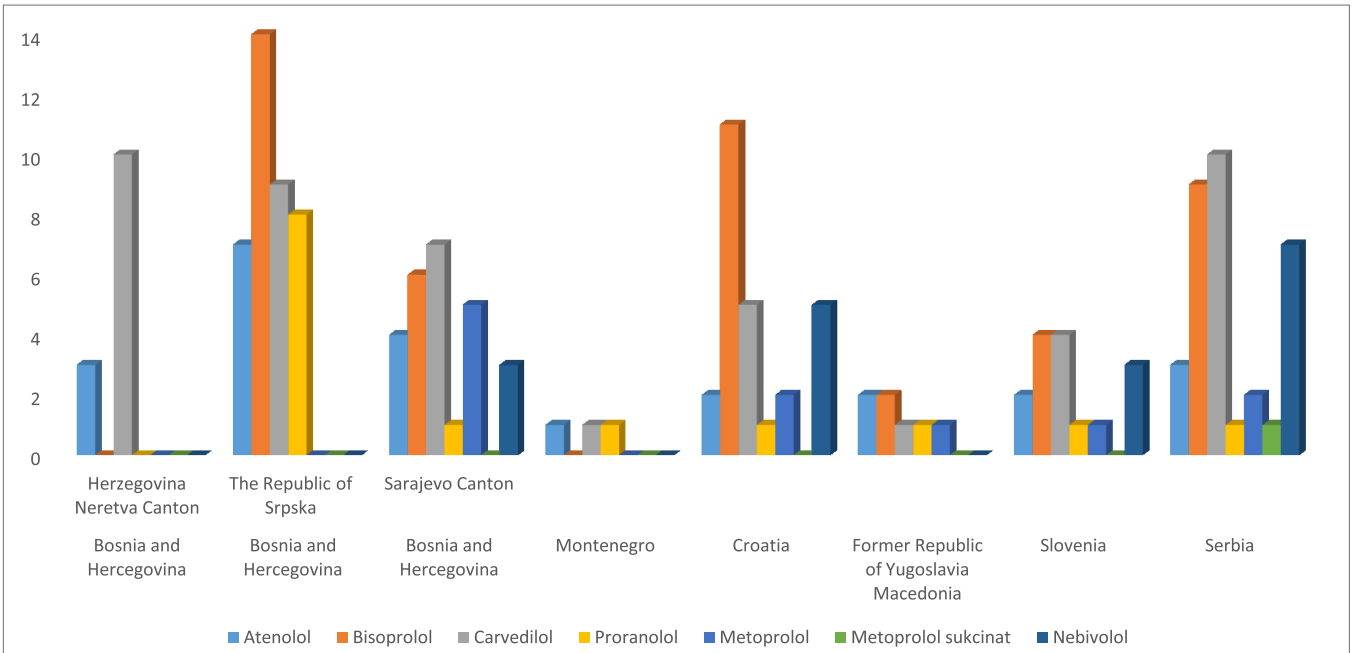

FIGURE 1 | Number of parallels of individual beta blocker in countries and cantons.

Oral hypolipidemic agents have different prescription mechanism in different countries and cantons. **Table 5** shows how many parallels an individual statin have and **Table 6** regulations regarding their prescribing.

Number of parallels of oral antidiabetic agents in countries and cantons is presented in **Table 7**. The majority of oral antidiabetic agents are prescribed with no restrictions for family practice, except for DPP-4 inhibitors and long-Acting Glucagon-Like Peptide 1 Receptor Agonists (GLP1 agonists). GLP1 are on the lists of The RS, Sarajevo Canton, Croatia and Slovenia.

Treatment of diabetes mellitus type 2 (DM2) faces a large variance and financial capabilities across countries/cantons. Insulin, according to the positive medicine lists, can be prescribed by family physicians only in Croatia, Slovenia, and RS (**Table 8**).

Possibilities of treating asthma and COPDs are also defined by guidelines and different fund restrictions. For example, salbutamol, aminophyline, and theophylline can be independently prescribed by family physicians in all doses. Salbutamol, as well as theophylline, is available with the exception of RS and Macedonia. The RS included aminophylline in their positive medicines list. Sarajevo Canton, Herzegovina Neretva Canton, Montenegro, and Macedonia do not reimburse for long-acting beta 2 agonists. Inhaled corticosteroids, as well as its combinations with long-acting beta agonists (multiple brands) are available in all countries, but can be prescribed independently by family physicians only in Croatia and Slovenia. Al l countries have ipratropium bromide and tiotropium bromide on their lists. In Serbia, only combination of fenoterol and ipratropium bromide can be prescribed by family physicians, while the

treatment with other inhaled medicines (except for salbutamol) needs to be recommended by consultants (e.g., patients in Macedonia need to be referred to asthma or COPD center). Montelukast is not available in the RS and Macedonia. There are no restrictions toward prescribing of this drug in family medicine of Croatia and Slovenia; however, only in Slovenia it can be prescribed as monotherapy, while in other countries it is indicated as additional therapy. Newer medications for treatment of asthma and COPD are available only in Slovenia and Croatia.

TABLE 2 | Prescribing-related restrictions for beta blockers in family practice.

Medicine	Restriction in country/canton	
Atenolol	No restrictions	
Bisoprolol	Sarajevo Canton	Medication can be prescribed by family physicians, specialists of occupational medicine, pediatricians, gynecologist, pulmonologist, internists, and emergence medicine specialists
	Former Republic of Yugoslavia Macedonia	Chronic heart failure, arterial hypertension, and angina pectoris
Carvedilol	Sarajevo Canton	Only for heart failure
	Former Republic of Yugoslavia Macedonia	Chronic heart failure, arterial hypertension, and angina pectoris—on the recommendation of a cardiologist or internist
	Serbia	For heart failure treatment, it is necessary to consult cardiologist, for arterial hypertension treatment not
Proranolol	No restrictions	
Metoprolol	No restrictions	
Metoprolol succinate	Serbia	Chronic heart failure, hypertension, and angina pectoris treatment; it is necessary to consult cardiologist
Nebivolol	Sarajevo Canton	Indications: 1. chronic heart failure, internist's recommendation is requested; 2. hypertension and angina pectoris

The indications for PPIs differ between the countries. In Slovenia and Croatia, duration of therapy is not limited and consultant's recommendation is not required. In Croatia, there are guidelines for prescribing, but gastroprotection as an indication is not included. PPIs in Montenegro, Serbia, and parts of BiH can be prescribed only for duodenal or gastric ulcer treatment, while in Macedonia, Health Insurance Fund also reimburses treatment of gastro esophageal reflux if diagnosed with endoscopy. There are many parallels of PPIs in all countries (e.g., 17 paralels of pantoprazole in the RS, 13 in the Herzegovina canton, 16 in Croatia).

Combinations of tramadol and paracetamol are available in the Sarajevo canton, Croatia and Slovenia, and morphine in RS, Montenegro, Croatia, Slovenia, Macedonia, and Serbia. Apart from Croatia, morphine cannot be prescribed without consultant's recommendation. Fentanyl patches are available in Croatia and Slovenia, and spray in Croatia with additional charge (over 30€). Other opioids (oxycodon, pentazocin, buprenofin patches, tapentadol, and combinations) are available only in Slovenia and Croatia.

DISCUSSION

For years, it has been well known that prevention of illness is the most effective way of health protection. This is especially true for NCDs because prevention does not only lead to health protection but also to reduction of expenses of treatment of illness and its consequences (21–23). Panamerican Health Organisation most efficiently points out to the problem of NCD. The costs of NCDs to the health system, businesses and individuals, are significant and growing. Governments, communities, and private industries are all affected by the high costs of premature death and disability as well as of treatments and caretaking for those living with NCDs. The burden is so great because of the large numbers of people affected, especially those men and women of working-age who are not able to secure productive employment. Without adequate prevention and early detection, these costs only rise, as they require expensive treatments, surgeries, and medications and cut productive lives short. Complications of NCDs incur considerable

TABLE 3 | Number of ACE and ARB inhibitor parallels; combination of ACE with diuretics, combination of ARB with diuretics.

	Bosnia and Hercegovina (Herzegovina Neretva Canton)	Bosnia and Hercegovina (The Republic of Srpska)	Bosnia and Hercegovina (Sarajevo Canton)	Montenegro	Croatia	Former Republic of Yugoslavia Macedonia	Slovenia	Serbia
Enalapril	10	11	5	1	1	4		7
Lisinopril	9	10	6	1	11	1	4	5
Perindopril	0	0	0	0	3	0	11	5
Ramipril	0	16	6	1	10	0	5	7
Losartan	0	0	0	1	7	2	6	7
Valsartan	0	0	5	0	8	0	6	3
Enalapril + hydrochlorothiazide	9	9	5	1	1	0	3	4
Lisinopril + hydrochlorothiazide	8	11	6	1	10	0	4	3
Ramipril + hydrochlorothiazide	0	9	4	1	7	0	4	6
Losartan + hydrochlorothiazide	0	3	0	1	5	0	7	3
Valsartan + hydrochlorothiazide	0	4	0	0	5	0	8	5

ACE, angiotensin-converting enzyme (ACE) inhibitors, ARB, angiotensin II receptor blockers.

costs; for example, diabetic nephropathy was estimated as the most costly complication of diabetes in the Americas (22).

Medicines recommended according to the World health's organization's Model List of Essential Medicines are included into positive medicine lists of all Western Balkan countries (23). There are a large number of parallels. In most countries, there are unnecessary restrictions regarding prescribing in family practice, what reduce family physicians' competencies, availability of health care and increase health-care costs.

Most countries and cantons possess their own guidelines for treating hypertension, which were mostly founded on European guidelines (24–28). Quality treatment of hypertension is enabled in all countries and cantons considering the fact that all lists are made of medication mentioned in international guidelines. There is, however, a degree of difficulty, as ARB inhibitors in some countries/cantons cannot be prescribed without consultant's recommendation, which greatly reduces the level of available health care. Even though we could not find the reasons for this decision made by the fund in every single local guideline, the funds still made such a recommendation. Likewise the recommendation of the Croatian fund that the ARB inhibitor can be introduced after 4 months of coughing is professionally inexplicable. Especially, so as prices of ACE and ARB inhibitors differ by a very small amount. Availability is reduced by increasing waiting lists for examinations and increased costs of transportation to the consultants in case of patients from rural areas. Another problem is that in some countries/cantons combinations of medicine are additionally charged. Considering the poor financial situation for many inhabitants of Western Balkan countries (29), using such medication could greatly burden a patient's household or reduce compliance as Selmanovic et al. found in their study (30). It would be interesting to explore in what way does a physician make a decision in favor of one brand when there are no restrictions placed by funds (31, 32). All restrictions regarding medication prescribing competency of family physicians involving certain ARB antagonists, diuretics, or beta blockers should be reexamined and adjusted to best evidence-based recommendations (32). Policymakers need to ensure that future reforms will adequately address such financial burden from NCDs and improve access to heahlthcare needed by the population (33).

With the exception of the Herzegovina Neretva canton, medicine for reducing cholesterol and triglycerides are on positive list of all countries/cantons. However, funds' guidelines are very confusing and are not in accordance with international guidelines. Greater priority to treating hyperlipidemia and improving the accessibility of medicines to treat them should be given. Development and use of evidence-based guidelines for the treatment and efficient procurement and distribution of statins are important mechanisms for providing sustainable access to hyperlipidema (23, 34, 35). Future research could show the effects of the restriction policy regarding statins prescribing on population's health (36).

TABLE 4 | Prescribing-related restrictions for angiotensin II receptor blockers in family practice.

Medicine	Restriction in country/canton	
Combination with diuretics	Serbia	Indicated if target values are not achieved *via* monotherapy after 3 months
Losartan	Croatia	For patients intolerant to angiotensin-converting enzyme (ACE) inhibitors and having a cough at least 4 months
	Serbia	For treatment of arterial hypertension and for patients whose ejection fraction is <40% Cardiologist's or internist's recommendation requested
Valsartan	Herzegovina Neretva Canton	For patients intolerant to ACE inhibitors, per internist's recommendation
	Croatia	For patients intolerant to ACE inhibitors and after cough lasting 4 months
	Serbia	For treatment of arterial hypertension, for patients whose ejection fraction is <40%, cardiologist's or internist's recommendation requested
Ibersartan	The Republic of Srpska	For patients with side effects of ACE inhibitors, per consultant's recommendation
	Croatia	For patients intolerant to ACE inhibitors and having a cough for at least 4 months

TABLE 5 | Number of parallels of oral hypolipidemic agents per country.

Medicine	Bosnia and Hercegovina (Herzegovina Neretva Canton)	Bosnia and Hercegovina (The Republic of Srpska)	Bosnia and Hercegovina (Sarajevo Canton)	Montenegro	Croatia	Former Republic of Yugoslavia Macedonia	Slovenia	Serbia
Simvastatin	0	8	6	1	11	0	7	8
Atorovostatin	0	17	7	1	11	1	14	7
Fluvastatin	0	0	1	0	3	0	2	0
Pravastatin	0	0	0	0	0	0	2	2
Rosuvastatin	0	6	3	0	7	0	10	9
Nicotinic acid	0	0	0	0	0	1	0	0
Ciprofibrate	0	0	0	1	0	0	0	1
Ezetimibe	0	0	0	0	1	0	6 (ezetimib alone or in combination with statin)	1
Fenofibrate	0	0	0	0	5	0	2	0
Cholestyramine	0	0	0	0	1	0	0	0

TABLE 6 | Prescribing-related restrictions for oral hypolipemic agents in family practice.

Medication	Restrictions in country/canton	
Statins	Serbia	(a) Medication completely free of charge for patients with inheritable hyperlipidemia, per recommendation by Clinic for endocrine diseases, diabetes, and metabolism disease Clinical center of Serbia (b) Patient partially charged for medication in case of previous myocardial infarction or stroke and as prevention of further occurrence
	The Republic of Srpska	(a) Secondary prevention of coronary disease (b) Diabetes mellitus with hyperlipidemia (c) Chronic kidney failure and condition of transplanted organ with hyperlipidemia
	Sarajevo Canton	In primary prevention for patients who after 3 months of non-pharmacological treatment still has a value of total cholesterol above 7 mmol/L
	Former Republic of Yugoslavia Macedonia	Patients with high cardiovascular risk and LDL cholesterol greater than 3.5 mmol/L (a) Verified coronary arterial disease (myocardial infarction, stabile angina, bypass). Cardiologist's or internist's recommendation requested (b) Verified diabetes, family physician prescribe independently (c) Stroke, per neurologist's and internist's recommendation (d) Verified coronary artery disease, stenosis >60%, per neurologist's and internist's recommendation (e) Patient with 10-year cardiovascular risk >20% according to Framingham score, or >5% according to SCORE model, family physicians are allowed to prescribe without consultant's recommendation
	Croatia	For secondary prevention in patients with myocardial infarction, ischemic cerebrovascular insult, transitory ischemic attack, carotid occlusive disease and peripheral artery disease, and coronary disease For patients with total cholesterol value greater than 7 mmol/L after three months of non-pharmacological treatment
Statins		For secondary prevention of cardiovascular diseases in patients with total value of total cholesterol >4.5 mmol/L and LDL >2.5 mmol/L. For primary prevention when total cardiovascular risk >20%, if total cholesterol value is >5 mmol/L and LDL cholesterol >3.0 mmol/L For patients with familial hypercholesterolemia
	Montenegro	For patients with myocardial infarction and cerebrovascular insult
Fibrates	Montenegro	Clinical consultant's recommendation requested
	Croatia	Prescribed only if, after 3 months of non-pharmacological treatment, triglycerides in blood are no less than 2 mmol/L
	Serbia	For patients with familial hypercholesterolemia Clinical consultant's recommendation requested
Ezetimibe	Croatia	For treatment of primary hypercholesterolemia in patients with very high or high cardiovascular risk who have, despite statin therapy, LDL cholesterol levels $\geq$ 2.5 mmol/L Clinical consultant's recommendation requested

Diabetes mellitus type 2 could become the leading public health problem considering the resources necessary for its early diagnosis and treatment (37). All countries and cantons have basic medications for treatment of diabetes, while few also provide newer antidiabetic agents, such as DPP4 inhibitors and SGLT2 inhibitors (which are additionally charged). The basic oral antidiabetic agents are not additionally charged, which helps patient's budget and increases his adherence. There are important restrictions regarding insulin prescribing-related competencies in family practice, but even in the countries where restrictions are not imposed, family physicians are reluctant to prescribe insulin (33, 38). As emphasized by Kovacevic et al., diabetes morbidity and mortality can be significantly reduced if pharmacotherapy is accessible and affordable (39). It is also necessary to transfer responsibilities for treating type 2 diabetes onto family physicians, with the appropriate education and work quality control.

The greatest restrictions set on family physicians are in the area of treating asthma and COPD. To treat these two diseases in every country and canton, with the exception of Slovenia and Croatia, a recommendation by a clinical consultant is needed. In some Western Balkan countries, inhaled medications are additionally charged (40, 41). We cannot explain why theophylline and aminophyline are left to be prescribed freely by family physicians (considering their narrow therapeutic window), while inhaled corticosteroids are not. Treatment of asthma in family practice is unsatisfactory on a global level, but if these restrictions are kept, family physicians cannot play important role in disease's control. Data from the PACE program serves as proof that far better results are achieved in treatment of asthma when family physicians take control over patient care (42).

Pain therapy is a basic human right; therefore, it is necessary to remind policymakers that in treating cancer pain there

TABLE 7 | Number of parallels of oral antidiabetic agents in countries and cantons.

	Bosnia and Hercegovina (Herzegovina Neretva Canton)	Bosnia and Hercegovina (The Republic of Srpska)	Bosnia and Hercegovina (Sarajevo Canton)	Montenegro	Croatia	Former Republic of Yugoslavia Macedonia	Slovenia	Serbia
Metformine	8	11	4	1	6	1	4	6
Glibenclamid	3	4	2	0	1	0	0	1
Glimepiride	8	10	6	1	7	1	1	3
Repaglinide	0	0	2*	0	5*	1	2	1 E
Gliclazide	0	3	0	1	6	0	3	5
Pioglitazone	0	0	0	0	2**	0	1	1 EK
Gliquidone	0	0	0	0	1	0	1	0
DPP4 inhibitors and SGLT2 inhibitors	0	6 EK1	0	0	13#	0	16##	0

TABLE 8 | Prescribing-related restrictions for insulin in family practice.

Country	Insulin type	Restrictions
Bosnia and Hercegovina (Herzegovina Neretva Canton)	Human insulin	Clinical consultant's recommendation requested
	Lispro, Aspart, and Glulisine	Diabetologist's recommendation requested
	Glargine and Detemir	Clinical consultant's recommendation requested and under special prescription regime
Bosnia and Hercegovina (The Republic of Srpska)	All insulins	No restrictions, however, patient is obligated to keep a journal for administrating insulin (journal can be acquired from the Fund)
Bosnia and Hercegovina (Sarajevo Canton)	Human, Lispro, Aspart, and Glulisine	Clinical consultant's recommendation requested
	Glargine and Detemir	Clinical consultant's recommendation requested
		For patients with unregulated glycemia (and HbA1C <6.5%), using oral antidiabetic agents
Montenegro	All insulins	Clinical consultant's recommendation requested
Croatia	Aspart	Without consultant's recommendation and within a guideline
		For patients with diabetes on intensive insulin therapy and unregulated glycemia
	Human insulin	Without consultant's recommendation and without guidelines
	Glulisine	Without consultant's recommendation and within a guideline
		For patients with diabetes on intensive insulin therapy and unregulated glycemia
	Lispro	Without consultant's recommendation and with a guideline: for patients with diabetes on intensive insulin therapy and unregulated glycemia
	Glargin	Without consultant's recommendation and with a guideline: for patients in intensive insulin therapy (1 or 2 daily injections of basal insulin + 3 injections of shortly-acting insulin alongside main meals), who during the past 6 months, despite changes in therapy scheme, fail to achieve satisfactory glicoregulation (HbA1c <6.5%), who have more than one hypoglicemia episode weekly, and who fail to achieve glycemia control with other types of insulin
	Detemir	Without consultant's recommendation and within a guideline
		For patients on intensive insulin therapy (1 or 2 daily injections of basal insulin+3 injections of shortly acting insulin alongside main meals), who during the past 6 months, despite changes in therapy scheme, fail to achieve satisfactory glucoregulation (HbA1c <6.5%), who have more than one hypoglycemia episode weekly, and who fail to achieve glycemia control with other types of insulin
Former Republic of Yugoslavia Macedonia	Insulin and analogs	Per consultant's recommendation under the Macedonian Government program
Slovenia	Detemir, Glargine, and Degludek	Only for patients with other hypoglycemic and other insulin
Serbia	Aspart, Glargine, Detemir, and Lispro	Hypoglycemia must be confirmed in a health-care institution (the remainder of restriction explanation is too great for to be included)
	Human	Per internist's, pediatrician's or endocrinologist's recommendation

should be no restrictions in prescribing analgesics of all kinds. Likewise, despite limited funds of the health-care system, all countries/cantons should have as great a number of analgesics as possible (43).

Previous studies showed that there is a trend of increasing pharmaceutical expenditure in Balkan countries, what led to the introduction of new policy measures (44). Although analysis of pharmaceutical expenditure represents important perspective of the overall drug utilization, it has only economic side and should be examined within the volume of prescribed drugs (45) as well as through other aspects of pharmaceutical utilization, such as rational prescribing and generic utilization (39, 46).

Jakovljevic and Souliotis found that restrictive policies toward medicines might have negative effects on health care system, creating significant costs to the system or worse health outcomes. The authors also stated that chronic illnesses (e.g., diabetes, COPD, and cancer) serve as the evidence of vulnerabilities, therefore presenting core targets for more responsible, evidence-based national resource allocation strategies (47). Rational use of drugs and rational prescribing are seen as an appropriate way of utilization of limited public resources that might affect pharmaceutical expenditure without compromising the rights of patients to obtain needed medicine (48, 49). Medicines are a dominant part of health system due to necessity to use them in the treatment of disease and high use of available resources in the health care system toward medicines. In addition to problems in jurisdiction conflict and overlaps in countries, significant funds are often spent on medicines that do not have therapeutic value, while there is a deviation in pricing and establishment of control (50). Primary challenge for sustainable funding of prescribed medicines is to manage the difficulties to withstand pressures arising from population aging and high prevalence of NCDs in the Western Balkan countries, what currently increases and will further increase a need for pharmaceuticals or their consumption in the future (51).

There are continuing demands for family physicians to keep the balance between gatekeeper and advocate role, increasingly being confronted with the consequences of allocation policies. Often, it is difficult to integrate gate keeping into heterogeneous family practice and the balance, in that case, cannot be maintained (52). In the countries of Western Balkan, physicians often pay fines if they have spent more money on their patients' treatment than planned by the contract with Health Insurance Funds, regardless of how many patients with chronic illnesses they saw in their practices or therapeutic indications. As we can see from the results, there are many restrictions on prescribing essential medicines in family practice. In such cases, consultants request to see patients several times per year, with the myriad of laboratory and diagnostic investigations, that family physicians have financial responsibilities for, but, at the same time, are not permitted to participate in decision-making. The question is whether such a policy related to prescribing really permits gate keeping? In addition to medicine reimbursement cost, fee-for-service payments for consultations and additional investigations are very high and unnecessarily burden the health care system. National and international clinical guidelines set up clear, clinical indications for treatment routes of NCDs that family physicians are very well trained in and can practically use to make the best therapeutic decision for their patients. These gaps in global prescribing policies need to be addressed in the future. Knowledge and technologies exist to bring down the burden of NCDs. Paying for NCD prevention and management is an investment (22).

Reimbursement policy based on cost-effectiveness principles and reference pricing by regulatory bodies to manage pharmaceutical costs should be improved in the future (53). Quantity and quality research and comparison of data on pharmaceutical expenditure are needed to explore the impact of different policies in diverse settings, particularly in the countries with limited financial resources (44).

One of the strengths of the current study is that it was performed in the countries with the same legacy toward health-care legislative. This is also the first study exploring prescribing-related competencies of family physicians in Western Balkan countries. Our findings can serve as a basis for further research on prescribing policy and legislation in the region or within other countries. Limitations of the study are those inbuilt with qualitative studies (54). The documents included into analysis are created independent of research question.

CONCLUSION

Western Balkan countries are capable of providing essential medicines for the treatment of NCDs, with full or partial reimbursement. There are some exceptions, related to statins, new generation of oral antidiabetic agents and few antihypertensive combinations. Opioid formulations for cancer pain treatment, in the form of codeine, morphine or fentanyl are not available in all countries. Prescribing-related competences of family physicians are limited. However, this practice is not compliant to the practices of family medicine, its principles and primary care structures, and may potentially result in increased healthcare financial ramifications to both the system and patients due to frequent referrals to the specialists. Future research in these areas is sorely needed as well as strengthening of family medicine in the region.

AUTHOR CONTRIBUTIONS

All the authors have provided substantial contributions to the development of the manuscript. TP-P, MR, and SK contributed to the overall conception and design. TP-P and MR gathered the data. TP-P and MR analyzed the data. All the authors contributed to the interpretation of the data and the drafting of the manuscript. All the authors have given final approval for the paper to be published in Frontiers and agree to be accountable for the content presented therein.

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SYSTEMATIC REVIEW
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Systematic Review of Health Economic Evaluation Studies Developed in Brazil from 1980 to 2013

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Background: Brazil has sought to use economic evaluation to support healthcare decision-making processes. While a number of health economic evaluations (HEEs) have been conducted, no study has systematically reviewed the quality of Brazilian HEE. The objective of this systematic review was to provide an overview regarding the state of HEE research and to evaluate the number, characteristics, and quality of reporting of published HEE studies conducted in a Brazilian setting.

Methods: We systematically searched electronic databases (MEDLINE, EMBASE, Latin American, and Caribbean Literature on Health Sciences Database, Scientific Electronic Library Online, NHS Economic Evaluation Database, health technology assessment Database, Bireme, and *Biblioteca Virtual em Saúde Economia da Saúde*); citation indexes (SCOPUS, Web of Science), and *Sistema de Informação da Rede Brasileira de Avaliação de Tecnologia em Saúde*. Partial and full HEEs published between 1980 and 2013 that referred to a Brazilian setting were considered for inclusion.

Results: In total, 535 studies were included in the review, 36.8% of these were considered to be full HEE. The category of healthcare technologies more frequently assessed were procedures (34.8%) and drugs (28.8%) which main objective was treatment (72.1%). Forty-four percent of the studies reported their funding source and 36% reported a conflict of interest. Overall, the full HEE quality of reporting was satisfactory. But some items were generally poorly reported and significant improvement is required: (1) methods used to estimate healthcare resource use quantities and unit costs, (2) methods used to estimate utility values, (3) sources of funding, and (4) conflicts of interest.

Conclusion: A steady number of HEE have been published in Brazil since 1980. To improve their contribution to inform national healthcare policy efforts need to be made to enhance the quality of reporting of HEEs and promote improvements in the way HEEs are designed, implemented (i.e., using sound methods for HEEs) and reported.

Keywords: economic evaluation, cost-effectiveness, Brazil, cost-benefit analysis, health technology assessment

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INTRODUCTION

Brazil is an upper middle-income country with a population of 200 million citizens, largely urban (85%). It is a federative republic with 26 states, a federal district, and 5,564 municipalities. The 1998 Brazilian Constitution offered the right to health for all citizens, and created the Unified Health System (SUS): a public system directed at provision of universal, comprehensive, collective, and individual healthcare. The major SUS funders are federal, states, and cities governments, through taxes and social contributions. Public and private providers deliver services which are free at the point of delivery. The private sector covers approximately 25% of the population (48 million people), and dominated by an emergent health insurance market (1).

In 2014, Brazil had a gross domestic product (GDP) per capita of US$15,200, and approximately 9% of its GDP was spent on healthcare. The health expenditure per capita is US$1,109, and 46% of this is funded by public sources (2). The SUS public health financing is considered insufficient, and the equilibrium between public and private systems is challenging with considerable funds flowing from public coffers to private providers (3).

Resource scarcity is a reality in the Brazilian health system. Due to this scarcity, efficient allocation of resources is essential. Economic evaluation methods in healthcare have evolved as an important tool to assess the costs and benefits of health technologies and help decision-makers inform efficient allocation.

Brazil has sought to use economic evaluation to support decision making for rational management of the health system. The Ministry of Health, through the Department of Science and Technology (DECIT), has fostered the development of economic evaluation studies. Since 2006, DECIT has collaborated with the Committee on Incorporation of Technologies of the Ministry of Health (CITEC), an health technology assessment (HTA) body responsible for evaluating the incorporation of new technologies by SUS (4). In 2011, CITEC was replaced by the National Incorporation of Technologies in SUS, CONITEC, introduced the requirement for health economic evaluation (HEE) studies either to help inform policy recommendations for the adoption of new technologies or to review policy recommendations made by SUS (5, 6). The first Brazilian guideline for HEE studies was published in 2009, but the concept of a reference case has not been prescriptively adopted in Brazil yet. The revised HEE Brazilian guideline (7) issued by the Ministry of Health in 2014, presents some recommendations that broadly agree on many methodological specifications of the National Institute for Health and Care Excellence reference case.

Abbreviations: HEEs, health economic evaluations; SUS, Unified Health System; GDP, gross domestic product; DECIT, Department of Science and Technology; CITEC, Committee on Incorporation of Technologies of the Ministry of Health; CONITEC, National Incorporation of Technologies in SUS; NICE, National Institute for Health and Care Excellence; CCA, cost-consequences analysis; CMA, cost-minimization analysis; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; CBA, cost-benefit analysis; CHEERS, Consolidated Health Economic Evaluation Reporting Standards; HTA, health technology assessment; BJHE, Brazilian Journal of Health Economics; SISREBRATS, *Sistema de Informação da Rede Brasileira de Avaliação de Tecnologia em Saúde*; QALY, quality-adjusted life year.

In recent decades, a large amount of local HEE studies have been published. There is a strong evidence of the upward stream of blossoming in HEE publications and its acceleration (8). The evolution of scientific literature in health economics published in Brazil between 1986 and 2007 has been evaluated and reported in the published literature (9–11). Recently, Brazil appeared among the top 15 countries in HE research, accounting for 1.7% of identified records, and has been identified as the South American country that published the largest number of HEE studies (8, 12, 13).

Systematic reviews of country-specific HEE studies were conducted earlier in other countries including developed countries, Latin America, Asian, and African countries (14–28).

While a number of HEE have been conducted in Brazil, no study has systematically reviewed the quality of Brazilian HEE. The objective of this systematic review was to assess the state of the HEE research capacity development in Brazil and the ability to conduct good quality HEE. Specifically, this review evaluated the number, characteristics, and quality of reporting of published economic studies in a Brazilian setting.

MATERIALS AND METHODS

This study followed the guidelines for systematic review of HEE studies published by the Centre for Reviews and Dissemination (CRD) and the preferred reporting items for systematic reviews and meta-analyses statement (29, 30). The protocol is available from the authors on request.

Systematic Search and Identification of Relevant Studies

A broad and exhaustive strategy search was formulated in order to identify all relevant studies published between January 1980 and December 2013. We systematically searched the following electronic data bases: MEDLINE (*via* PubMed), EMBASE, Latin American, and Caribbean Literature on Health Sciences Database, Scientific Electronic Library Online, NHS Economic Evaluation Database, HTA Database (CRD), Bireme, and *Biblioteca Virtual em Saúde Economia da Saúde*; citation indexes: SCOPUS, Web of Science, and the *Sistema de informação da Rede Brasileira de Avaliação Tecnologia e Saúde* (SISREBRATS). We also performed manual searches from the reference lists of included articles, and all issues of the Brazilian Journal of Health Economics (BJHE), a non-indexed journal in the previously mentioned databases in 2013.

The search strategy was reviewed by a librarian specialist and combined subject headings (MeSH and EMTREE) and free text terms ("Health Economics" OR "Economics, Hospital" OR "Economics, Medical" OR "Economics, Nursing" OR "Economics, Pharmaceutical" OR "Economics" OR "costs and cost analysis" OR "Cost" OR "Cost savings" OR "Cost of illness" OR "Analyses, Cost-Benefit" OR "Analysis, Cost-Benefit" OR "Cost-Benefit Analyses" OR "Cost Benefit Analysis" OR "Analyses, Cost Benefit" OR "Analysis, Cost Benefit" OR "Cost Benefit Analyses" OR "cost Effectiveness" OR "Effectiveness, Cost" OR "cost effectiveness analysis" OR "cost-Benefit Date" OR "cost Benefit Date" OR "Date, Cost-Benefit" OR "cost Benefit" OR "Benefits and Costs"

OR "Costs and Benefits") for "economic/cost" concept with subject headings (MeSH and EMTREE) and free text terms ("Brazil" OR "Brazilian" OR "Brazi*") for "Brazil" concept. Keywords were matched to database specific indexing terms, taking into account the change in the indexing or classification of economic studies in different databases.

Eligibility: Selection Criteria

Articles were included if they were partial or full HEE according to internationally recognized criteria (31, 32), referred to the Brazilian setting, and at least one of the authors was Brazilian and affiliated to a Brazilian institution. Multicenter studies, where Brazil was one of the participating countries, as well as studies conducted on Brazil by foreign authors, were excluded.

Studies were considered partial HEE if they examined only costs (cost description), described costs of a particular disease to society (cost of illness), described costs and outcomes of a single service or program (cost-outcome description), described financial consequences of technology adoption [budget impact analysis (BIA)] or compared only costs of two or more interventions (cost analysis). Studies were considered full HEE if they compared costs and consequences of two or more healthcare interventions alternatives, including cost-consequences analysis (CCA), cost-minimization analysis (CMA), cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and cost-benefit analysis (CBA).

Abstracts, editorials, letters, posters and congress communications, methodological, discussion and review articles, and economic evaluation of other than health technologies (for example, environment) were excluded.

The titles and abstracts of identified citations were screened for relevance independently by two reviewers (Tassia Cristina Decimoni and Roseli Leandro). Disagreements were resolved through discussion or through consultation with a third reviewer (Patrícia Coelho de Soárez). Full texts of selected and those for which inclusion was in doubt were retrieved and independently screened by both reviewers.

Data Extraction

Two reviewers (Tassia Cristina DecimoniTCD and Roseli Leandro) independently extracted data from each of the included studies on year and journal of publication, economic evaluation type, category of technology assessed (drugs, vaccines, equipment, clinical, surgical and diagnostic procedures, public health and health promotion programs), objective of the technology assessed (treatment, prevention, screening, and diagnosis), health problem studied (International statistical classification of diseases and related health problems, 10th revision, ICD-10) (33), first author affiliation (academy, government, research institutes, health organization, consulting, pharmaceuticals or equipment industry, international body), region of the first author, source of funding (research funding agencies, government, consulting, pharmaceuticals, or equipment industry), and authors' conflict of interest. Conflict of interest was defined according to Valachis et al. (34) who argued that an author may need to declare having a conflict of interest in if she/he has received remuneration in payment or in kind (e.g., stocks or shares) from the manufacturer as a result of any of the following: research support or employment contract (salary, equipment, supply, reimbursement for participation in symposia, and other expenses), or consulting services.

In addition to the above, the standardized extraction form used also contained 17 questions from a systematic review of quality assessment tools (35), and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) instrument (36). These questions were intended to assess the quality of reporting of full HEE. Quality was defined as the extent to which a study complied and reported items included in the quality assessment tool and CHEERS checklist mentioned above (35, 36). The quality of the sources of evidence used in the studies was assessed with the hierarchy proposed by Coyle and Lee (37, 38). Where data sources ranked 1 are considered to be the most appropriate source (highest quality), and those assigned a rank of 6 are considered the least appropriate (lowest quality) (39) (**Table 1**). Disagreements on the extracted data were resolved through discussion or through consultation with a third reviewer (Patrícia Coelho de Soárez).

Data Summary

Data were summarized using qualitative narrative synthesis. The study characteristics are summarized in figures and summary tables.

Data Analysis

Data analysis was performed with descriptive statistics such as absolute frequencies (raw counts) for each category of the discrete variable, relative frequencies (proportions or percentages of the total number of observations), along with analytic statistics that included Pearson correlations to investigate the relationship between the quality of reporting of the full HEE and the publication time period (1980–2005, 2006–2009, and 2010–2013), conflict of interest and source of funding. The publication time periods were chosen because they represent three different stages of the HTA in Brazil (1980–2005: before the establishment of the General Coordination Office for HTA; 2006–2009: establishment of CITEC; 2010–2013; after the publication of the Brazilian guideline for HEE studies). Linear regression models were used to evaluate changes in study characteristics over time. Data analyses were conducted using STATA/SE version 12.1 (Stata Corp, College Station, USA). An alpha level of 5% was used for statistical significance ($P \leq 0.05$).

RESULTS

Literature Search

In total 11,841 records were identified from database searches, and 105 further articles were identified through hand-searching in BJHE, SISREBRATS, and other sources. **Figure 1** depicts a flow diagram with full details of searches output, and reasons for inclusion/exclusion. We identified 9,304 non-duplicate citations, of which 721 were recognized as potentially relevant and full papers were retrieved. Out of the 721 studies 186 of them were excluded, reasons for exclusion included: thesis (50 studies), not

TABLE 1 | Hierarchies of data sources for health economic evaluation studies modified from Coyle and Lee (37–39).

Rank	Data components
Clinical effect sizes, adverse events, and complications	
1+	Meta-analysis of RCTs with direct comparison between comparator therapies measuring final outcomes
1	Single RCT with direct comparison between comparator therapies measuring final outcomes
2+	Meta-analysis or RCTs with direct comparison between comparator therapies measuring the surrogate outcomes Meta-analysis or placebo-controlled RCTs with similar trial populations, measuring final outcomes for each individual therapy
2	Single RCT with direct comparison between comparator therapies measuring the surrogate outcomes Single placebo-controlled RCTs with similar trial populations, measuring final outcomes for each individual therapy
3+	Meta-analysis or placebo-controlled RCTs with similar trial populations, measuring the surrogate outcomes
3	Single placebo-controlled RCTs with similar trial populations, measuring the surrogate outcomes for each individual therapy
4	Case control or cohort studies
5	Nom-analytic studies, for example, case reports, case series
6	Expert opinion
Resource use	
1	Prospective data collection or analysis of reliable data for specific study
2	Recently published results of prospective data collection or recent analysis of reliable administrative data—same jurisdiction
3	Unsourced data from previous economic evaluation—same jurisdiction
4	Recently published results of prospective data collection or recent analysis of reliable administrative data—different jurisdiction
5	Unsourced data from previous economic evaluation—different jurisdiction
6	Expert opinion
Costs	
1	Cost calculations based on reliable databases or data sources conducted for specific study—same jurisdiction
2	Recently published cost calculations based on reliable databases or data sources—same jurisdiction
3	Unsourced data from previous economic evaluation—same jurisdiction
4	Recently published cost calculations based on reliable databases or data sources—different jurisdiction
5	Unsourced data from previous economic evaluation—different jurisdiction
6	Expert opinion
Utilities (if applicable)	
1	Direct utility assessment for the specific study from a sample either: (a) of the general population (b) with knowledge of the disease(s) of interest (c) of patients with the disease(s) of interest Indirect utility assessment from specific study from patient sample with the disease(s) of interest, using a tool validated for the patient population
2	Indirect utility assessment from a patient sample with the disease(s) of interest, using a tool not validated for the patient population
3	Direct utility assessment from previous study from a sample either: (a) of the general population (b) with knowledge of the disease(s) of interest (c) of patients with the disease(s) of interest Indirect utility assessment from previous study from patient sample with the disease(s) of interest, using a tool validated for the patient population
4	Unsourced utility data from previous study—method of elicitation unknown
5	Patient preference values obtained from a visual analog scale
6	Delphi panels, expert opinion

RCT, randomized control trial.

HEE (88 studies), no Brazilian author (19 studies), reviews (18), and other (11 studies), see **Figure 1** for detailed description. Scientific papers derived from excluded thesis and reports were included.

Study Characteristics

The publication of HEE studies in Brazil started in the 1980s. Since then, there has been an upward trend with a slight increase at the end of the 1990s, and a sharp increase in 2007 with the publication of 356 (67%, 356/535) articles (**Figure 2**). A total of 535 studies were identified as suitable for inclusion in this review and their characteristics are described in **Table 2**.

According to internationally agreed classifications of HEE studies (31, 32), more than half of included studies were partial HEE (63.2%, 338/535). Of these, the majority (66%, 223/338) were cost description followed by cost analysis studies (32.2%, 109/338). Of the 197 full HEE, 39.1% (77/197) were CEA, 20.3% (40/197) were CCA, 11% (21/197) were CEA and CUA, 8.6% (17/197) were CUA, 7.1% (14/197) were CMA, and 4.6% (9/197) were CBA. Nine percent (19/197) of the studies concurrently performed more than one type of analysis. CMA evaluated mainly medications (corticosteroids, antihistamines, antibiotics, biologics, monoclonal antibodies, tyrosine kinase inhibitors, chemotherapeutics, anticoagulants, etc.). Prior to 2008, the

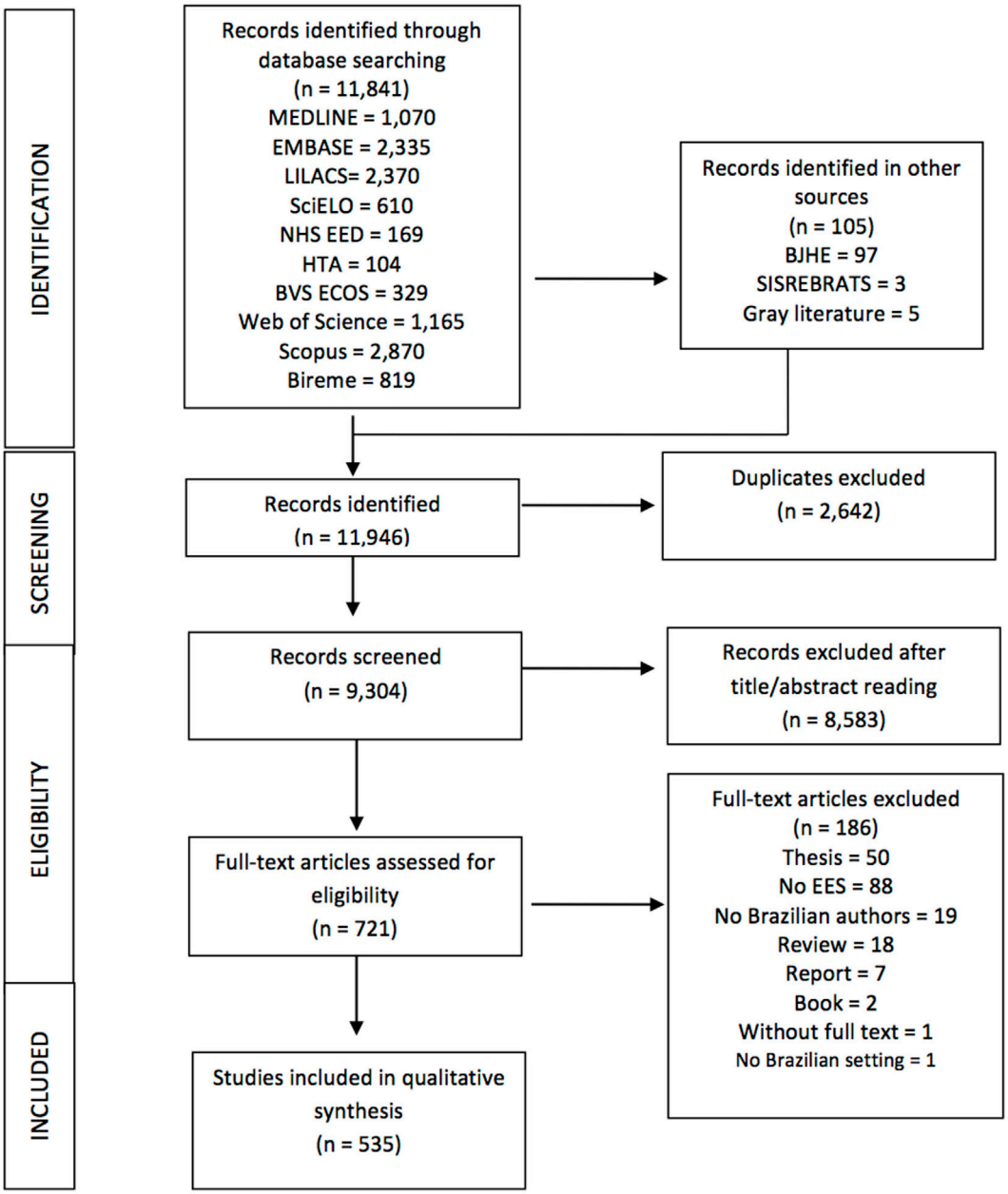

FIGURE 1 | Flow diagram of health economic evaluation studies in Brazil, 1980–2013.

majority of published evaluations were partial HEE. From 2008 onward, there was an increase in the number of full HEE, and the distribution of full and partial HEE studies became almost equivalent. An initial increase in the number of CEA studies has been followed by a sharp rise in the number of CUA, these have almost quadrupled in the last 3 years. The proportion of CUA studies increased from 17.6% between 2004 and 2009 to 82.4% between 2010 and 2013 ($P = 0.028$) (**Table 2**; **Figure 3**). Out of the 535 included studies, nearly half ($n = 248$, 46.3%) did not report the type of HEE study performed. Among these, 228 were partial and 20 were full HEE.

The review indicated an issue with the classification of study design in the identified HEE studies. According to international criteria (31, 32) of the 287 HEE that reported study type, 28.5% (82/287) had been classified incorrectly. Fifty-two (63.4%, 52/82) were partial analysis and 36.6% (30/82) full analysis. The most frequent misclassification among full HEE was to describe studies as CEA, where on investigation they were found to be CCA (53%, 16/30). Similarly, partial analyses described as cost analyses were cost descriptions (33%, 17/52). Some studies reported as CBA only performed cost analyses (29%, 15/52). Finally, some studies described as cost descriptions were cost analyses (15%, 8/52).

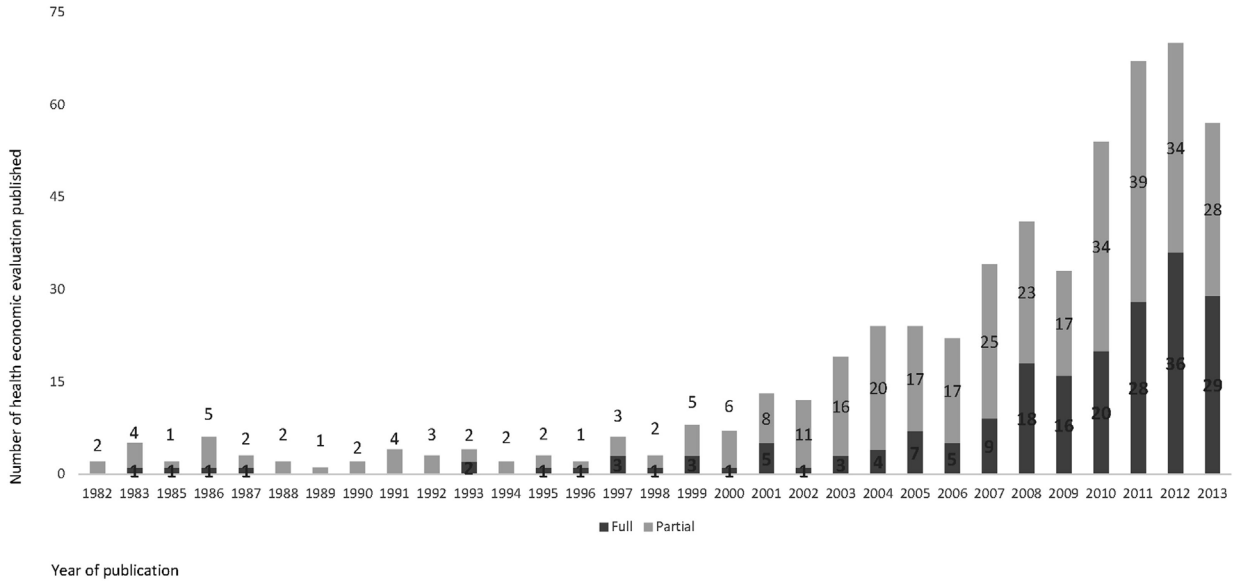

FIGURE 2 | Number of health economic evaluation studies in Brazil, by type, 1980–2013.

The categories of healthcare technologies that were most frequently assessed were procedures (34.8%, 186/535) and drugs (28.8%, 154/535). The proportion of studies that evaluate procedures increased from 4.3% during the 1980s to 39.2% between 2010 and 2013 ($P = 0.002$). Technologies assessed included treatment (72.1%, 386/535), prevention (8.6%, 46/535), and diagnostic and treatment (6%, 32/535).

The technologies evaluated in the studies were mainly related to the group of diseases of the Chapter I—certain infectious and parasitic diseases of ICD-10 (17.4%, 93/535), followed by Chapter IX—diseases of the circulatory system (12.9%, 69/535), Chapter II—neoplasms (10.3%, 55/535), and Chapter IV—endocrine, nutritional, and metabolic diseases (9.2%, 49/535).

Studies by Authorship, Journal, Funding Source, and Conflict of Interest

In most of the studies evaluated, the first authors were affiliated to academic institutions (65.1%, 348/535), followed by health organizations (19.8%, 106/535), public administration (5.8%, 31/535), consultancy firms (4.5%, 24/353), pharmaceuticals or equipment industry (2.8%, 15/535), research institutes (1.9%, 10/535), and international organizations (0.2%, 1/535). Although in the majority of publications, the first author was affiliated to an academic institution, there has been an increase of first authors affiliated to health organizations and consultancy firms (**Figure 4**).

The majority of Brazilian HEE studies were published in medical (55.5%, 297/535), and, public health (20%, 107/535) journals. Only 11.9% (64/535) were published in specialized health economics journals. Three hundred and eighty-eight studies (72.5%, 388/535) were published in Brazilian journals. Of those, 10.6% (41/388) were published in a non-indexed journal.

Regarding the geographical distribution of the first authors, southeast region stands out as a major producer of HEE (73.6%), followed by south (12.5%), and northeast (8.2%). The proportion of publications by regions remained constant during the study period. São Paulo and Rio de Janeiro were the Brazilian states more productive, 51.6 and 14.6%, respectively.

Two hundred and thirty-four studies (44%, 234/535) reported the funding source, among these, 12.4% (29/234) reported no funding and 87.6% (205/234) reported some funding source. Of these, 39% (80/205) were funded by research agencies, 32% (65/205) by industry, 15% (31/205) by the government, and 14% (29/205) had other or multiple funding sources.

Of the 535 studies included in the review, 36% (193/535) declared a conflict of interest, 82% (159/193) declared no conflict of interest. Of the 159 studies that declared no conflicts of interest, 13% (21/159) were considered (according to Valachis et al.) (34) to have a potential conflict of interest due to authors being industry or consultancy firm employees. Similarly, applying Valachis criteria to all 535 included studies, 84% (449/535) would be considered to not have a conflict of interest and 16% (86/535) could be considered to have a conflict of interest. Identified reasons for potential conflict of interest were: 49% (42/86) were developed by consultancy firms and industry; 45% (39/86) had at least one author contractually employed by the industry or funded by it; and 6% (5/86) were related to consultancy work.

Compliance with international recommendations for good reporting in the 197 studies identified as full HEE are presented in **Figure 5**. Most studies complied with the following items clearly stated: the research question (100%), competing alternatives (99%), primary outcome measure (95%), source of effectiveness estimates (94%), type of model (92%), and economic study design (90%).

Studies by Reporting Quality and Quality of the Sources of Evidence

Thirty-two percent (63/197) of the studies did not state a perspective for their analysis. Only 37% (73/197) described the methods for the estimation of total volume of healthcare resources used in

TABLE 2 | Characteristics of health economic evaluation (HEE), according time period, Brazil, 1980–2013.

Characteristics	1980–1989	1990–1999	2000–2004	2005–2009	2010–2013	Total	*P*-value
Type of HEE							
Partial	***N*(%)**	***N*(%)**	***N*(%)**	***N*(%)**	***N*(%)**	***N*(%)**	
Cost description	11 (4.9)	15 (6.7)	37 (16.6)	64 (28.7)	96 (43.0)	223 (100)	0.133
Cost analysis	5 (4.6)	11 (10.1)	23 (21.1)	35 (32.1)	35 (32.1)	109 (100)	0.155
Cost-outcome description	1 (25.0)	–	1 (25.0)	–	2 (50.0)	4 (100)	0.472
Cost analysis and BIA	–	–	–	–	2 (100)	2 (100)	0.183
Total	17 (5.0)	26 (7.7)	61 (18.0)	99 (29.3)	135 (39.9)	338 (100)	0.168
Full	***N*(%)**	***N*(%)**	***N*(%)**	***N*(%)**	***N*(%)**	***N*(%)**	
Cost-effectiveness analysis	2 (2.6)	–	4 (5.2)	26 (33.8)	45 (58.4)	77 (100)	0.150
Cost-consequence analysis	–	6 (15.0)	8 (20.0)	12 (30.0)	14 (35.0)	40 (100)	0.0001
CEA and CUA	–	1 (4.8)	–	5 (23.8)	15 (71.4)	21 (100)	0.150
Cost–utility analysis	–	–	–	3 (17.6)	14 (82.4)	17 (100)	0.028
Cost-minimization analysis	2 (14.3)	1 (7.1)	1 (7.1)	4 (28.6)	6 (42.9)	14 (100)	0.03
Cost-benefit analysis	–	2 (22.2)	–	1 (11.1)	6 (66.7)	9 (100)	0.133
More than one	–	1 (5.3)	1 (5.3)	4 (21.1)	13 (68.4)	19 (100)	0.355
Total	4 (2.0)	11 (5.6)	14 (7.1)	55 (27.9)	113 (57.4)	197 (100)	0.995
Type of technology	***N*(%)**	***N*(%)**	***N*(%)**	***N*(%)**	***N*(%)**	***N*(%)**	
Procedures	8 (4.3)	20 (10.8)	35 (18.8)	50 (26.9)	73 (39.2)	186 (100)	0.002
Medications	8 (5.2)	4 (2.6)	14 (9.1)	50 (32.5)	78 (50.6)	154 (100)	0.063
Procedures and medications	3 (4.6)	1 (1.5)	8 (12.3)	17 (26.2)	36 (55.4)	65 (100)	0.132
Public health and health promotion programs	–	4 (8.5)	4 (8.5)	14 (29.8)	25 (53.2)	47 (100)	0.176
Devices	1 (4.3)	2 (8.7)	5 (21.7)	7 (30.4)	8 (34.8)	23 (100)	0.287
Vaccines	–	3 (14.3)	2 (9.5)	8 (38.1)	8 (38.1)	21 (100)	0.777
Procedure, medications, and devices	–	1 (8.3)	1 (8.3)	4 (33.3)	6 (50.0)	12 (100)	0.564
Equipment	–	1 (33.3)	1 (33.3)	–	1 (33.3)	3 (100)	0.251
Other	1 (4.2)	1 (4.2)	5 (20.8)	4 (16.7)	13 (54.2)	24 (100)	0.795
Objective	***N*(%)**	***N*(%)**	***N*(%)**	***N*(%)**	***N*(%)**	***N*(%)**	
Treatment	18 (4.7)	22 (5.7)	55 (14.2)	115 (29.8)	176 (45.6)	386 (100)	0.796
Prevention	–	5 (10.9)	4 (8.7)	16 (34.8)	21 (45.7)	46 (100)	0.588
Diagnostic and treatment	–	–	8 (25.0)	6 (18.8)	18 (56.3)	32 (100)	0.197
Diagnostic	1 (3.2)	4 (12.9)	2 (6.5)	9 (29.0)	15 (48.4)	31 (100)	0.989
Screening	–	2 (15.4)	–	4 (30.8)	7 (53.8)	13 (100)	0.591
Prevention and treatment	–	2 (40.0)	1 (20.0)	1 (20.0)	1 (20.0)	5 (100)	0.079
Screening, diagnostic, and treatment	–	–	1 (100)	–	–	1 (100)	0.336
Other	2 (9.5)	2 (9.5)	4 (19.0)	3 (14.3)	10 (47.6)	21 (100)	0.278
Total	21 (3.9)	37 (6.9)	75 (14.0)	154 (28.8)	248 (46.4)	535 (100)	0.734

BIA, budget impact analysis; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; more than one: 19 studies concurrently performed more than one type of analysis: 13 studies CEA and BIA; 1 study CMA and BIA; 1 study CUA and CBA; 1 study CEA and CBA; 1 study CMA and CBA; 1 study CEA, CUA, and BIA; 1 study CMA, CBA, and CCA.

a transparent manner (i.e., reporting quantities and prices/unit costs separately). Less than half (43%, 85/197) of the studies stated the discount rate applied. Other identified caveats associated with studies' reporting were: failure to declare a conflict of interest, not stating a time horizon for the analysis, omitting to perform, and describe a sensitivity analysis. Of the 197 full HEE, 64.5% (127/197) were model-based economic evaluation. Of these, 92.1% (117/127) reported the type of model used: 41.9% (49/117) used Markov models, 34.2% (40/117) used decision trees, 6% (7/117) used Markov models with decision trees, 6% (7/117) dynamic models, and 12% (14/117) used other types of models.

The reporting quality association with the publication period was statistically significant ($P < 0.001$). The reporting quality increased progressively during the study period. Most recent periods showed better reporting quality. Studies published between 2010 and 2013 showed better reporting quality compared with those published between 2005 and 2009 and those published between 1980 and 2004. No association was found between the reporting quality and the study source of funding. Moreover, positive association was observed between the reporting quality and the variable conflict of interest. Studies with conflict of interest are associated with a better reporting quality ($P < 0.001$).

The quality of the sources of evidence used in the studies performed in the Brazilian setting was analyzed in depth using the hierarchy proposed by Coyle and Lee (37–39). **Figure 6** presents a graphical representation of results from this analysis. Our findings suggest that poorer quality of information was available for estimating utilities values than costs, resource use, and clinical effect size. No study directly (e.g., *via* a health state preference evaluation exercise) or indirectly (e.g., used utility

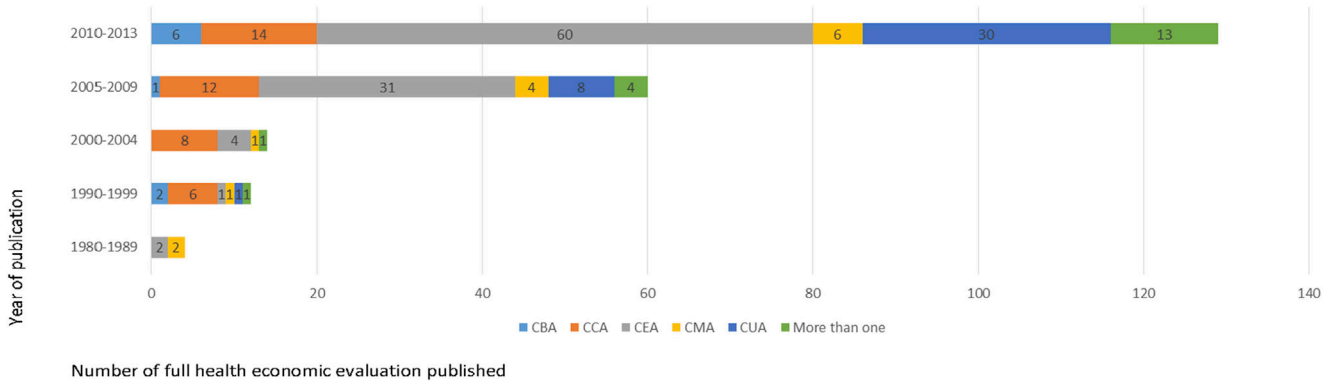

FIGURE 3 | Full health economic evaluation published in Brazil, 1980–2013. More than one: cost-effectiveness analysis (CEA) and budget impact analysis (BIA); cost-minimization analysis (CMA) and BIA; CMA, cost-benefit analysis (CBA), and cost-consequences analysis (CCA); ACU and ACB; CMA and CBA; CEA, cost-utility analysis (CUA), and BIA.

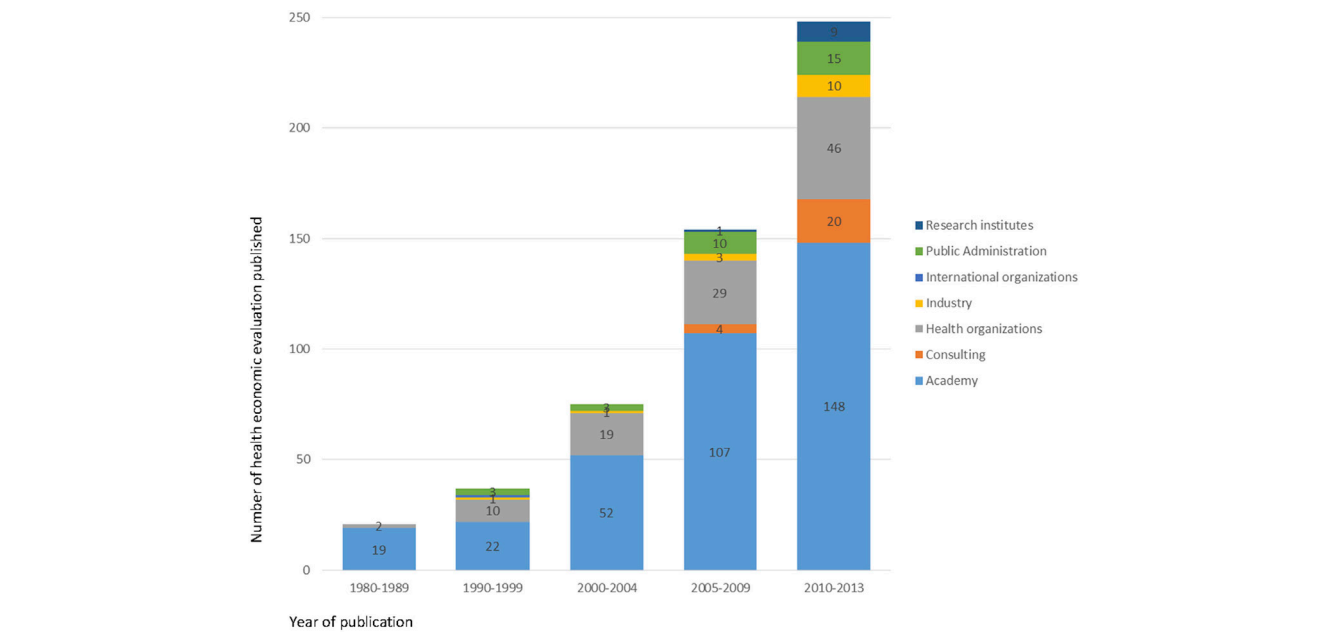

FIGURE 4 | Number of health economic evaluation studies in Brazil, by first author affiliation, 1980–2013.

values from an alternative patient sample but with the disease of interest) performed utility assessment. Twenty-two percent of the studies estimated utilities parameters from a previous study, 37% had data source or method of elicitation unknown, 12% was based on expert opinion, and 29% was not possible to evaluate. In contrast to utility value estimates data on costs, resource use and clinical effect size were mostly estimated using high-ranked evidence. For instance, more than 50% of the studies used cost information from sources where quality was ranked as 1+, 1, 2+, 2. Costs calculations were mainly based on reliable administrative database or data sources conducted for the specific study, and on recently published cost calculations based on reliable databases. Similarly, in 58% of the studies clinical effect sizes were estimated from meta-analysis or RCTs.

DISCUSSION

To the best of our knowledge, this the first systematic review describing the number, characteristics, and quality of reporting of HEE studies in Brazil.

The absolute number of all HEE published in Brazil between 1980 and 2013 ($n = 535$) is substantial. The volume of full HEE ($n = 197$) directly relevant to Brazilian settings is considerably higher than the number of HEE identified in other countries

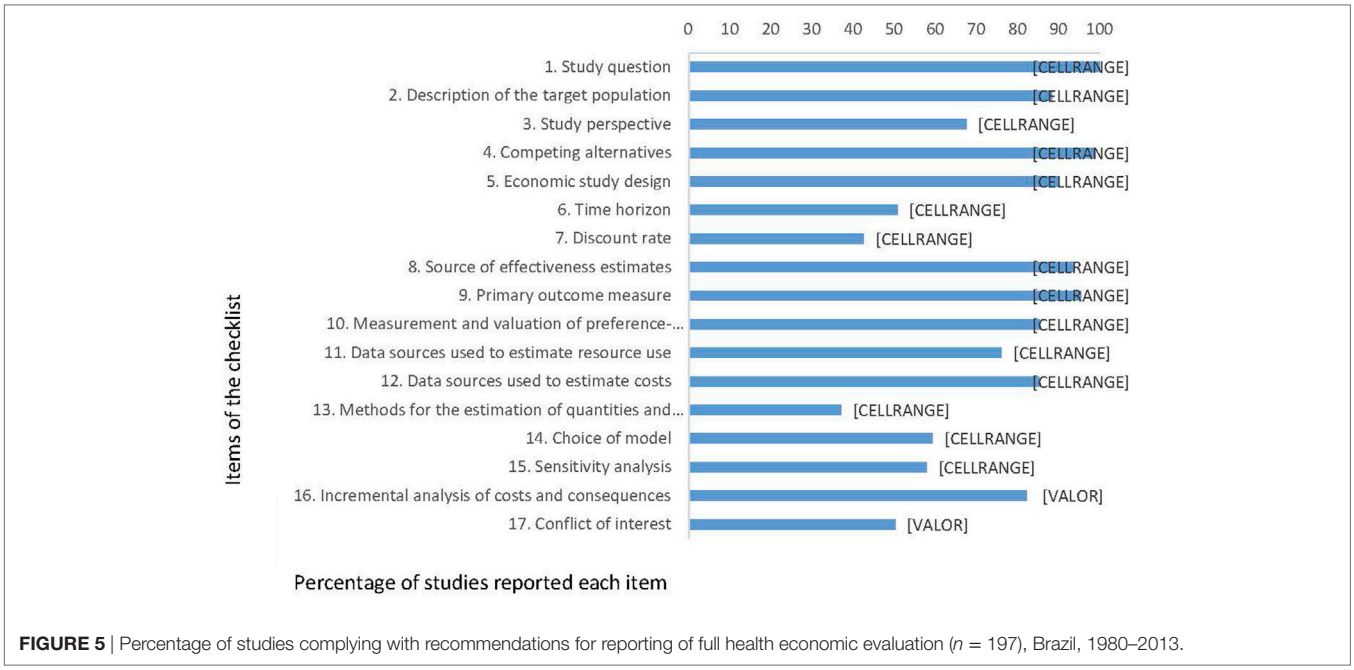

FIGURE 5 | Percentage of studies complying with recommendations for reporting of full health economic evaluation (*n* = 197), Brazil, 1980–2013.

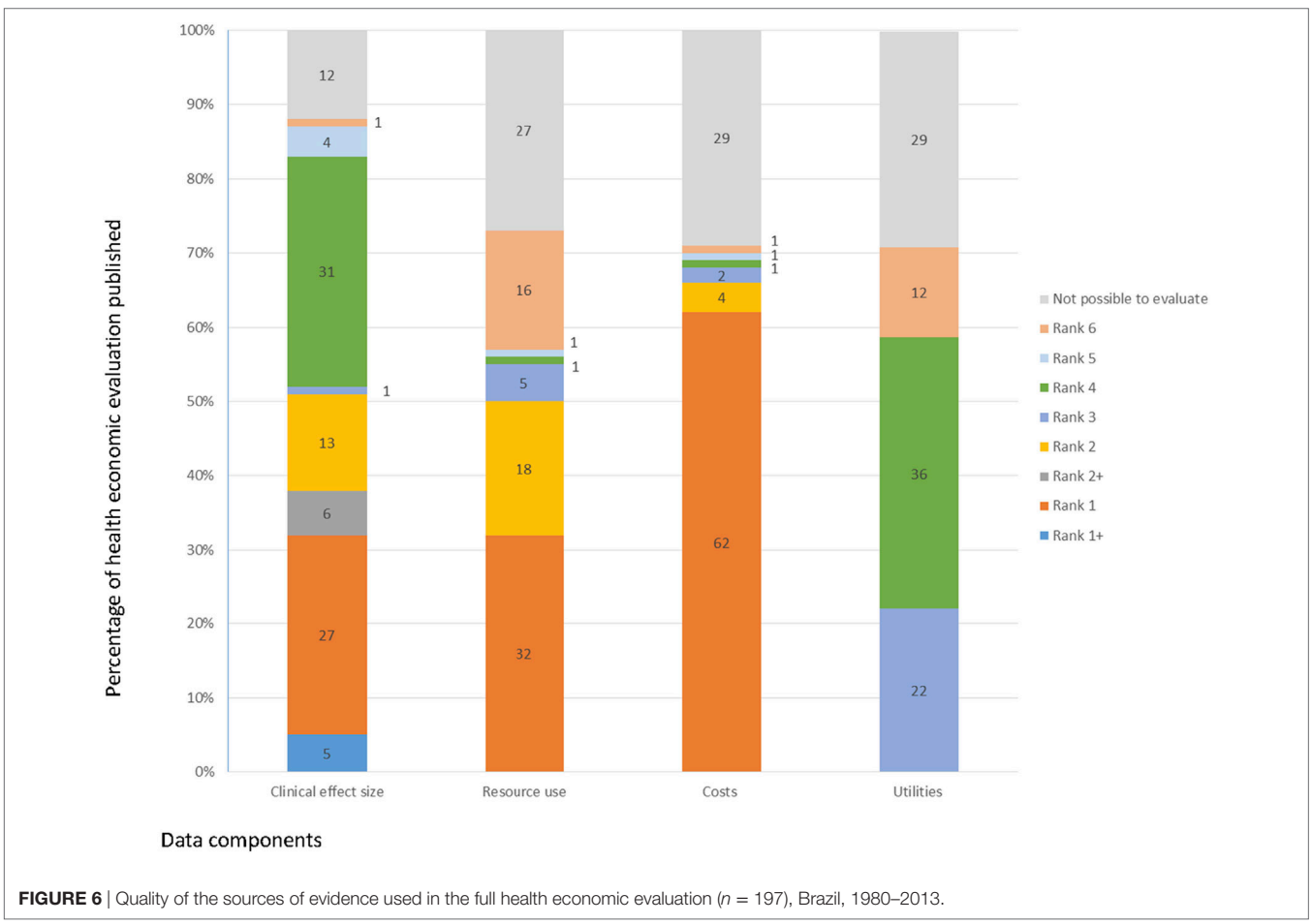

FIGURE 6 | Quality of the sources of evidence used in the full health economic evaluation (*n* = 197), Brazil, 1980–2013.

such as: Italy ($n = 92$), Colombia ($n = 48$), South Africa ($n = 45$), Thailand ($n = 39$), Korea ($n = 33$), Iran ($n = 30$), Vietnam ($n = 26$), China ($n = 26$), Saudi Arabia ($n = 10$), Bangladesh ($n = 12$), Nigeria ($n = 10$), and Zimbabwe ($n = 3$) (14, 15, 17, 19, 21, 24–28, 40). Conversely, Brazil still produces a lower number of HEE compared with high-income countries such as United Kingdom ($n = 675$), Canada ($n = 300$), German ($n = 283$), and Australia ($n = 245$), where economic evaluation is well established and formally used for regulating reimbursement policies for the adoption of new technologies (16, 20, 41).

BRICS (Brazil, Russia, India, and China) share in global wealth grew tremendously over past decade. In parallel to that, healthcare spending, health economic productivity, and research funding for health economics shifted toward low- and middle-income countries, especially in top emerging BRICS. These circumstances created drivers for further development of health economics in these countries (8, 42–44).

In recent years in Brazil, as in other LAC countries, there has been increased interest in incorporating HEEs as a formal tool to inform decision-making processes (12). This systematic review reveals a steady growing trend in the number of HEE studies being published in the last 6 years (2008–2013). Interestingly, this phenomenon is also observed in Colombia (26).

The steady growth in the economic evaluation literature relevant at national level in Brazil—the focus of this analysis—reached a peak in the year 2007. The reason for this may be multi-fold; firstly, from as early as 1980 Brazilian researchers, funders, and public health system users have successfully promoted the conduct and use of HEE studies. Secondly, internationally there was been an increased interest in HEE studies demonstrated by a continuous growth of published articles and books, as well as the creation of several new specialist journals in this field (45). A third crucially important factor is some recent initiatives of the Brazilian Ministry of Health such as CITEC and CONITEC establishments. The development of this formal structure for regulating reimbursement policies for the adoption of new technologies, provides a strong incentive to promote the implementation and publication of a growing number of HEE studies.

Findings from systematics reviews suggest that the increase in the number of HEE studies published internationally may be related to requirements to use information from these studies to inform reimbursement decisions (41).

As reported in earlier systematic reviews of HEE studies in Latin America (17, 26, 27), our findings indicated that CEA was the most prevalent (39.1%, 77/197) study type for full HEE conducted in Brazilian settings between 1980 and 2013. This might be explained by the relative simplicity of the CEA approach compared with CUA that requires developing robust methodology to value health state preferences.

Despite this, the current review found considerable growth in CUA for the Brazilian setting from 2005 onward ($P = 0.028$), in line with a growth in CUA observed in the international literature (41). The absolute number of CUA in Brazil ($n = 40$), however, is still small. This may, in part, be explained by the fact that CUA is more labor and resource intensive than CEA. In addition to this, the 2009 Brazilian HTA guideline gave equal weight to CEA and CUA (46). While CONITEC came into force in 2011 it did not update its methods guidelines to recommend the use of CUA. This is in contrast with current recommendations in a number of countries worldwide (e.g., Australia, Canada, Ireland, New Zealand, Scotland, Sweden, and United Kingdom) (47). CUA was indicated as the preferred type of study, only in the update of the Brazilian HEE guideline published in 2014 (48).

National Incorporation of Technologies in SUS has a formal requirement for BIA alongside a full HEE. In spite of this, the number of published BIA is still limited ($n = 15$), and most of the so-called BIA submitted to CONITEC are cost studies with 2–5-year annual costs for a specific cohort instead of a real estimate of the financial impact of a new intervention for the Brazilian healthcare system. These findings are consistent with a review of BIA studies (49).

Like other HEE in Latin America, Africa, and South/West Asia most studies focused on infectious disease (14, 21, 23, 36). The majority of these studies focused on vaccines, driven largely by increased investment on CEA and related activities by major global health players such as Bill & Melinda Gates Foundation, GAVI alliance, and the World Health Organization (48).

We found that 75.5% (297/535) of the studies were published in medical and public heath journals. In reviews of Spanish, Iran, German, and South African, HEE studies covering earlier years of publication, the majority of studies (77, 77, 79, and 88%, respectively) were also published in medical journals (13, 21, 24, 49). This high numbers may be related to lower publication standards in medical and public health journals when compared with specialized health economic journals.

Even though researchers prefer to publish their research in international journals, with higher impact factors, and a wider audience. Most of the studies (72.5%) were published in Brazilian journals. Among the 12% published in health economics specialized journals, 8% were published in a national health economic journal, which was not even indexed until 2013.

This may be related to publication requirements as editors of Brazilian journals have less stringent requirements to make use of international methodological guidelines as part of their peer reviewing processes. Consequently, articles with an inferior quality of reporting and equivocal methodological quality are published. Our data also suggest a need for improvements in the peer review process, especially among journals with limited experience publishing economic evaluations (50).

The majority (75%, 148/197) of identified full HEE studies were published between 2008 and 2013, and the reporting quality increased progressively during the study period ($P < 0.001$). Although overall quality of reporting was considered satisfactory, the review highlighted a number of issues associated with the reporting and methodological quality of the included HEE studies.

Two issues on quality of reporting deserve further attention. Firstly, reporting of funding source, 56%, 110 of the 197 full HEE studies identified here did not state their source of funding. This is in line with findings from reviews on the state of HEE studies conducted in South Africa (45%, 49/108) (24), Nigeria (55%, 24/44) (21), and Zimbabwe (62%, 16/26) (19). Secondly, and directly related to reporting source of funding is declaring potential for any conflicts of interest. Only 36% of the articles

reported conflict of interest. As highlighted by Valachis et al. (34), conflicts of interest may be directly related to sources of funding. This is a phenomenon that has been researched by several authors (51–53), if studies are funded by the healthcare industry this could have a direct impact on the conclusion drawn. Industry-sponsored HEE are believed to be more likely to report incremental cost-effectiveness ratios that favor products manufactured by the sponsor. Missing details on these two crucial pieces of information described above may impact on the credibility and transparency of results from HEE studies.

Two final points are identified as requiring further consideration and recommendations for improvement, these are (1) methods for the estimation of resources quantities and unit costs and (2) methods for the estimation of utilities parameters. While the majority of studies provided a source for resource utilization and costs, they omitted details on the identification and quantification of categories of resources and estimation of unit costs. This is in contrast to HEE guidelines (54–56), which indicate that all the relevant quantities of resources should be measured in a correct and transparent manner, and reported separately from the prices (unit costs) of those resources. This lack of detailed reporting on the quantification of healthcare resources and methods used for their valuation limits the ability to replicate costing processes in future studies.

The final critical issue identified for discussion was the poor quality of information used for estimating utilities parameters. Authors' often reported their main sources of information for the measurement and valuation of preference-based outcomes, these sources of evidence, however, were studies ranked as low quality. Many studies reported having used international data from previously published studies or expert opinion. This is in contrast with international guidelines on HEE which state that utility values obtained from other countries are, in general, not transferable because of cultural differences (57). Recently, in 2011, two of the most widely used generic preference-based utility instruments—EQ-5D and SF-6D—were cross-cultural adapted and validated, in addition societal preferences weights were estimated for the Brazilian population in 2013 (58–61). We expect that current efforts to estimate Brazilian utility weight "tariffs" will increase consistency in quality-adjusted life year calculations in future HEE studies.

One limitation of our study was that we critiqued the reporting, and not necessarily the actual manner that authors conducted their studies. However, this review was useful to assess the practice of HEE in the Brazilian setting.

CONCLUSION

This review identified that an increasing number of HEE studies are being conducted and published in Brazil. Their reporting quality has increased progressively during the study period. Overall, the quality of these HEE studies is satisfactory, but we identified key areas where significant improvements could be made such as: reporting of funding source, conflict of interest, methods for the estimation of resources quantities and unit costs, methods and source of evidence to estimate utility parameters utilities parameters. Our findings can contribute to improve the way HEE studies are designed, implemented, and reported in Brazil.

CONSENT FOR PUBLICATION

There are no any individual person's data.

ETHICS STATEMENT

There are no human participants involved.

AUTHOR CONTRIBUTIONS

All authors drafted the systematic review protocol. TD, RL, and PS conducted the search, selection of records, and data extraction. Quality appraisal was conducted by TD, LR, and PS. All authors have read and approved the final manuscript.

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Are There Striking Differences in Outpatient Use of Antibiotics Between South Backa District, Serbia, and Some Scandinavian Countries?

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There is little published information about antibiotic utilization in outpatients in Serbia. The objective of this study was to determine the amount and structure of outpatient antibiotic use in South Backa District (SBD) in Serbia, to assess prescibing quality of antibiotics and to compare with results from Scandinavian countries. Data on the antibiotic use were collected from all private and state-owned pharmacies from January through March 2008 in SBD. Results were expressed as the number of defined daily doses/1,000 inhabitants/day. The drug utilization 90% method was also used. Penicillins were the most frequently used antibiotic subgroup in SBD (35.20%), followed by cephalosporins (19.16%) and macrolides (13.18%). Thirteen drugs accounted for 90% of total antibiotics consumption (DU90% segment). The average cost/DDD within the DU90% segment was 0.95 euros, whereas the average cost/DDD beyond the DU90% segment was 1.89 euros, indicating that less expensive antibiotics were more frequently used. High use of ampicillin, third-generation cefalosporins, co-trimoxazole, and gentamicin, will aggravate the alarming problem of resistance in Serbia. Differences in the amount and structure of antibiotic consumption between SBD and Scandinavian countries indicate the need of updated national guidelines for rational antimicrobial drug use in Serbia.

Keywords: antibiotics, outpatients, serbia, defined daily dose, pharmacoepidemiology

INTRODUCTION

The current worldwide increase in antimicrobial resistance is multifactorial, but the leading cause is the high consumtion of antibiotics. Outpatient use of antibiotics accounts for about 80–90% of antibiotic sales worldwide (1). Thorough surveillance of outpatient antibiotic use is one of the strategies to manage and control innapropriate utilization of antibiotics. For that purpose, the European Surveillance of Antimicrobial Consumption (ESAC) project established an extensive database of outpatient antibacterial consumption in Europe (2, 3).

Abbreviations: ATC, anatomical therapeutic chemical; DDD, defined daily dose; DDDs/TID, defined daily doses per 1,000 inhabitants per day; DU90%, drug utilization 90% segment; ESAC, European Surveillance of Antimicrobial Consumption; SBD, south backa district.

The Republic of Serbia is a southern European country undergoing a socio-economical transition. After Yugoslavia split, Serbia became an independent state in 2006. Serbia, together with Federation of Bosnia and Herzegovina, the former Yugoslav Republic of Macedonia and Montenegro, is one of the few countries not participating in the ESAC project.

Some endeavors have been made to monitor antibiotic use in Serbia. After Yugoslavia disintegrated, Serbia, started with implementation of educational (i.e., Continuing Medical Education) and administrative measures (related to promotion of rationalization of antibiotic use through restriction of available antibiotics funded by the Republic Fund of Health Insurance and introduction of capitation), in order to prevent overuse of antibiotics. However, the situation is still far from ideal because of several reasons. First, there is a need for updated national guidelines on antimicrobial use in the outpatient primary care. Second, private pharmacies are not completely implemented in the Health Insurance Institution and they are not so strictly controlled by the state. Finally, the system of health professionals' continuous education in Serbia has only recently been implemented. Besides, there is an official statics on drug utilization of the Agency for Drugs and Medical Devices of the Republic of Serbia. However, the agency obtains data from actual drug sales from manufacturers or their representatives and does not report separately inpatient and outpatient consumption of antibiotics.

Because the information about antibiotic utilization in Serbia is scanty and there are rare publications on the topic and the ones we have are incomplete (4–6), especially about outpatient use, the aims of the present study were to determine the amount and structure of outpatient antibiotics use issued in all state-owned and private pharmacies in the South Backa District (SBD), to estimate prescribing quality of antibiotics (drug utilization 90% method), as well as to compare results of this study with those in Denmark and Finland (the countries with well-developed pharmacotherapeutic practices) for the same year.

MATERIALS AND METHODS

The investigation was carried out in SBD with over a 3-month period in 2008. SBD is one of 29 Serbian districts. It is situated in the northern part of the country with 605,720 inhabitants (according to the 2008 cenzus), which correspond to 8.2% of the total Serbian population and is representative for the whole Serbian population, in terms of demographics.

The data on the number of packages, size of packages, and retail price of antibiotics [anatomical therapeutic chemical (ATC) group J01] from 1 January to 31 March 2008 were obtained from all state-owned and private pharmacies in SBD. The number of defined daily doses per 1,000 inhabitants per day (DDDs/TID) was calculated using ATC/DDD methodology valid in 2008 (7). The proportion of parenteral use of the total outpatient use was assessed. Parenteral use was expressed as a percentage of the total outpatient use in DDDs/TID.

Drug utilization 90% methodology was also used. This ranks drugs by volume of DDDs and determines how many and which drugs account for 90% of total consumption. The principle is to focus on the drugs that account for 90% of the prescribed volume and the adherence to guidelines in this DU90% segment (8). The price per DDD for each antibiotic in the DU90% segment, mean total price per DDD for all antibiotics within and beyond the DU90% segment, and the mean price per DDD for all antibiotics dispensed in SBD over a 3-month period were also calculated.

Data on the antibiotic consumption in Denmark and Finland for the same year as in SBD were taken from the annual reports that are regularly issued in electronic format, and they represent outpatient consumption (9, 10).

RESULTS

Utilization of antibiotics for systemic use (ATC group J01) in SBD, Denmark, and Finland is presented in **Table 1**. The total outpatient utilization of group J01 antibiotics in the SBD (26.93 DDDs/TID) was higher than in Denmark (16.2 DDDs/TID) and in Finland (18.13 DDDs/TID).

Penicillins were the most frequently used antibiotic subgroup in all tree investigated countries. In SBD and Finland it accounted for approximately 35% of overall outpatient consumption, while in Denmark the use was almost twice as high (61.73%).

The main difference was observed in consumption of cephalosporins: in SBD and Finland the percentage of cephalosporins

TABLE 1 | Total outpatient use of antibacterials for systemic use (J01) in South Backa District (SBD), Denmark, and Finland in 2008, expressed in defined daily doses per 1,000 inhabitants per day (DDDs/TID) and percentages.

ATC code	Name of therapeutic subgroup	SBD		Denmark		Finland	
		DDDs/TID	%	DDDs/TID	%	DDDs/TID	%
J01C	Penicillins	9.48	35.20	10	61.73	6.11	33.71
J01D	Cephalosporins	5.16	19.16	0	0	2.31	12.47
J01A	Tetracyclines	3.17	11.17	1.7	10.49	4.02	22.17
J01F	Macrolides, lincosamides	3.55	13.18	2.4	14.82	1.32	7.28
J01M	Quinolones	2.15	7.98	0.5	3.08	0.86	4.74
J01E	Sulfonamides and trimethoprim	1.86	6.91	0.8	4.93	1.44	7.94
	Other J01 Classes	1.56	5.71	0.8	4.63	2.07	11.72
J01	Total	26.93	100.0	16.2	100.0	18.13	100.0

ATC, anatomical therapeutic chemical.

was similar (19.16 and 12.47%, respectively), while there was no consumption of cephalosporins at all in Denmark.

On the other hand, the percentage of tetracyclines consumption in Finland (22.17%) was approximately two-hold of that in Denmark (10.49%) and SBD (11.17%), but the percentage of macrolides consumption was approximately twice lower in Finland (7.28%) than in Denmark (14.82%) and SBD (13.18%).

The quinolones consumption was approximately two times as high in SBD than in Scandinavian countries and the consumption of sulfonamides and trimethoprim was lower in Denmark compared to SBD and Finland.

Distribution of drug utilization within the therapeutic subgroup of penicillins (J01C) expressed in DDDs/TID SBD is shown in **Table 2**.

The most frequently used penicillin in SBD and in Finland was amoxicillin (60.2 and 43.37%), while in Denmark it occupied the third place with 13%. In Denmark, phenoxymethylpenicillin was the most used antibiotic with 53%, while in SBD and Finland it occupied the second place with 14.1 and 26.02%.

Amoxicillin+clavulanic acid was the third most commonly used penicillin antibiotics in SBD and Finland (12.1 and 19.15%) while in Denmark in was on the last place within this subgroup with only 3%.

While in SBD, ampicillin in the form of capsules was still used and with 11.8% occupied forth place, in Scandinavian countries only a prodrugs of ampicillin, with greater lipophilicity and better oral bioavailability compared to that of ampicillin were used.

Penicillins for parenteral use were recorded in outpatients only in SBD. On the other hand, beta lactamase-resistant penicillins were used only in Denmark and Finland. The only representative on the market in Serbia, cloxacillin, was not reimbursed by the Republic fund for health insurance.

In cephalosporine subgroup (J01DA), the first-generation cephalosporins showed a dominant utilization in SBD and in Finland (**Table 3**), represented mainly with cephalexin (3.57 and 2.26 DDDs/TID, respectively). Out of the second-generation cefalosporins, cefaclor was most commonly used, while in Finland it was cefuroxime. Cefixime, the third-generation cefalosporine for oral use, was located on the third place in SBD; while in Scandinavian countries, the third-generation cefalosporins were not used at all.

While in SBD and Finland the utilization of doxycyclin was especially pronounced, in Denmark tetracycline was located on the first place (**Table 4**).

The utilization of long acting-macrolides (azithromycin) was dominant in SBD and Finland (**Table 5**). On the other hand, the intermediate acting macrolides (mainly roxithromycin) was predominantly used in Denmark.

Among quinolones, ciprofloxacine was the leading drug in all three investigated countries (**Table 6**). The use of pipemidic acid was recorded only in SBD.

The J01E subgroup was represented only by co-trimoxazole (the only member on market, 1.86 DDDs/TID) in SBD, while in Denmark and Finland the utilization of thrimetoprim was pronounced (**Table 7**).

In SBD, 5.68% of total outpatient antibiotic consumption was used parenteraly. The three most commonly used antibiotic groups for parenteral treatment were the aminoglycosides (J01G; 81.04%), the penicillins (J01C; 11.11%) and the cephalosporins (J01D; 7.84%). The most commonly used parenteral antibiotics were gentamicin (75%), procain-benzylpenicillin (11%) and ceftriaxone (8%) (**Figure 1**). In Finland, only tobramycin in negligible percentage (0.05%) was used for parenteral treatment, while in Denmark no injectable drug appeared.

DU90% segment in SBD included 13 antibiotics (**Table 8**). Financial expenses for DU90% segment accounted for 91.3% of overall cost in J01 group, whereas 10% utilization in DDD accounted for 8.7% of overall cost.

DISCUSSION

According to our knowledge, this study was first to examine the outpatient consumption of 100% sample of antibiotic (issued by prescription and bought without prescription) in one region in Serbia covering more than 6000,000 inhabitants; calculation of DU90% segment to estimate the prevalence and the structure of

TABLE 2 | Utilization of antibiotics within penicillins subgroup (J01C) in South Backa District (SBD), Denmark, and Finland in 2008.

ATC code	Drug name	SBD		Denmark		Finland	
		Defined daily doses per 1,000 inhabitants per day (DDDs/TID)	Share (%)	DDDs/TID	Share (%)	DDDs/TID	Share (%)
J01CA01	Ampicillin[a]	1.12	11.8				
J01CA02	Pivampicillin			0.5	5		
J01CA04	Amoxicillin	5.71	60.2	1.3	13	2.65	43.37
J01CA08	Pivmecillinam			1.5	15	0.67	10.97
JO1CE02	Phenoxymethylpenicillin[a]	1.34	14.1	5.3	53	1.59	26.02
J01CE30	Procaine benzyl penicillin	0.17	1.8				
J01CF01	Dicloxacillin			1.1	11	0.02	0.33
J01CF02	Cloxacillin					0.01	0.16
J01CR02	Amoxicillin+clavulanic acid[a]	1.15	12.1	0.3	3	1.17	19.15
TOTAL J01C		9.48	100.0	10	100.0	6.11	100.0

ATC, anatomical therapeutic chemical.

[a]*Drugs fully reimbursed by the Republic Fund for Health Insurance of Serbia in 2008.*

TABLE 3 | Utilization of cephalosporins (J01C) in South Backa District (SBD), Denmark, and Finland in 2008.

ATC code	Drug name	SBD		Denmark		Finland	
		Defined daily doses per 1,000 inhabitants per day (DDDs/TID)	Share (%)	DDDs/TID	Share (%)	DDDs/TID	Share (%)
J01DB01	Cefalexin[a]	3.57	69.00	–		2.16	93.51
J01DB05	Cefadroxil[a]	0.08	1.61	–		0.06	2.60
J01DC02	Cefuroxime	0.08	1.51	–		0.06	2.60
J01DC04	Cefaclor	0.13	2.60	–		0.03	1.30
JO1DC10	Cefprozil[a]	0.06	1.16	–			
J01DD04	Ceftriaxone	0.12	2.36	–			
J01DD08	Cefixime[a]	1.08	20.92	–			
J01DD14	Ceftibuten	0.04	0.78	–			
TOTAL J01D		5.17	100.0	–		2.31	100.0

ATC, anatomical therapeutic chemical.
[a]Drugs fully reimbursed by the Republic Fund for Health Insurance of Serbia in 2008.

TABLE 4 | Utilization of antibiotics within tetracyclines subgroup (J01A) in South Backa District (SBD), Denmark and Finland in 2008.

ATC code	Drug name	SBD		Denmark		Finland	
		DDDs/TID	Share (%)	DDDs/TID	Share (%)	DDDs/TID	Share (%)
J01AA02	Doxycycline[a]	3.09	97.47	0.6	35.3	2.39	59.45
J01AA04	Limecycline			0.3	17.6	0.67	16.67
J01AA06	Oxyitetracycline			0.1	5.8		
J01AA07	Tetracycline	0.08	2.53	0.7	41.7	0.96	23.88
TOTAL J01A		3.17	100.0	1.7	100.0	4.02	100.0

ATC, anatomical therapeutic chemical.
[a]Drugs fully reimbursed by the Republic Fund for Health Insurance of Serbia in 2008.

TABLE 5 | Utilization of antibiotics within macrolides and lincosamides subgroup (J01F) in South Backa District (SBD), Denmark and Finland in 2008.

ATC code	Drug name	SBD		Denmark		Finland	
		Defined daily doses per 1,000 inhabitants per day (DDDs/TID)	Share (%)	DDDs/TID	Share (%)	DDDs/TID	Share (%)
J01FA01	Erithromycin[a]	0.36	10.1	0.7	29.2	0.08	6.06
J01FA06	Roxithromycin	0.49	13.8	0.9	37.5	0.26	19.70
J01FA09	Clarithromycin[a]	0.78	22	0.3	12.5	0.36	27.27
J01FA10	Azithromycin[a]	1.72	48.5	0.5	20.8	0.57	43.18
J01FA15	Telithromycin					0.05	3.79
J01FF01	Clindamycin	0.20	5.6				
TOTAL J01F		3.55	100.0	2.4	100.0	1.32	100.0

ATC, anatomical therapeutic chemical.
[a]Drugs fully reimbursed by the Republic Fund for Health Insurance of Serbia in 2008.

TABLE 6 | Utilization of antibiotics within quinolones subgroup (J01M) in South Backa District (SBD), Denmark, and Finland in 2008.

ATC code	Drug name	SBD		Denmark		Finland	
		Defined daily doses per 1,000 Inhabitants per day (DDDs/TID)	Share (%)	DDDs/TID	Share (%)	DDDs/TID	Share (%)
J01MA01	Ofloxacin[a]	0.07	3.43			0.05	5.81
J01MA02	Ciprofloxacin[a]	1.39	64.44	0.5	100	0.46	53.49
J01MA06	Norfloxacin[a]	0.11	5.28			0.12	13.95
J01MA12	Levofloxacin					0.16	18.60
J01MA14	Moxifloxacin					0.07	8.14
J01MB04	Pipemidic acid[a]	0.58	26.85				
TOTAL J01M		2.16	100.0	0.5	100.0	0.86	100.0

ATC, anatomical therapeutic chemical.
[a]Drugs fully reimbursed by the Republic Fund for Health Insurance of Serbia in 2008.

TABLE 7 | Utilization of antibiotics within sulfonamides and trimethoprim subgroup (J01A) in South Backa District (SBD), Denmark, and Finland in 2008.

ATC code	Drug name	SBD		Denmark		Finland	
		Defined daily doses per 1,000 Inhabitants per day (DDDs/TID)	Share (%)	DDDs/TID	Share (%)	DDDs/TID	Share (%)
J01EE01	Co-trimoxazole[a]	1.86	100			0.04	2.78
J01EE02	Sulfadiazine and trimethoprim					0.33	22.92
J01EA01	Trimethoprim			0.5	62.5	1.07	74.31
J01EB02	Sulfamethizol			0.3	37.5		
TOTAL J01E		1.86	100.0	0.8	100.0	1.44	100.0

ATC, anatomical therapeutic chemical.
[a]Drugs fully reimbursed by the Republic Fund for Health Insurance of Serbia in 2008.

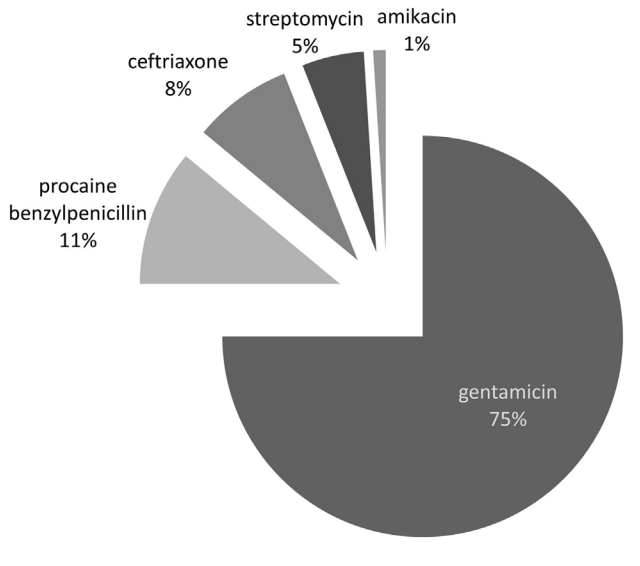

FIGURE 1 | Parenteral outpatient antibiotic use in South Backa District expressed in percentage.

TABLE 8 | Antibiotics for systemic use (J01) within DU90% segment expressed in the number of DDDs/TID, and the cost per defined daily dose (DDD) in Euros within and beyond DU90% segment in south backa district (SBD).

No	ATC	INN	%	Defined daily doses per 1,000 inhabitants per day	Cost (euro)/ DDD
1	J01CA04	Amoxicillin[a]	21.17	5.71	0.21
2	J01DB01	Cefalexin[a]	13.24	3.57	0.70
3	J01AA02	Doxycycline[a]	11.47	3.09	0.12
4	J01EE01	Co-trimoxazole[a]	6.91	1.86	0.24
5	J01FA10	Azythromycin[a]	6.38	1.72	1.52
6	J01MA02	Ciprofloxacin[a]	5.17	1.39	1.52
7	J01CE02	Phenoxymethylpenicillin[a]	4.98	1.34	0.65
8	J01GB03	Gentamicin	4.27	1.15	1.15
9	J01CR02	Amoxicillin+clavulanic acid[a]	4.25	1.15	0.83
10	J01CA01	Ampicillin	4.15	1.12	0.31
11	J01DD08	Cefixime[a]	4.01	1.08	2.16
12	J01FA09	Clarithromycin[a]	2.89	0.78	0.86
13	J01MB04	Pipemidic acid[a]	2.14	0.58	2.11
DU90% 1–13 (average)			91.04	24.54	0.95
Others 14–37 (average)			8.96	2.40	1.89
TOTAL 1–37			100.00	26.94	1.56

ATC, anatomical therapeutic chemical; INN, International Nonproprietary Name.
[a]Drugs fully reimbursed by the Republic Fund for Health Insurance of Serbia in 2008.

antibiotics, and the share of parenteral preparations in the total outpatient use.

We compared the results obtained with the drug utilization data in Denmark and Finland. These Scandinavian countries were chosen because they are stable middle-ranking countries according to the antibiotic consumption in Europe (2, 11). Aforementioned countries were also selected for comparison because of their well-developed pharmacotherapeutic practice. Namely, they possess publicly available data sets for drug consumption, well-established methods for drug consumption monitoring, as well as sufficient financial resources for constant development and implementation of pharmacotherapeutic treatment guidelines thereby providing their population with optimal treatment options.

The total outpatient utilization of antibiotics in SBD is high (26.93 DDDs/TID), although it is lower than the total use of antibiotics in Serbia according to the data retrieved from the annual report issued by the Agency for Drugs and Medical Devices of the Republic of Serbia for the same year (47.39 DDDs/TID) (6). This difference could be the consequence of the fact that our data were based on antibiotics issued on prescription in all state-owned and antibiotics bought without prescription in all private pharmacies in SBD, while national data was based on antimicrobial wholesale data. The total outpatient utilization of antibiotics in SBD is 1.6 times higher than in Denmark (9) and 1.48 times greater than in Finland (10), and it is in accordance with the utilization in Belgium (27.66 DDDs/TID), France (27.99 DDDs/TID), and Italy (28.45 DDDs/TID) (2), European countires with the highest outpatient antibiotic use. This is in accordance with the finding related to the first valid, representative, and comparable published data on antimicrobial use in Serbia, according to which Serbia is among the countries with an above average antibiotic use (12). Interestingly, high antibiotic consumption in our study reflects similar prescribing habits with surrounding countries. For example, in Montenegro (which was part of Yugoslavia and afterward the State Union of Serbia and Montenegro until 2006),

the total outpatient amount of antibiotic was 39.29 DDDs/TID in 2009 (13). Furthermore, in Zagreb, the capital of Croatia, the total outpatient consumption was 38.31 DDDs/TID in 2007 (14). The similarities between these countries could be influenced by the common cultural, educational, and prescription behavior habits (15, 16).

Furthermore, the possibility to procure antibiotics without prescription could be one of the factors driving high consumption of antibiotics in SBD. Namely, out of the total antibiotic consumption in our study, almost 30% was bought in private pharmacies, most often without prescription. This study was conducted before the implementation of stricter laws on antibiotics purchasing without medical prescription in 2011 (17). Although antibiotics are not available without prescription nowadays, some private pharmacies in Serbia do not adhere to this regulation. Namely, a recent study conducted in Novi Sad as a major city of the SBD reported, 50% self-medicating with antibiotics during their lifetime and that 25% of the patients opted for self-medication during the last infection. These results indicated that self-medication rate is higher than in other countries in Europe (18). The self-medication practice with antibiotics with antibiotics in Europe from 3% in northern region to 30% in eastern Europe which is in accordance with the percentage of antibiotics bought without prescription recorded in our study (18, 19).

Although the consumption of penicillin drugs is prevailing in all three observed settings, there are some differences between the structure of their use. Unlike Denmark, in SBD and Finland, a higher use of broadspectrum penicillins was noticed, which is similar to other settings in Europe (20). However, the latest study related to antibiotic consumption in the primary care sector in Denmark also showed the increase in the use of broad-spectrum penicillins between 2004 and 2013, which is worrisome (21). Decreasing trend of ampicillin use has been in Europe in SBD ampicillin is still among 10 most frequently used antibiotics. The reason of this high consumpion could be the historical consumption habits of inhabitants; it has been the most popular antibiotic in Serbia for years (4, 22). The utilization of combination of penicillin with β-lactamase inhibitor in SBD (1.15 DDD/TID) was similar to the consumption in Finland but it was lower than in neighboring ex-Yugoslavia countries. In Croatia, the amoxicillin+clavulanic acid was with 5.34 DDD/TID leading drug in outpatients consumption (23), while in Montenegro (13) in 2009 year the total outpatient utilization of this antibiotic was 3.9 times greater than in SBD. It is interesting that in neighboring Hungary, amoxicillin+clavulanic acid was one of the most widely sold antibiotic without prescription (24).

Unlike Denmark, the only country in Europe that does not use cephalosporins in outpatients, in SBD cephalosporins represent almost 20% of total use of antibiotics (21). The first-generation cephalosporins represents more than 70% of the total cephalosporins use (mainly cephalexine) what is less than in Finland (95%), similar to the utilization found in Luxembourg, Israel and Croatia in 2008 (2). While the second-generation cephalosporins was used in less than 7% in SBD, the consumption of the third generation was high (more than 24%), comparable to a few countries (Italy, France) with the highest consumption of this generation of cephalosporins (25). The consumption of the second generation was mainly presented with cefaclor, although the dosage regime is inconvenient, whereas in Finland cefuroxime was the most frequently used cephalosporin of the second generation, a drug with better pharmacokinetc properties regarding dosing frequency. The reason of this high consumpion of cefaclor could be the historical consumption habits of inhabitants; it has been one of the most popular antibiotic in Serbia for years (5, 22). In addition, the third generation of cephalosporins are expensive drugs with a very broad antibacterial spectrum, that is why their irrational use contributes not only to the development of antibacterial resistance but also represents a significant impose significant financial burden on health expenses (26–28). In addition, this innapropriate use of the third generation for parenteral use presented by ceftriaxone in our study could be explained by its good pharmacokinetic properties such as once-daily administration, which is convinient for patients. Likewise, cefixime is an attractive option for outpatients for oral therapy, because of the broad antibacterial spectrum and once-daily dosing regime.

The consumption of co-trimoxazole in SBD (1.86 DDDs/TID) was higher than consumption of sulfonamides and trimetoprim in Finland, country with the highest consumption among 31 European countries participating in the ESAC project in 2008 (2). Despite the high resistance of *E. coli* isolated from the urine of outpatients in SBD to co-trimoxazole (36.23%) in 2008 as well as in 2012, it is still first- choice agent for the treatment of uncomplicated urinary infections outpatients according to the national guideline for antimicrobial drug use (issued in 2004) in Serbia (29, 30). Because co-trimoxazole is financialy affordable (0.24euro/DDD), it has been commonly used for various infections in Serbia. Increased resistance to these drugs is a problem not only in outpatients but also particularly in inpatients in Serbia (29–31). Resistence to co-trimoxazole among isolates of E. coli ranges from 10 to 70% in different part of the world (32). Therefore, co-trimoxazole may no longer be effective in the treatment of *E. coli* strains resistant to this antibiotic. This should be taken into consideration in the making and updating of pharmacotherapeutic guidelines in Serbia.

Doxycyclin was among the three most frequntly used antibiotics in outpatients in our study, despite the limited number of indications for its administration nowadays. The high consumption was a consequence of several reason: low price (the cheapest antibiotic with the price of 0.12euro/DDD), possibility to buy it without prescription in private pharmacies before the restriction of free sale of antibiotics in 2011 and convenient administration once a day. As for the total consumption of tetracycline in Serbia, a gradual decrease in the utilization was recorded from 2006 (4.58 DDD/TID) to 2015 (2.25 DDD/TID) (33, 34). However, according to the recent survey aimed to report the first valid, representative, and comparable data on antimicrobial use in non-European Union countries of the WHO European region, Serbia is still among the countries with the highest use of tetracycline (12).

Similarly, high use of macrolide was noted in SBD, mainly azithromycin, whereas the use in Denmark and Finland was lower 2.4 and 1.27 DDD/TID, respectively. According to the above mentioned study on antimicrobial use in the non-European Union southern and eastern European countries, Montenegro and Serbia were the highest consumers of macrolides, mainly azithromycin. According to the guides for good clinical practice, issued by Ministry of Health of the Republic of Serbia, penicillins and/or macrolides are recommended as first line therapy for the treatment of respiratory infections in adults, which are the most common infections in outpatients (35).

Besides this, the once a day regimen and good safety profile of azitromycin contributes to the frequent us of macrolide antibiotics for empirical therapy in Serbia.

In relation to the group of macrolides, an increase in the overall consumption of these medications is also noticable in the whole of the Serbia from 2006 (3.55 DDDs/TID) to 2015 (5.34 DDDs/TID).

The utilization of quinolones was several times higher than in Scandinavian countries, with ciprofloxacine being the most widely used fluorinated quinolone. Use of ciprofloxacine was 2.5 and 4.3 times higher than in Finland and Denmark. The first- and the second generations of quinolones were most commonly used in SBD, which is comparable to the utilzation in most countries in Europe (2). The utilization of pipemidic acid (0.58 DDDs/TID) was higher than in Italy (0.25 DDDs/TID), where the consumption of pipemidic acid is the highest within ESAC participating countries (36). Quinolones are not recommended as a drug of first choice for the treatment of many infectious diseases, their high use recorded in our District raises concern regarding their appropriate use, especially for the treatment of multi-drug-resistant infections, such as tuberculosis.

The proportion of outpatient parenteral antibiotic use in SBD (5.68%) was in accordance with the proportion in 20 European countries in 2006, where it ranged from 0.001% in Iceland to 6.75% in Russia (37). The tree most commonly used groups were the same in European countries as in SBD, but with different order and proportion: cephalosporins (44.58%), the aminoglycosides (25.27%) and the penicillins (17.78%). The high utilization of aminoglycosides in SBD represented almost completely with gentamicin is a result of empirical prescribing of gentamicin by the general practitioner without the previous antibiogram usually for the treatment of urinary tract infections in outpatients (29).

In SBD and Finland, the prescription of antibiotics was split among greater number of compounds (37 and 31, respectively) than in Denmark (only 19 antibiotics). An interesting fact is that DU90% segment included 13 drugs in all three compared countries. In SBD, the cost/DDD within DU90% segment was 0.95 EUR, whereas the cost/DDD beyond this segment was 1.89 EUR/DDD, indicating that the cheaper antibiotics were more often used than the expensive ones (38, 39). In Finland these figures were 1.08 EUR/DDD and 3.46 EUR/DDD and in Denmark 3.1 EUR/DDD and 0.88 EUR/DDD, demonstrating that cheaper drugs were consumed in SBD and Finland than in Denmark (8, 9).

One of the reasons for the difference in average price within DU90% segment is the high price of phenoxymethylpenicillin in Denmark (9.74 EUR/DDD), the most used antibiotic, representing almost 33% of the prescription. In Denmark, only six antibiotics were beyond DU90% segment with the most expensive drug within this segment being sulfamethizol with 1.54 EUR/DDD (representing only 1.85% of the prescription).

The limitation of the study was the lack of follow up the patients indications. As with any study on drug consumption, it was not possible to compare the objective compliance use with the dosing regime. The study was conducted in SBD, Serbia which may not be representative for Serbia as a whole, due to distinct socieconomic and cultural characteristics.

Strength of the Study

The strength of this study is 100% sample of antibiotics used from one area in Serbia, covering more than 600,000 inhabitants. So far such data were not available in Serbia for the follow up and the comparison of use of antibacterials. Also, extensive application of ATC/DDD classification system, and the drug utilization 90% method to assess the prevalence and the structure were shown in order to analyze the structure of antibiotics.

CONCLUSION

Our study on the utilization of antibiotics in SBD, which accounts almost 8.2% of the Serbian population, indicate high utilization in Serbia as a whole. The comparison of our data with those from Scandinavian countries for the year 2008, the use of antibacterials is significantly higher in SBD. However, the use of antibiotics is still not as high as in countries with the highest outpatient consumption in Europe.

Irrational use of ampicillin, III generation cefalosporins, cotrimoxazole, and gentamicin, as showed in our study, will aggravate the existing problem of antimicrobial resistance, leading to further increase in the morbidity and mortality of infections caused by resistant bacteria and treatment-related costs due to the lack of an appropriate treatment.

Interventions to improve antibiotic use and education on rational antibiotic use should be essential for this District. Besides national monitoring of antibiotic consumption, availability of internationally comparable data on antibacterial consumption would be a valuable oportunity for continuous comparison of our consumption with those in other countries in Europe. Furthermore, differences in antibiotic consumption between SBD and Scandinavian countries, indicate the need of updated guidelines for in- and especially outpatients regarding rational antimicrobial drug use in Serbia.

AUTHOR CONTRIBUTIONS

All the authors have provided substantial contributions to the development of the manuscript. OH, AS, and ZT contributed

to the overall conception and design. VM and BM gathered the data. MK, AT, OH, and AS analyzed the data. All the authors contributed to the interpretation of the data and the drafting of the manuscript. All the authors have given final approval for the paper to be published in Frontiers and agree to be accountable for the content presented therein.

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GENERAL COMMENTARY
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Commentary: Growth of Global Health Spending Share in Low and Middle Income Countries

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Keywords: global health, health expenditure, medical spending, low-income countries, middle-income countries

A Commentary on

Growth of Global Health Spending Share in Low and Middle Income Countries
by Jakovljevic M, Getzen TE. Front Pharmacol (2016) 7:21. doi:10.3389/fphar.2016.00021

The paper by Jakovljevic and Getzen highlighted the fact that low- and middle-income countries have been grabbing an ever larger share of global health spending over the last couple of decades (1). Share of global health spending of low- and middle-income countries as of 1995 expressed in million current PPP international $US grew from 26.1% in 1995 to 39.7% in 2013 (1). These countries are led by nations of BRICS (Brazil, Russia, India, China, and South Africa), followed by Next-11 nations (Bangladesh, Egypt, Indonesia, Iran, Mexico, Nigeria, Pakistan, the Philippines, Republic of Korea (South Korea), Turkey, and Vietnam) with a joint contribution to the global total health expenditure several times below the one of BRICS (1–5). Low- and middle-income countries, which represent an immense range of health system contexts, are likely to have more significant contribution in the global health-care market in the future as it is estimated that per-capita health spending will increase annually by 2.4, 3.0, and 3.4% in low-, lower-middle-, and upper-middle-income countries by 2040, respectively (1, 6). For high-income countries this rate is estimated at 2.7% (6).

One interesting question can be raised. What is happening with population health outcomes in low- and middle-income countries as health expenditure is increasing? The authors mentioned that "substantial gains in overall welfare are reflected in the expansion of health insurance coverage and diversity of medical services provided" (1). Some other aspects would also be valuable for discussion.

First, determining the impact of health expenditure on health outcomes is a challenging and complex issue as health outcomes are determined by a vast number of socioeconomic and environmental factors (7–9). Solely increasing public health expenditure, may not significantly affect health outcomes if its efficiency is inadequate (8, 9). It has been suggested that, on average, inefficiency of allocating health expenditures in emerging and developing economies is highest in Africa, while Western Hemisphere and Asian economies are relatively more efficient, with significant variations within the aforementioned regions (8). One systematic review has shown that private health-care system sectors in low- and middle-income countries appear to have lower efficiency compared to public sector as a result of weak regulation, higher costs of drugs, improper incentives for unnecessary testing, and treatment, but that, on the other hand, public sector tends to be less responsive to patients and susceptible to the lack of availability of supplies (10). Higher public health expenditure is generally associated with better health outcomes, but still there are substantial differences within the emerging and developing economies groups (8). The relationship between public health expenditure and health-adjusted life expectancy, as well as immunization rates, is generally found to be positive and significant, whereas it is negative and significant with mortality rates (8). For example, favorable effect of higher public

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health expenditure on mortality under 5 years is significantly larger for low- and middle-income countries (11). However, this might not be applicable to all low- and middle-income settings. In some African countries, like Nigeria, increasing public health expenditure alone, without properly addressing issue of corruption, is not enough to lead to improvement in population health status (12).

Health-care quality improvement is very important for improving population health outcomes (13). However, it has been shown that increasing health-care expenditure does not necessarily reflect increasing quality of delivered health care (14, 15). The evidence from BRICS nations confirms that sole increase in public health expenditure cannot assure better health outcomes unless the quality of delivered health care is substantially improved (9). Even in the United States, where per-capita spending on health care is estimated to be 50–200% greater than in other developed countries, this does not yield much better health outcomes compared to other OECD countries (16) and higher spending is not highly correlated with the quality of care, as price of the same service may vary and expensive new therapies may be adopted without good evidence that they improve patient outcomes (17).

In 2012, International Journal for Quality in Health Care dedicated a special issue to address status of health-care quality improvement research in low- and middle-income countries with many papers that highlighted that "much remains to be studied and understood to optimally promote quality improvement" (18). Data on quality of health-care services in low- and middle-income countries are scarce, probably due to the past emphasis on health-care coverage rather than the quality of provided care and insufficient validation of the existing quality measures (19). Quality assessment in terms of infrastructure and staffing, technical quality, and patients' experiences was not done consistently in low- and middle-income countries, thus comparing of measurements made in different settings is difficult (19). A systematic review based on limited data from comparative studies conducted in low- and middle-income countries suggested that the quality of private and public ambulatory care is similarly low in terms of infrastructure, clinical competence, and practice for both types of providers, although private sector tends to perform better in drug availability and aspects of delivery of care, such as responsiveness and effort (20).

Increasing burden of rising incidence of non-communicable diseases and accelerated population aging in low- and middle-income countries will pose a major problem for national policy makers (21–29). As Jakovljevic and Getzen pointed out, achievement of universal health coverage, types, and costs of services covered by basic insurance package will certainly remain the major imperatives for national policy makers of these countries (1). Governments will also need a comprehensive approach in order to develop and implement effective strategies to ensure adequate efficiency of forecast increase in health spending along with improving quality of care. Policy lessons from high-income countries may be useful, but they might not transfer well to all low- and middle-income countries' settings due to the key context differences regarding widespread poverty and relative weakness of political and social institutions (15). In order to develop successful approaches, countries should take into consideration their own specific circumstances after careful evaluation and prioritization of underlying problems.

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Ethical and Legal Considerations in Biometric Data Usage—Bulgarian Perspective

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Ethical and legal considerations with regards to biometric data usage are directly related to the right to protection of personal data, which is part of the rights protected under the European Convention of human rights. Specific protection is required to the process and use of sensitive data which reveals certain personal characteristic and is related to the health status of individuals. Biometric data and information on individual upon which people could be identified based on specifics and distinguishing signs. Bulgaria, as a country progressing in terms of integration of digital technologies and as a European Union member state has adopted international and universal legal instruments related on the procession and use of digital data and data protection. On legislative and ethical grounds, it has been established the particular importance of not violating human rights and individual freedoms when processing and using personal data. It has been noted that the processing of special categories of personal data may be necessary for reasons of public interest in the field of public health and that is why under such circumstances it has been permitted the procession to be carried on without the consent of the data subject. Lack of transparency and lawfulness of the processing of personal data could lead to physical, tangible, or intangible damages where processing could lead to discrimination, identity theft, or identity fraud as a result of which may be significant adverse economic or social consequences. Increasingly, widespread use of biometrics in the implementation of medical activities requires the application of a new approach in terms of awareness regarding existing risks to the rights, ethics, and freedoms of all of us, as a user of medical service.

Keywords: biometrics, data, human rights, protection, legislation

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INTRODUCTION

Human life has as its foundation the health of humans and that is the reason why health has to be effectively protected by solid actions all around the world. The prevention of health and the opportunity people to benefit from medical treatment has been recognized in legal acts as personal right. Acts recognizing such rights are the Charter of Fundamental Rights and the European Convention on Human Rights. The first act recognizes the right of access to preventive health care as well as the right to benefit from medical treatment. As part of the right to respect for private life, the European Convention on Human Rights proclaims the right to protection against collection and use of personal data.

In international legal act adopted in 1948, for the first time was recognized the right of privacy against interference from others, as in article 12 of the UN Universal Declaration of Human Rights, the right to privacy is proclaimed. The right to privacy as well as the right to health are both part of main fundamental human rights recognized in international legal instruments, such as the Universal Declaration of Human Rights, the United Nation International Covenant on Economic, Social and Cultural Rights of the United Nations, and the European Convention on Human Rights in Biomedicine.

In the treaty establishing the European Community and in numerous European Union legal, the protection of human health has been referred as an obligation, as the European union has responsibility for the health of third parties. The obligation for health protection is established under article 152 of the European Community Treaty, as in the European Community health policy, the improvement of personal health, the security, and the protection of human health has been a main focus.

An important fundamental human right with regards to biometric data usage is the right of protection with regards to the processing of personal data. Basic aspects of this right have been introduced in various international legal acts as the Charter of Fundamental Rights of the European Union (Article 8, paragraph 1), the Treaty on the Functioning of the European Union (Article 16 paragraph 1). According to legal instruments, the right to protection of personal data is a universal right, which is provided to everyone, as this protection has to comply with person's fundamental rights and freedom.

The European Convention on Human Rights in its article 8 proclaims the right to personal data protection. Through this mechanism the right to respect private life has been guaranteed, as well as the right to home and correspondence. It lays down the conditions under which restrictions of the right are permitted (1).

At European Union Level, basic legal instrument related to protection of individuals with regards to the processing of personal data is Directive 95/46/EC. This legal act, also known as Data Protection Directive,[1] refers to the free movement of personal data.

Reform of data protection issues at European Union level was put forward by the European Commission at the beginning of 2012 with regards to fit for the digital age, as the objective of all regulations in the area of personal data protection is to guarantee security. The security of the procession of personal data is an issue part of the Schengen Information System, a system supporting the law enforcement cooperation between Schengen States. Another objective which needs to be carefully observed is the determination of the conditions for date protection.

In times of digitalization, the strengthen of fundamental rights with regards to personal data is essential as this process would result to facilitation of management activities. Regulation is essential for simplifying rules for companies in the Digital Single Market internationally and on national level. In that aspect, Bulgaria does not make an exception.

[1]Data Protection Directive, OJ 1995 L 281, p. 31.

Bulgaria, as a country progressing in terms of integration of digital technologies and as a European Union member state has adopted international and universal legal instruments related on the procession and use of digital data and data protection. The country has ratified the United Nations Universal Declaration of Human Rights and has incorporated the norms of the European Convention of Human Rights into its national legislative framework.

Bulgaria has transposed into national legislative act, norms of the European Union Directive 95/46/EC and as of January 1, 2002 the state enforces Personal Data Protection Act, promulgated in the State Gazette No. 1 of January 4, 2002 (2).

Bulgarian Personal Data Protection Act defines the term "personal data" which refers to information related to individuals. Personal data are information about individual who are identified or who can be identified by specific signs. This identification could be direct or indirect by ID or it can refer to one or more than one specific signs. The legal act also includes into its scope scientific approach on biometrics, as a science of identifying people. This identification distinguishes people according to their physical characteristics and it is performed by usage of various technologies analyzing characteristics as fingerprint, palm print, retina scan, voice patterns, facial structure, etc.

With regards to fundamental rights and freedoms, used data which is particularly sensitive by its nature, needs to be under special protection in terms of processing and usage (3). Data related to the health status of individuals as well as personal data revealing ethnic origin or racial origin falls into the scope of sensitive data. The legislation pays particular attention to specific categories of personal data and when it comes to processing of sensitive data such action could be established for health purposes when specific goals needs to be achieved for the benefit of the entire society or for the benefit of private individuals.

DISCUSSION

People unique and distinctive characteristics are those used by biometric technologies, when it is needed for identification of a person and that is the reason why these characteristics are being collected for automated verification of identity. Identification is not made by the system itself, as a biometric system compared to information submitted by individuals when a claim is made (4).

There are certain qualities of human characteristics which are mandatory as they shall be universal and persistent. Universal characteristics are the ones which shall be present with all human beings. An example of universal biometric characteristic is human fingerprint. When it comes to identification, there needs to consider the fact that persons may have lost a biometrically relevant characteristic. This could be resulted through accident, sickness, or peculiar circumstances. It is also important to be considered that in some ethnic groups of the population, some human characteristics are different or even less pronounced than average. This influences the way biometric systems work and that is the reason why general systems may be never accessible universally to all persons.

Fingerprints are one of the most distinguished and unique human biometric characteristic which contains ridges and valleys. Most biometric properties are based on patterns, and in fingerprints these patterns are formed by ridge-flows which are used by the classification systems for identification. Biometric systems use sensors to collect fingerprints, but sometimes fingerprints could be latent, as it is the case when a fingerprint is left by a person on an object. In cases when fingerprints are found and collected over the surface of on object, cooperation of the data subject is not required, and in such cases biometric data could be collected without the knowledge of the data subject.

There are various circumstances when procession of personal data could be performed without the knowledge of the data subject, and it is the case when processing may be necessary in the field of public health for reasons of public interest. It is particularly important not to be violated human rights and individual freedoms when personal data are processed, and that is why treatment of personal data should be subject to appropriate and concrete measures.

From legal perspective, the term "public health" should be interpreted within the meaning of Regulation (EC) 1338/2008 in the context of the treatment of special categories of personal data. All elements related to public and personal health, including morbidity and disability, which affect the need for health care and resources devoted to it, as well as providing health care and universal access, fall within the scope of this European Union legal act.

Data processing for the health of persons on grounds of public interest must not lead to the processing of personal data for other purposes by third parties, such as employers or insurance companies and banks (5).

The principle of transparency requires that any information about the data subject to be brief, clear, understandable, and easily accessible form, using clear and unambiguous formulations, including visualization. This information may be submitted in electronic form, such as through a website when it is addressed to the public. This is particularly important in cases where information platform is a technological complexity with a large number of participants, which actually hinders the data subject, as it prevents known and understood that gather related data, by whom and for what purpose.

Children are placed under special protection and are entitled with special protection when processing of information affects them. All information and communication regarding children should be provided with clear and plain language that can be easily understood.

Several principles are in line with legal regulation data processing on European Union level, as in the Directive on the protection of personal, the principles of honest, and transparent data processing has been established as well as the principle of limited conservation of data.

The data subject has to be informed of the existence of the processing operation and information needs to be provided on the scope of the procession. This information needs to be provided to the subject by the data controller as he has to ensure good faith and transparent handling of the data. Another important aspect that needs to be taken under consideration is the specific circumstances and context in which personal data is processed.

The principle of limited conservation of data refers to the form in which personal data is kept with regards to identification of data subjects. Data should be kept no longer than necessary for the purposes for which it has been collected. This rule also applies for the further procession of personal data.

Data should be anonymized, if the administrator wants to keep them once they have become obsolete and no longer serve their original purpose. Data are anonymous if all identifiable elements are removed from one set of personal data. Elements that could serve for re-identification of individuals should not be left in the data. When data are anonymized successful, there is no longer personal data.

The right to every person with regards to protection of personal data is established in Charter of Fundamental Rights, where in paragraph 2 of article 8 is established, that data must be processed fairly for specified purposes. The procession of personal data in relation to fundamental is required to be handled on the basis of the consent of the person concerned with regards to the procession of personal data (6).

Based on the provision of article 52, paragraph 1 of the Charter of Fundamental Rights, everyone has the right to access the data related to him and this norm also provides the right to the person to whom the data refers to have it rectified. Any restriction on this right must be provided by law. Such restriction should respect the essence of the relevant fundamental right and principle of proportionality.

The processing of personal data is regulated on national basis in Bulgarian legislative framework by the adoption of Personal Data Protection Act, where in 1, item 1 of the Supplementary Provisions of this act a definition of the term "personal data processing" has been implemented. The procession itself refers to actions which are performed upon personal data. These actions are performed by automated or other means, such as collection, recording, organization, storage, adaptation, or alteration, etc. The procession of personal data could be also performed by retrieval, consultation, use, disclosure by transmission, dissemination, making available, alignment or combination, blocking, erasure, or destruction.

There is a legal possibility in certain cases fingerprints to be categorized as "sensitive data" along with information about data which relate to the health, sex life, or human genome of a person. In this hypothesis, cases falling within the scope of Article 5, paragraph 1, item 3 of the Personal Data Protection Act needs to be aligned with the prohibition of processing of sensitive data.

The provision of the Bulgarian legal act establishing restriction of the processing of sensitive personal data does not apply in some cases, such as when the procession is required for the performance of specific rights and obligations of the controller. The restrictive provision is not applicable when the individual to whom sensitive data refers, has given explicit consent to the processing of his personal data, with the exception when a special law provides otherwise.

The restriction does not apply when processing is necessary for the protection of human life and health, but referring to the individual to whom the data relates. It is also not applicable in cases when the procession of personal data is carried out by nonprofit organization of its legitimate activities with appropriate safeguards, provided that:

- the processing relates to the members of this profit organization or to persons who have regular contact with it;
- data are not disclosed to third parties without the consent of the individual to whom it relates.

When processing is carried out for the purposes of journalism, literary, or artistic expression, the restriction does not apply as long as the processing of personal data does not violate the right to privacy of the person to whom such data refers.

In cases when an individual makes public his own personal data or in cases when the processing is necessary for the establishment, exercise, or defense of legal claims, the restriction of the Bulgarian legal norm does not apply.

The restriction of the processing of sensitive personal data does not apply in cases when it is necessary for the purposes of preventive medicine or medical diagnosis, as well as in cases when providing or managing health services. The specific requirement in that case is that data is processed by a medical specialist obliged by law to observe professional secrecy.

In practical terms, a question arises, in which case it is permissible—the processing of personal data by scanning random fingerprint points. The answer to this question is directly linked to the provision of consent of the person whose personal data will be processed. To be able to do specific and informed statement, the person should be informed of the compulsory or voluntary nature of data provision and the consequences of refusing to provide them. In all cases, the person whose statement is required to provide information about the right of access and the right to correct the data, erasure or blocking of data collected, and the right to object to the processing of personal data in case of legal basis thereof.

Consent should be expressed in terms of the purpose of data processing, as after achieving the purpose of processing, personal data controller is obliged to destroy the information. Another possibility for the controller is to transfer the data to another administrator, but in that case he has to inform the Commission for Personal Data Protection in advance. The obligation for informing the Commission is set in situations when the transfer is provided by law and when there is an identity of purpose processing.

The term "individual's consent" in Bulgarian Personal Data Protection Act has been defined expression of will. The consent has to be specific and it is obligatory to be freely given. By the expression of will, the individual to whom the sensitive personal data relates, agrees upon its procession. According to §1, item 13 of the additional provisions of the Personal Data Protection Act, consent should be always available in relation to the purpose of data processing.

Personal consent refers to the compulsory or voluntary nature of data provision and the consequences of refusing to provide consent, as in all cases people should be provided with information on the right of access and right of rectification, erasure or blocking of collected data. Information has to be also provided on the right to object to the processing of their personal data if there is legal basis for this.

Information processed for health purposes particularly with regards to management services and systems for health care and social care needs to be provided additional protection. Data procession for specific purposes may be related to treatment by management bodies and central national health authorities. Sensitive data may be processed for the purposes of quality control, information management, and overall monitoring of national and local levels of the health care system or social services.

When recording or disclosure of personal data is explicitly provided by law, or in cases when providing information is impossible or involves disproportionate efforts, it is not necessary to impose an obligation to provide information to the data subject. This would be the case in particular, where the processing is done for the purpose of archiving in the public interest, for the purposes of scientific or historical research or statistics. In this context, it should be taken into account the number of data subjects, timeliness of data, and appropriate safeguards established.

CONCLUSION

Lack of transparency and lawfulness of the processing of personal data could lead to physical, tangible, or intangible damages, where processing could lead to discrimination, in identifying theft or identifying fraud as a result of which may be lead to significant adverse economic or social consequences.

Increasingly widespread use of biometrics in the implementation of medical activities requires the application of a new approach in terms of awareness regarding existing risks to the rights, ethics, and freedoms of all of us, as a user of medical service.

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JD—ethical and practical aspects on the application of biometric data usage with regards to regulatory framework. Analysis of the identification of physical characteristics in technology usage with regards to personal biometric data. Specific cases on processing sensitive data with regards to the application of Personal Data Protection Act. Anonymization of personal biometric data with regards to administration of sensitive data. MD—international legal aspect of the consideration on usage of biometric data. The Charter of Fundamental rights with regards to the establishment of the right to every person to the protection of personal data. Public Health aspect with regards to personal data revealing.

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Growth of Global Publishing Output of Health Economics in the Twenty-First Century: A Bibliographic Insight

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Background: Strong growth of interdisciplinary sciences might find exceptional example in academic health economics. We decided to observe the quantitative output in this science since the beginning of the twenty-first century.

Methods: Electronic search of the published literature was conducted in four different databases: one medical database—MEDLINE/PubMed, two general databases—Scopus/Elsevier and Web of Science (WoS), and one specialized health economic database—NHS Economic Evaluation Database (EED). The applied combination of key words was carefully chosen to cover the most commonly used terms in titles of publications dealing with conceptual areas of health economics. All bibliographic units were taken into account.

Results: Within the time horizon from January 1, 2000 to December 31, 2016, without language or limitations on bibliographic unit types, we identified an output ranging approximately from 60,345 to 88,246 records with applied search strategy in MEDLINE/PubMed, Scopus/Elsevier, and WoS. In NHS EED, we detected 14,761 records of economic evaluations of health interventions during the period in which database was maintained and regularly updated. With slightly more than one-third of the identified records, USA clearly dominates in this field. United Kingdom takes a strong second place with about 12% of identified records. Consistently, USA and UK universities are the most frequent among the top 15 affiliations/organizations of the authors of the identified records. Authors from Harvard University contributed to the largest number of the identified records.

Conclusion: There is a clear evidence of both the upward stream of blossoming in health economics publications and its acceleration. Based on this bibliographic data set, it is difficult to distinguish the actual impact growth of this output provided dominantly by academia with modest contribution by pharmaceutical/medicinal device industry and diverse national government-based agencies. Further insight into the citation track record of these individual publications could provide helpful upgrade and a perspective on ongoing development.

Keywords: health, economics, interdisciplinary, bibliography, literature, INTREPID

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INTRODUCTION

In the centuries preceding European Renaissance knowledge in medicine and many other areas tended to be rather syncretic. It represented a body of knowledge integrated into the existing religious system and a perception of life. Probably the most representative example is the Persian philosopher Avicenna's encyclopedia "The Canon of Medicine." However, since the awakening of scientific way of thinking in the fifteenth century Europe, there has been a huge blossoming of knowledge that tended to narrowly specialize.

These long-term changes in build-up and practical application of scientific knowledge underwent a huge extent of overspecialization. In such a gnostic evolution, it became obvious that certain, originally related disciplines, moved so much away from each other. They lost both mutual understanding and complementarity in real-life applications (1).

The mainstream of scientific development already had thousands of branch disciplines as we approached the twenty-first century. It became obvious that this pose a serious obstacle to further meaningful development (2). Modern day thinkers and researchers are finding it harder than ever to grasp the big picture in their areas of endeavor (3). A need for building bridges among the existing sciences emerged. In fact, it was very early embraced as the concept of interdisciplinarity (4).

With this bibliographic piece our effort was aimed at observing the quantitative scale of evidence on publishing output in one exemplary mature interdisciplinary science. We decided to observe health economics for several reasons. The first reason is that the need for interdisciplinary research was early recognized in health sciences in decades following the World War II (5). The second reason is the fact that integration between medicine and social sciences recorded bold growth during the twentieth century (6, 7). And last, but not the least, health economics itself presents a convenient example as probably one of the most developed sciences bridging this gap from a historical perspective (8).

METHODS

The methods we relied on were chosen to show rather simple crosscuts of academic publishing in the area, while adopting time horizon from January 1, 2000 to December 31, 2016. We focused on comparing quantitative outputs in health economics across four different databases. Electronic search of the published literature was conducted in one medical database—MEDLINE/PubMed, two general databases—Scopus/Elsevier and Web of Science (WoS), and one specialized health economic database—NHS Economic Evaluation Database (EED). NHS EED contains economic evaluations of health-care interventions (cost–benefit analyses, cost–utility analyses, and cost-effectiveness analyses) and was produced by the NIHR Centre for Reviews and Dissemination at the University of York, United Kingdom (9). Funding for producing NHS EED ceased at the end of March 2015, whereas electronic searches for compiling the database were continued until the end of the 2014.

Search Strategy

The search strategies for each database are presented in detail in the Data Sheet S1 in Supplementary Material. Electronic searches were conducted until July 15, 2017. The applied combination of key words was carefully chosen to cover the most commonly used terms in the titles of publications dealing with conceptual areas of health economics. We tried to ensure inclusion of the largest possible number of the publications really dealing with health economics, and on the other hand exclusion of the largest possible number of irrelevant publications. Each time we considered to include or exclude a key word we reviewed the first 100 identified records in order to evaluate whether their main topic belongs to the health economics area. Final applied combination included 88 key words combined with the Boolean search operators "OR" and "AND." This combination of key words was used across three databases (MEDLINE/PubMed, Scopus, and WoS). Appropriate operator, as instructed in each database, was used to limit finding key words only in the titles of the records. There were no restrictions regarding countries where authors' affiliations are based or language of full text publishing. All bibliographic units were taken into account (articles, reviews, books, dissertations, etc.). No filter was applied in the MEDLINE database. In the general databases (Scopus/Elsevier and WoS) filters related to medical and economics subject areas were applied as indicated in the search strategy in the Data Sheet S1 in Supplementary Material. Since NHS EED database contains only economic evaluations of health economic interventions, only publication year filter was applied and key words were not used in the search. Also, we used feature provided by Scopus/Elsevier and WoS databases to additionally analyze identified records by the fields Country/Territory and Organizations (in WoS) and Affiliations (in Scopus) of authors.

RESULTS

Results of the literature search are shown in the **Table 1** and **Figure 1**. Numbers which are presented there depict number of

TABLE 1 | Approximate quantitative output in diverse health economics areas worldwide is presented across four major indexing databases in chronological order below.

Year	Web of Science	Scopus	MEDLINE	NHS Economic Evaluation Database
2000	2,577	2,794	2,145	600
2001	2,371	2,805	2,169	585
2002	2,797	2,875	2,281	622
2003	3,240	3,356	2,501	671
2004	3,432	3,338	2,577	640
2005	3,747	3,577	2,645	725
2006	3,940	3,937	2,790	800
2007	4,419	4,291	2,773	867
2008	4,915	4,648	3,034	1,033
2009	5,471	5,058	3,250	1,023
2010	5,520	5,504	3,532	1,075
2011	6,047	5,800	3,689	1,224
2012	6,819	6,535	4,270	1,551
2013	7,411	7,081	4,671	1,956
2014	7,843	7,652	5,913	1,386
2015	8,704	7,867	6,412	3
2016	8,993	7,721	5,693	0

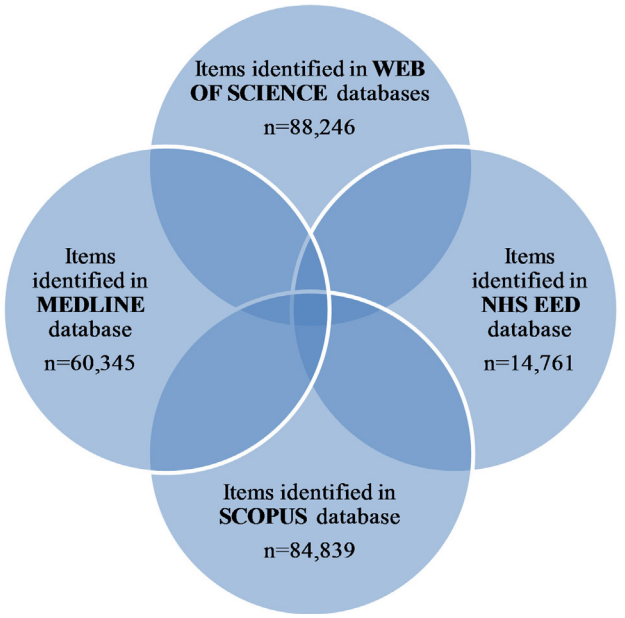

FIGURE 1 | Selection of publications.

TABLE 2 | Representation of defined countries/territories associated with identified records in Web of Science (WoS) and Scopus (the top 15 countries/territories shown).

	WoS		Scopus	
	Country/territory	Number of records (%)	Country/territory	Number of records (%)
1	USA	34,779 (39.4)	USA	29,116 (34.3)
2	England	10,581 (12.0)	United Kingdom	9,853 (11.6)
3	Canada	5,106 (5.8)	Germany	5,296 (6.2)
4	Germany	4,955 (5.6)	Canada	4,344 (5.1)
5	The Netherlands	3,808 (4.3)	Australia	3,324 (3.9)
6	France	3,410 (3.9)	The Netherlands	3,285 (3.9)
7	Australia	3,343 (3.8)	France	3,051 (3.6)
8	Spain	3,006 (3.4)	Spain	2,853 (3.4)
9	Italy	2,924 (3.3)	Italy	2,707 (3.2)
10	China	2,856 (3.2)	Switzerland	1,977 (2.3)
11	Switzerland	2,545 (2.9)	China	1,967 (2.3)
12	Sweden	1,999 (2.3)	Sweden	1,698 (2.0)
13	Belgium	1,812 (2.1)	India	1,544 (1.8)
14	Brazil	1,620 (1.8)	Belgium	1,407 (1.7)
15	Japan	1,295 (1.5)	Japan	1,380 (1.6)

identified records in the given year with applied search strategy in each database. The largest absolute number of records for 2000–2016 time span was detected in the WoS database (88,246). The smallest number of records (14,761) was detected in the NHS EED, and this number reflects only economic evaluations of health interventions (cost–benefit analyses, cost–utility analyses, and cost-effectiveness analyses), which satisfied criteria for inclusion in this database. As the electronic searches for production of NHS EED were conducted until the end of the 2014 and the database was no longer updated after the funding was stopped, number of records in 2014 and afterward may not reflect actual output of the health economic evaluations for that period. Annual number of records was similar across WoS and Scopus, whereas slightly smaller annual number of records was observed in MEDLINE. We can observe that number of records increased over the years.

Analysis of the identified records by Country/Territory field in WoS and Scopus is presented in the **Table 2**. With slightly more than one-third of the identified records, USA clearly dominates in this field. United Kingdom takes a strong second place with about 12% of identified records. Majority of other countries in the top 15 are high-income European countries (Germany, the Netherlands, France, Spain, Italy, Switzerland, Sweden, and Belgium), along with Canada, Australia, China, Brazil, Japan, and India with contribution which varies from 1.5 to 6.2% of identified records. If we expand our analysis to the top 50 countries/territories, we can observe that about one-third of them belong to the middle-income group according to the World Bank list of economies, while remaining share belongs to the high-income group (Data Sheet S2 in Supplementary Material). Consistently, USA and UK universities are the most frequent among the top 15 affiliations/organizations of the authors of the identified records with slight variations in the rank order between the two databases (**Table 3**). Among the top 15 are also one Canadian university (University of Toronto) and one Dutch university (Erasmus University Rotterdam), as well as one multinational pharmaceutical company (Pfizer Inc.). Authors from Harvard University contributed to the largest number of the identified records. List of the top 50 Affiliations/Organization of the authors of the identified records is provided in the Data Sheet S2 in Supplementary Material.

DISCUSSION

There were several serious attempts to grasp a development of academic publishing in health economics. We would like to point out two prominent examples: Rubin and Chang in 2003 (10) and Wagstaff and Culyer in 2012 (11). Both were extraordinary bibliographic research efforts. The first one concentrated on EconLit using JEL codes on time horizon 1991–2000 processing ~5,500 articles. The latter had far broader time horizon (1969–2009) and processed ~33,000 articles by relying on EconLit and JEL codes as well. However, analysis based only on EconLit database has an important limitation (10). EconLit encompasses a wide range of economics and business journals, but it does not index numerous social welfare, health-care and biomedical journals that publish a significant number of health economics articles (10). This disparity was particularly noticed in a recent bibliometric analysis of economic evaluations of health interventions by Pitt et al. (12). This analysis identified 2,844 full economic evaluations which met predefined set of criteria by searching 14 databases for articles published between January 2012 and May 2014 (12). EconLit database captured only 1% of all identified economic evaluations in this analysis (12).

Our search strategy identified an increasing number of health economics related records across the four databases. However, it should be noted that the numbers presented in the results provide only an estimate of the growth of the health economics

TABLE 3 | Representation of affiliations/organizations of the authors of the identified records in Web of Science (WoS) and Scopus (the top 15 affiliations/organizations shown).

	WoS		Scopus	
	Organization	**Number of records (%)**	**Affiliation**	**Number of records (%)**
1	Harvard University	2,125 (2.4)	Harvard Medical School	1,124 (1.3)
2	University of Toronto	1,044 (1.2)	VA Medical Center	1,077 (1.3)
3	University of Washington	1,016 (1.2)	University of Toronto	945 (1.1)
4	University of Michigan	990 (1.1)	London School of Hygiene & Tropical Medicine	787 (0.9)
5	University of California, San Francisco	903 (1.0)	Centers for Disease Control and Prevention	768 (0.9)
6	University of York	788 (0.9)	Harvard School of Public Health	765 (0.9)
7	University of Pennsylvania	717 (0.8)	University of Washington, Seattle	759 (0.9)
8	University of California, Los Angeles	701 (0.8)	University of California, San Francisco	748 (0.9)
9	Stanford University	697 (0.8)	University of York	739 (0.9)
10	Johns Hopkins University	685 (0.8)	University of Oxford	627 (0.7)
11	Duke University	681 (0.8)	Pfizer Inc.	613 (0.7)
12	Erasmus University Rotterdam	673 (0.8)	Brigham and Women's Hospital	601 (0.7)
13	University of North Carolina	650 (0.7)	University of Pennsylvania	571 (0.7)
14	Centers for Disease Control and Prevention	649 (0.7)	Erasmus University Medical Center	558 (0.7)
15	University of Oxford	613 (0.7)	King's College London	554 (0.7)

publications, as more detailed analysis of all identified records was precluded. Excluding NHS EED, search of remaining three databases relying on the combination of key words and categories (where category filter was available) carries a risk of omitting genuine health economic publications as well as including those that perhaps are not related to the field. Similar limitation was noted when relying on health JEL codes in EconLit as was the case in previous bibliographic efforts (11). The authors acknowledged that health economics publications could be missed when the author did not choose health JEL code even if the publication contains substantial amount of material on health, or irrelevant publications could be included if the article, despite having a health JEL code, contains small or negligible content on health (11).

USA was identified as the top country in health economics research, followed by the UK. Of all identified institutions, Harvard University seems to be a leader in this field. This finding is consistent with previous reviews despite differences in methodology (11, 12). However, middle-income countries are also becoming more noticeable. As pointed out by some earlier investigators, it is evident that health economics productivity is shifting its geographic outreach from mostly Western, OECD economies, toward the low and middle-income countries worldwide (13). This profound change is aligned with the global shift of health-care spending in the same direction, particularly since the beginning of the twenty-first century (14). Changes in priority of the governmental health-care investment and research funding for health economics are most visible when comparing the top emerging BRICS with G7 nations (15, 16).

In addition, this short bibliographic insight reveals one key issue. The conditions aimed at supporting social drivers of research which connects medicine and social sciences are successfully leading to the long-run outcomes. Societal imperative to increase cost-effective resource allocation in health care becomes more obvious. Heavy burden of population aging and prosperity diseases posed on contemporary societies is certainly a substantial contributing factor. Even the richest of OECD nations are facing the challenge of financial sustainability regarding health share of national GDP.

The broad area of interdisciplinary research continues to develop. In response to this, supranational authorities recognized the need to invest in its fostering. Prime example of such funding priorities is a grant funded by the European Commission—INTREPID COST action which is a network of 27 countries established with the aim to better understand how to achieve more efficient and effective interdisciplinary research in Europe (17). Similar initiatives have spread across the globe and include noticeable grants of the US federal agencies (18–21) and Japan (22). In this sense, our example with health economics should only depict the same mainstream process of bridging scientific knowledge that happens simultaneously elsewhere on a number of crossroads among diverse disciplines (23). However, there are also the opposed concerning tendencies affecting social interdisciplinary scientists who claim to be underfunded or that such proposals are significantly less likely to get funded (24). These and similar trends should raise attention of policy makers against such rooted practice in many funding agencies (25). Broad societal perspective on gains and losses from narrow and deep overspecialization of research could only be provided by strong interdisciplinary development (26).

CONCLUSION

We may conclude that there is a clear evidence of rise in global quantitative output of academic publishing in interdisciplinary science of health economics. Each of the large databases grasps another angle of this research proliferation. MEDLINE is leaning toward applications in clinical medicine. Scopus and WoS are somewhere in between, catching slightly different cross-sections of both economics and medicine. NHS EED is probably the most precisely matching academic research growth in health economics, although with the risk of omitting borderline materials published elsewhere, outside of reach of this registry. However, in all four registries we have evidence of bold rise in research

output. This example might serve as a promising one for further interdisciplinary development in other areas (27).

AUTHOR CONTRIBUTIONS

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

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://journal.frontiersin.org/article/10.3389/fpubh.2017.00211/full#supplementary-material.

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