GLOBAL HEALTH AND PHARMACOLOGY

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GLOBAL HEALTH AND PHARMACOLOGY

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EDITORIAL
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Editorial: Global Health and Pharmacology

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Editorial on the Research Topic

Global Health and Pharmacology

TROUBLING ACCESS

Across the many issues pertaining to pharmaceuticals worldwide, 'access' is a common denominator and a critical facet of what makes pharmaceuticals life changing, heartbreaking, deeply problematic, dangerous, complex, and successful. As such, in this issue, we seek to critically appraise what constitutes access in the arena of global pharmaceuticals. Over the last few decades, for example, human rights campaigns have pushed for access globally to affordable antiretrovirals and for the development of drugs for neglected diseases. Both of these in different ways made visible the increasingly key role of pharmaceuticals in defining our lives and what constitutes health; the difficulties of achieving equitable geopolitical governance of pharmaceutical development and distribution; and the differential valuation of human lives made evident by the presence or absence of essential medicines and vaccines. While access usually is invoked as a positive, however, it also carries its own risks. Access to too many pharmaceuticals because of pharmaceutical industry efforts to significantly expand markets for old and new pharmaceuticals is the example most often noted in the media and scholarship. But other kinds of problematic access also need further interrogation, such as access to the wrong kinds of pharmaceuticals including counterfeit, contaminated, or substandard; the predominance of biomedical over so-called alternative medicines; and the highly controversial means, such as bioprospecting, that sometimes characterize the discovery, development, and control of new drugs. All of these and other facets of access can wreak serious havoc with public and personal health, economies and ecologies, global economic and political relations, productions of knowledge, and regulatory systems.

The COVID-19 pandemic brought with it its own set of access issues, some a consequence of the urgency that pandemics mobilize, some unique to the disease, and others, accentuations of longer standing issues. In the early days of covid for example there were highly politicized discussions over the efficacy, or not, of potential treatments for covid such as the malaria medication hydroxychloroquine. On the one hand the then-US President Trump touted the role of hydroxychloroquine in curing his own case of covid, while scientists and public health officials decried Trump's advocacy for a drug that did not have rigorous evidence from clinical trials affirming its success in treating SARS-CoV-2. As the Brookings Institute aptly pointed out in a subsequent report, the collective responses to hydroxychloroquine not only exemplified the challenges of how various publics weigh health risks versus action in times of fear and uncertainty; it also made clear that under situations of crisis the very definitions of 'adequate evidence' and 'science' become unsettled. As the authors summarize, "While the hydroxychloroquine story is sometimes viewed as a battle between legitimate scientific information vs. dangerous misinformation, this fails to consider debates within medicine about when new evidence reaches the level of 'actionability'" (Khorana and Owens 2020). Such decisions over safety and efficacy of vaccines or drugs versus urgency in the face

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of high morbidity and mortality have been seen with other epidemics as well, including HIV/AIDS treatment activist's calls in the early 1990s for using "surrogate markers" of treatment efficacy rather than mortality data to get drugs developed and approved more quickly (Epstein, 1997), or more recently, a rapidly developed vaccine for Ebola.

As the world watched covid spread from China to the EU to the US, the inextricable interrelations of medical treatments, global supply chains, and the strength of health care and public health systems became more glaringly obvious. As skyrocketing cases of covid overwhelmed one health system after another in high-income countries proud of their state-of-the-art facilities, the underlying fragility of such systems in the face of machine, technology, and ingredient shortages became all too apparent. Though ventilators, PPE, and oxygen are not technically pharmaceuticals, they play parallel roles in being ensconced within health care systems, keeping people alive, and highlighting the broader array of facets beyond patents and prices involved in making available critically important tools. In the case of ventilators, it laid bare the inequities across hospital facilities in affording expensive equipment for their patients, and the too-frequent reality that where you live determines whether you get to live. In the case of both ventilators and PPE, it evidenced the role of governments in incentivizing manufacture of needed equipment, such as the US's Defense Production Act signed by Trump to galvanize production of PPE by the military (Soucheray, 2020) and by companies like General Motors. It attested as well to the flexibility of global companies in adapting their commodities to pandemic need. Yet, the ugly underbelly of global capitalism also came to the forefront as some of these same companies profited handsomely from emergency sale of medical equipment while paying their workers suboptimal wages and failing to provide them with any of the PPE they were manufacturing and exporting. As they helped save lives in other parts of the world with their protective equipment, they put the lives of thousands of their own workers at higher risk (Beech, 2020).

The role of intellectual property regimes during Covid also, not surprisingly, came to the forefront as attention turned toward pharmaceutical technologies with the potential to staunch exploding caseloads across wide swaths of the globe. On the one hand there were many positive examples of activism towards greater biomedical collaboration in the face of pandemic. Scientists and scientific journals started keeping channels of knowledge sharing open; a longstanding student organization, Universities Allied for Essential Medicines (UAEM), created an online dashboard tracking funding levels of institutions and countries for pharmaceutical R&D (Myhr, 2020); and calls were issued from multiple agencies including the Medicines Patent Pool and Unitaid for creating or expanding patent pools to expedite research and development of potential treatments, medical equipment, and diagnostics (Thievenaz, 2020; 't Hoen, 2020). Yet calls for changes in the way pharmaceutical development and distribution happen were met with pushback at the corporate, national, and transnational levels. South Africa's call for a waiver for some provisions of the TRIPS Agreement in the midst of Covid, for example, was opposed by most higher income countries including those with robust pharmaceutical industries. Those joining South Africa were almost entirely low-income countries, signaling a geopolitical division all too often seen in questions of pharmaceutical access, and a division that remains curiously under-scrutinized (Balasubramaniam, 2020). Pharmaceutical and biotech companies also reacted variably to the calls for knowledge sharing. As Ellen 't Hoen of the Medicines, Law, and Policy organization notes, Abbvie waived patent rights to one of their candidate drugs for treating Covid (2020) while also joining public-private partnerships like ACTIV - a collaboration of the NIH, regulatory agencies, the CDC, academics, philanthropies, and biopharmaceutical companies—in order to expedite development of Covid treatments and vaccines (nih.gov). Gilead, on the other hand, convinced the FDA to ascribe Orphan Drug status for remdesivir in a move to strengthen their proprietary rights over the only antiviral medication proven to shorten recovery times for those hospitalized with Covid and approved by the FDA ('t Hoen 2020; NIH 2020). Only following a huge outcry did Gilead remove remdesivir from orphan drug status ('t Hoen 2020).

Vaccines have been the latest battle ground for issues of equity in pharmaceutical access under Covid, the pandemic bringing renewed urgency to an old and persistent issue. Despite attempts early on to create tools for addressing the highly unequal distribution of vaccines, low-income countries have once again been relegated to the back of the line. In the absence of progress in TRIPS waivers or new policies, the Global Vaccine Alliance (GAVI), the Coalition for Epidemic Preparedness Innovations (CEPI) and the WHO came up with COVAX, a voluntary mechanism for pooling available vaccine doses and subsequently serving as the common market through which countries could purchase doses for their populations. Though many countries bought in to COVAX, those that could (i.e., the US, EU, and United Kingdom) also prepurchased the vast majority of Covid vaccines while they were still in the pipeline. As has happened before, national responsibilities quickly eviscerated any moral obligation towards equitable global rollout, despite the logic that geographic hoarding will only delay the end of the pandemic. In other words, whether in 2009 H1N1 flu or COVID, the US and other high income countries first took care of their own populations before donating leftover doses of vaccine to lower income countries (Enserink 2009; Craddock and Giles-Vernick 2010). Renewed calls for requiring patent waivers have gained some traction, even seeing President Biden get on board with the idea; yet as others have noted (Schellekens 2021), removing patents will not fix the problem when chronically underfunded public health infrastructures, inadequate health personnel, inability to sustain cold chain storage in the face of frequent electricity failures, and other issues translate into huge challenges in getting vaccines into bodies even if they got into more countries.

The call we put out for this Research Topic predated the pandemic, and therefore our contributors do not specifically address the many facets of global pharmacology galvanized by SARS-CoV-2. Yet as is evidenced by the papers we received, Covid-19 has highlighted many issues in pharmaceutical

research, development, marketing, and distribution that are not new, but whose possibilities, deficits, and constraints are newly spotlighted in the midst of urgency. Our collection reminds us that we need to valorize those aspects that are working in our public health and health systems, while heeding those facets that remain problematic even when our heightened awareness fades post-pandemic.

In our call for papers, we solicited scholarship on facets of access that are new and underexplored, as well as scholarship that revisits issues, such as access to ARVs, that have largely faded from our collective attention even while still all too trenchant in many parts of the world. We also encouraged empirical studies focused on particular regions, as well as more theoretical and conceptual treatments of past, present, or future interventions in the relationship between pharmaceuticals and global health. We encouraged an array of disciplinary perspectives across the sciences, social sciences, and humanities, as well as multi- or transdisciplinary scholarship. Our goal with this volume was to trouble the very concept of access, raising critical questions about the processes through which access assumes meaning, is circumscribed, contested, and politicized; for whom, under what conditions, and for what purpose. Our goal was to offer insights into past and current global health interventions while also raising possibilities for future policy changes in the ongoing crises of pharmaceutical access. What we got was a rich array of articles examining pharmaceutical access along three broad thematics: multidimensional facets of consumption; the relations between policies and access; and relations between health care systems and access.

FACETS OF CONSUMPTION AND 'DRUGS INTO BODIES'

The first category recognizes that access extends beyond the existence or availability of drugs and into areas of how and whether drugs get into relevant bodies. Consumption politics and practices matter to policy analysts and government health officials tasked not just with whether particular pharmaceuticals are available in their respective countries, but what factors determine how and whether individuals are able or willing to consume them. As the articles in this section attest, these factors have a wide range encompassing the media, practitioner expertise, increasing contentions over the pharmaceuticalization of health (cf Biehl 2007), drug use guidelines and oversight, and disease awareness and understanding.

Mekuria and othercolleagues look at self-medicating practices among college students in Amhara, Ethiopia. What they find is that 68% of the students they surveyed practice self-medication, and that pharmacies were the most common places where they obtained medication. Though the pharmaceuticals used without expert guidance were for minor ailments such as headaches, the authors point out the dangers involved in the practice of self-medicating overall—the potential for adverse reactions, drug resistance, treatment failure, drug dependence, and waste of resources prime among them. Though the article did not go into policy recommendations, it seems clear that pharmacists might be targeted for training individuals in how and when to use pharmaceuticals obtained from their pharmacies.

Tousignant's ethnography of hepatitis B virus (HBV) infection and care in Senegal reveals a reversal of the typical lack of drugs in a low-resource setting to treat high burdens of disease. Instead, Tousignant uncovers complex interplays between low levels of knowledge of HBV even among many practitioners, inadequate screening of the virus, and high cost and urban concentration of diagnostic technologies - all in the midst of general availability of tenofovir to treat against potential development of liver cancer. Tousignant's fascinating analysis troubles low consumption of an effective and accessible drug by questioning, *inter alia*, the many reasons behind HBV's relative invisibility even when most public health officials estimate high burdens of infection. The politics of international funding that not only target specific diseases rather than broader facets of public health, and that have for some time now privileged HIV/AIDS, is part of her answer.

Ortega and Müller article on ADHD in Brazil remind us that pharmaceuticals play a differently controversial role in many mental health issues including ADHD—namely, that ADHD is debated at both a global and national level as to whether it is a diagnosable illness best managed through pharmaceutical treatment, or a social-cultural construction. The former contingency, including the Global Mental Health movement, claims that a treatment gap exists in low- and middle-income countries (LMICs) which needs addressing, while the latter contingency claims that this position aids the expansion of the pharmaceutical industry unnecessarily while ignoring differences in interpretation of what constitutes acceptable ranges of behavior. They argue, too, that the literature on this topic has not taken into account the many variations across national settings that themselves encompass both camps and the tensions thereof. Brazil is no exception, and Ortega and Müller provide a meticulous examination of the powerful sway of psychiatry and the argument for treating ADHD on the one hand, and the activism of many who stridently oppose the medicalization of childhood and the imposition of western-centric biomedical models of behavior. Consumption of pharmaceuticals prescribed for ADHD, then, becomes a political stance as well as a contested method of behavioral engineering.

RELATIONS BETWEEN POLICY AND ACCESS

Exorbitant prices for drugs in the US have become increasingly visible and controversial over the last 2 decades or more. Patents, too, came into the spotlight more than twenty years ago for their critical role in keeping prices high and consequently denying essential medicines to those without the means, government subsidies, or insurance to afford them. Antiretrovirals entering the market, but out of reach for the vast majority of those living with AIDS, catapulted access to medicines into a global movement and a human rights issue. But high prices and patents are not the only facets shaping access to medicines,

diagnostics, and vaccines around the world. Various policies from a multitude of sources can also play vital roles in shaping who is able to obtain life-saving or life-improving pharmaceuticals, and who is not; and whether the access constraints are from high prices, or from other deterrents. As the articles in this section demonstrate, these policies are emanating from governments, global organizations, and pharmaceutical companies themselves, and each contribution attests to the importance of discerning the mechanisms through which parameters of access are determined, what the supporting architectures of those mechanisms are, and who is included vs. excluded.

With his case study of Novartis's Zolgensma, Sergio Sismondo extends important scholarship on the ways in which pharmaceutical companies navigate a balancing act between sky high new drug prices, public condemnation, and accessibility around the globe. At $2 million for a one-time gene therapy treatment for spinal muscular atrophy, it would seem that Novartis arrived at a price no one could afford. Sismondo walks readers through the entangled landscape of insurance structures, the global health access to medicines movement, corporate social responsibility schemes, and the WHO's statement on the rights of citizens everywhere to essential medicines and the ethical impetus on pharmaceutical companies to ensure that. One of the critical moves Sismondo makes in this piece is to not take at face value the existence of global movements or WHO essential medicines lists, but rather to uncover how and why these entities come into being and gain traction if not institutional normalization. And as they do gain traction, pharmaceutical companies like Novartis become adept at outmaneuvering their reach through a combination of language appropriation and public relations policies. In Sismondo's hands, policies, guidelines, and movements form a highly dynamic and constantly shifting terrain where pharmaceutical companies, not publics, are the winner.

In her article on changing pharmaceutical governance in China, Li elucidates the multiple facets constituting access to medicines, from availability, accessibility, appropriateness, and affordability, while also questioning the contradiction and relations of these facets as they reside uneasily within national health policies. As she suggests, few scholars have historicized and deconstructed how and why particular countries shift their policies over time to focus on one facet or another within the access to medicines arena. More specifically, Li argues that not only are these various dimensions often in tension with each other, but the reasons for a country to shift prioritization of one over another facet can involve social, economic, political, or other contexts. Taking China as her case example, Li proceeds to incorporate macro-level (political economies of pharmaceutical and health sectors) and micro-level (organizational, cultural, and community) analyses of why the Chinese government shifted focus from availability, to affordability, or both, across multiple decades beginning in 1949 with Mao's ascension to power. In those earlier days drugs were affordable, yet they were scarce given levels of economic disruption from war and poverty. Availability of drugs was thus the focus through the 1970s, with various government initiatives geared toward expanding pharmaceutical industry capacity while simultaneously strengthening health sector efficiency. With economic liberalization and the collapse of centralized payment schemes in the 1980s came greater availability yet lower affordability for drugs, mobilizing new efforts to drive down prices through various policies from establishing an essential medicines list to creating procurement schemes. In the last 6 years, China has struggled towards a balance between both affordability and availability as it faces continued high prices, shifting demands for greater coverage of cancer and chronic diseases, and a need for greater innovation within the pharmaceutical industry.

Atuk turns toward a specific pharmaceutical company, Gilead, and one of their particular drugs, Truvada (known as PrEP), to provide an exploration of pathopolitics as it is playing out with gay populations in the US in the age of HIV/AIDS. As Atuk explains it, pathopolitics is biopolitics as practiced by pharmaceutical companies that address certain pathologies while simultaneously producing new ones. More specifically, pharma's relentless quest to find new markets for drugs means creating new categories of risk, which in turn demand pharmaceutical investment. This capitalization of bodies, as Atuk argues, keeps pharmaceutical companies healthy while pathologizing those bodies and populations as perpetually at risk—in Atuk's case, of HIV/AIDS. So, antiretrovirals for treating AIDS are no longer sufficient; Truvada has come to stand as a requisite supplement for gay men constantly at risk of, but wanting to avoid, HIV. And yet, significant populations of gay men are left out of this chance at warding off HIV because of Truvada's price tag. That results in more literal pathologies as those hundreds of thousands most at risk of HIV in the US, namely gay men of color and transgender women, are the least able to afford Truvada and thus acquire HIV through lack of 'PrEParation.' Atuk subsequently traces the paths of pharmaceutical violence against these marginalized populations, invoking Rob Nixon's concept of slow violence (Nixon, 2011) in elucidating those declines and death that are neither spectacular nor particularly visible, but that are nonetheless violent because they are preventable, and occur through the exacting calculations of profitability. The bottom line, as Atuk argues, is that "human life is protected only insomuch as it promises financial returns."

Cappello et al. examine the history and contemporary implications of the 'square box' concept used in the World Health Organization's Model List of Essential Medicines. The square box, which was first introduced in 1983 (5 years after the first Model List was introduced) designates a representative medicine in a group of equivalent and interchangeable medicines. It is intended "to highlight pharmacological classes or groups of medicines for which countries, institutions, and health professionals can assume homogenous therapeutic efficacy and safety and select the most appropriate single medicine based on price, local availability, and acceptability." (p. 1). Collectively, the Model List and square box concept are intended as a mechanism for increasing access to essential medicines. However, as Cappello et al. note, many countries find it difficult to navigate the utility of the Model List including how to make best decisions concerning their national pharmaceutical needs and budget, versus what is listed within the Model List. These authors then don't just critique the square box concept but

seek to clarify both the interpretations and the practical applications of the Model List so that countries may better arrive at appropriate pharmaceuticals for their national needs. They pay particular attention to the distinctive problems presented by biologic medicines, which tend to come with very high price tags and for which generic equivalents do not exist. Instead, there are biosimilar medicines, which as their name implies are highly similar to the original biologic medicines and which are approved by regulatory agencies to be manufactured when the original patent product expires. Biosimilars are neither identical nor bioequivalent to the original innovator product, which in turn raises another set of questions about whether and how to apply the square box concept to biologic essential medicines. In addressing these questions, Capello and others make clear the promise but also the limitations of any one-fits-all tool for navigating such a complicated arena.

Shahriar and Alpern problematize the effects—intended and otherwise—that the Food and Drug Administration's policies have had on prescription drug prices in the U.S. by analyzing the pricing story of two antiparasitic essential drugs. The antiparastic drug market is an example of a relatively low-volume drug market which, the authors argue, can "become incubators for opportunistic manufacturer behavior." In their first example, albendazole, which has been marketed outside the US since 1982 and was FDA approved in 1996, Shahriar and Alpern document the pharmaceutical industry practice of instituting price-hikes on old, off patent essential drugs. In this case, a series of corporate acquisitions of albendazole's manufacturers led to delayed entry of generic albendazole and enabled monopoly-like conditions on the drug which allowed sequential and significant price-hikes. Shahriar and Alpern suggest, however, that the FDA's policy, since 2017, to incentivize generic entry in non-competitive markets finally led generic manufacturers to enter the market in September 2018. However, a significant reduction in average wholesale price for albendazole—anticipated when generic competitors enter the market - is yet to materialize. The author's second example, in contrast, problematizes a different FDA policy. The tropical disease priority review voucher program, introduced by the FDA in 2007, was intended to incentivize research and development for neglected tropical disease drugs. But as Shahriar and Alpern show using the example of miltefosine, rather than lead to the development of new and innovative drugs, the voucher program instead helped drug firms bring already-existent drugs to the U.S. market and to make profits from them, rather than using the voucher to prioritize new, and very much needed, drugs. In addition to raising the alarm about the unintended pricing effects of FDA policies, Shahriar and Alpern also offer recommendations for closing the loopholes and limitations of those policies.

Suh examines the contested role of misoprostol as an essential reproductive health medicine in sub-Saharan Africa, a region with some of the highest rates of maternal mortality and fertility in the world. Misoprostol is safe and effective as an off-label treatment for post-partum hemorrhage, post-abortion care, and the provision of first trimester pregnancy termination. However, its potential as an abortifacient complicates misoprostol's status as an essential obstetric medicine. In her essay, Suh analyzes the ways in which the WHO, national and international NGOs, funding organizations like the USAID, and philanthropic agencies have negotiated misoprostol's abortifacient qualities and integrated misoprostol into reproductive health policy and practice. She does so in the context of the region's restrictive abortion laws, institutionalized abortion stigma, the anti-abortion policies that govern USAID's work, the imperatives to pharmaceuticalize global health, and the long history of (neo) colonial population governance in sub-Saharan Africa, making clear that having a drug listed as an essential medicine is not sufficient to guarantee access. Although community-based health workers, including traditional birth attendants, can safely administer misoprostol, the continued privileging of neoliberal health reform, Suh argues, significantly undermines access to misoprostol. Indeed, the privatized distribution of misoprostol in health facilities and pharmacies reinforces the marginalization of community-based health workers upon whom low-income and rural women often depend for maternal and reproductive health care. Suh's analysis thus highlights the influence of the region's complex transnational politics on shaping how and where misoprostol is available and used (or not), and by whom. In doing so, Suh makes clear both the benefits and limits of pharmaceuticalizing reproductive health, not least the inability to secure reproductive justice for low-income and rural women seeking access to safe and effective reproductive care in SSA.

RELATIONS BETWEEN HEALTH CARE SYSTEMS AND ACCESS

The third category recognizes that the ways in which governments organize, fund, manage, and deliver care within a health system has a determinative impact on individual and community access to pharmaceuticals. Whether governments finance, manage, and deliver care through centralized national health systems or utilize a mix of public and private sector financing and provision, different types of health systems and the political economies that underpin them lead to different opportunities for, and barriers to, access. Publicly financed provision of pharmaceuticals, for example, is rarely sufficient to guarantee access to pharmaceuticals; there also need to be enough health care facilities and workers with prescriptive authority to provide and ensure proper consumption of pharmaceuticals in the communities that need them. In health systems that rely on private health provision, individuals may face prohibitively high out of pocket expenditures for prescription drugs because they are either uninsured or their insurance does not provide adequate coverage for the drugs they need. In such cases, individuals may either forego filling their prescriptions or ration their use of life-saving medicines, which in turn can result in preventable deaths and unnecessary morbidity. In 2015 and reaffirmed again in 2019, nations that signed onto the United Nation's Sustainable Development Goals made the achievement of universal health coverage, including "access to safe, effective, quality and affordable essential medicines and vaccines for all," a target of those SDG goals.[1] But as countries work toward achieving universal health coverage, there is no

[1]https://www.un.org/sustainabledevelopment/health/

consensus on how best to organize, fund, and manage health systems to meet that goal. The next set of authors interrogate the complex relationship between health systems and pharmaceutical access, considering different approaches for achieving universal health coverage for medicines, as well as different systems of pharmaceutical research and development, and the complexities and access barriers that emerge from those systems.

As Garcia et al. discuss in their essay, although Brazil's public health system is premised on achieving universal health coverage for medicines, access to medicines remains a significant problem. For example, despite increased public funding for the provision of medicines, in 2014, there was no more than 62% availability of medicines in Brazil's public healthcare system. As the authors note, the lack of access to medicine can induce increased costs elsewhere in the healthcare system, as untreated diseases lead to increased ambulatory care and hospitalization expenses. Governments, of course, have available to them different options for implementing the public provision of medicines. For example, they can pursue a strictly state-operated approach in which the public infrastructure of health care is used to finance and promote access to medicines. Or they can utilize public sector-private sector collaborative approach. In their article, Garcia et al. share the result of their economic analysis in which they compare the costs and access implications of two different approaches to funding and providing universal health coverage of medicines. The first model is representative of the current system in Brazil whereby the payment and logistic provision of medicines occurs entirely within the public healthcare system. The second model is that of a public-private sector collaboration in which private community pharmacies are accredited to dispense publicly-funded medicines. Both models retained the concept currently operational within Brazil's NHS whereby there are no limits on medicines expenditures among families. Based on the results of their economic analysis, Garcia et al. propose an optimal private sector-public sector collaboration in which Brazilian citizens are referred to public health service centers in their neighborhood, where they receive medical care, prescriptions, and the authorization to obtain medicines in a private pharmacy of the citizen's choice. Garcia et al. argue that this public-private collaboration "looks to be the key to achieve universal health coverage for medicines reducing avoidable hospitalization and mortality as well as inequalities among families concerning household expenses." (p. 16).

In their article, Al-Hanawi et al. also explore the relationship between the public sector and private sector in government efforts to achieve universal health coverage. Focusing on the Kingdom of Saudi Arabia, Al-Hanawi et al. examine whether health insurance is an effective option for governments with public healthcare systems seeking to reduce out-of-pocket expenditures for health care as a potential way to increase the health and wellbeing of the country's citizens through better access to medical care. As a high-income country with a mixed political economy of healthcare provision, the Kingdom of Saudi Arabia provides a compelling case study for addressing this question. Specifically, the Kingdom of Saudi Arabia provides free public healthcare to all public employees and to Saudi citizens. But Saudis who work in the private sector are required by law to receive employer-financed private health insurance. Using data from the 2018 Saudi Family Health Survey, the authors perform an econometric analysis to examine how health insurance relates to out-of-pocket expenditures on health and medicines along different levels of income. Their analysis shows that at low levels of income health insurance reduces out-of-pocket expenditures. They thus argue that "if the objective of policy is to cushion the relatively poor, then health insurance is a key." (p. 8). However, as income levels rise, so too does the impact on out-of-pocket expenditures. Their findings also suggest that health insurance contributes to inequalities in both the quality of and access to healthcare. As such, Al-Hanawi et al. argue, policymakers in countries with public healthcare systems who are considering using health insurance as a means of insuring sustainability of healthcare financing while pursuing universal health coverage, need to consider "the possible welfare distribution impacts of upscaling or downscaling the coverage of insurance amongst the populations," (pp. 1–2) as they pursue the goal of universal health coverage.

In his essay, Light calls for us to rethink the entire system of healthcare and pharmaceutical development. In the current market-driven system, "controlling disease through costly interventions creates or increases health disparities, as people with more knowledge, money, and beneficial social connections have greater access and ability to harness medical advances and treatment than those with less." (p. 1). But as Light argues, the paradox of creating or increasing health disparities is not an inevitable outcome of controlling disease but rather the product of a neoliberal, market-based, inegalitarian society. Instead of leaving the research, development, and marketing of new pharmaceuticals and vaccines in the hands of private pharmaceutical companies, Light makes the case for non-profit health care and pharmaceutical development as a means of ameliorating health disparities. Light puts forth an alternative model, a "radical proposal" as he calls it, in which a virtual, non-profit, multi-stakeholder collaborative is responsible for researching, developing, testing, and manufacturing new, innovative, and affordable drugs that prioritizes treating those who are most disadvantaged and most ill. Light uses the Drugs for Neglected Diseases initiative (DNDi), particularly the DNDi's success developing highly effective, low-cost drugs to eradicate Hepatitis C and creating markets to maximize public health rather than profits, as an example of his proposal in action. At the center of Light's proposal (and the DNDi model) is the development of patent rights for public health, whereby patent and licensing powers are used to guarantee low prices and broad access at low profits.

As with any Research Topic covering almost limitless terrain, there are broad areas we were not able to cover. Among those specifically mentioned in our call for papers, we did not get articles covering the spectrum of pharmacology and indigenous systems of therapeutic knowledge; political economies and ecologies of sourcing and supplying pharmaceutical ingredients; the widespread problem of counterfeit and substandard drug trades; use of and impacts upon lab animals

in the early testing of new drugs; the various means through which therapeutics are produced, paid for, sourced, and distributed; the growing field of alternative therapies and the politics of their regulation; or extended analyses of what Susan Reynolds-Whyte and others called 'the social life of drugs' (Whyte et al., 2006) - that is, the shift in relations among family members and communities resulting from having or lacking access to drugs.

The list could go on. And in part, this itself is evidence of the preeminent role pharmaceuticals play in our social, medical, political, financial, and quotidian lives. As such, this collection has from the beginning consciously limited our scrutiny to the importance of pharmaceuticals and the entangled terrains they create and occupy. It is worth noting, however, that equal attention needs to remain on what João Biehl has called 'the pharmaceuticalization of health,' that is, the over-reliance on pharmaceuticals in national healthcare systems, a practice that rests upon a dominant narrative of biotechnological capabilities and efficiencies in solving most health problems. We hope that in addition to this issue on pharmacology and global health, there will be future issues that interrogate what privileging pharmaceutical production and distribution does: what alternatives it might displace, or more salubrious futures might be possible with equal emphasis on other interventions. As COVID-19 has made so painfully clear, it is longstanding national or international inequities in wages, education, housing, nutrition, clean air and water, and other structural issues that determine health or its absence. The changes in government policies and global economic systems thus necessary to make more meaningful and lasting improvements in health have, so far, gained little traction. Rolling out COVID vaccines, though certainly life-saving and cause for celebration, will be equally effective in redirecting our collective attention away from the even more challenging social, systemic, economic, and political reconfiguring that is too long overdue. It will have to suffice at this point to acknowledge that we believe in the necessity of these broader changes and the ameliorative effects they could have on millions of lives, and to argue for further examination of those changes that are happening on smaller scales all over the world.

In the meantime, what our contributors have provided are incisive analyses of trenchant issues in the capacious arena of pharmaceutical access. Their optics have spanned theoretical frameworks, time periods, and geographies; and perhaps best of all, they have all raised at least as many questions as they have addressed, giving all of us more to think about and, hopefully, to share more insights in the future.

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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ORIGINAL RESEARCH
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Funding and Service Organization to Achieve Universal Health Coverage for Medicines: An Economic Evaluation of the Best Investment and Service Organization for the Brazilian Scenario.

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Background: There are many health benefits since 31 years after the foundation of the National Health Service (NHS) in Brazil, especially the increase in life expectancy. However, family-income inequalities, insufficient funding, and suboptimal private sector–public sector collaboration are still areas for improvement. The efforts of Brazil to achieve universal health coverage (UHC) for medicines have resulted in increased public financing of medicines and their availability, reducing avoidable hospitalization and mortality. However, lack of access to medicines still remains. Due to historical reasons, pharmaceutical service organization in developing countries may have important differences from high-income countries. In some cases, developing countries finance and promote medicine access by using the public infrastructure of health care/medical units as dispensing sites and cover all costs of medicines dispensed. In contrast, many high-income countries use private community pharmacies and cover the costs of medicines dispensed plus a fee, which includes all logistic costs. In this study, we will undertake an economic evaluation to understand the funding needs of the Brazilian NHS to reduce inequalities in access to medicines through adopting a pharmaceutical service organization similar to that seen in many high-income countries with hiring/accrediting private pharmacies.

Methods: We performed an economic evaluation of a model to provide access to medicines within public funds based on a decision tree model with two alternative scenarios public pharmacies (NHS, state-owned facilities) *versus* private pharmacies

(NHS, agreements). The analysis assumed the perspective of the NHS. We identified the types of resources consumed, the amount, and costs in both scenarios. We also performed a budget impact forecast to estimate the incremental funding required to reduce inequalities in access to essential medicines in Brazil.

Findings: The model without rebates for medicines estimated an incremental cost of US $3.1 billion in purchasing power parity (PPP) but with an increase in the average availability of medicines from 65% to 90% for citizens across the country irrespective of family income. This amount places the NHS in a very good position to negotiate extensive rebates without the need for external reference pricing for government purchases. Forecast scenarios above 35% rebates place the alternative of hiring private pharmacies as dominant. Higher rebate rates are feasible and may lead to savings of more than US$1.3 billion per year (30%). The impact of incremental funding is related to medicine access improvement of 25% in the second year when paying by dispensing fee. The estimate of the incremental budget in five years would be US$4.8 billion PPP. We have yet to explore the potential reduction in hospital and outpatient costs, as well as in lawsuits, with increased availability with the yearly expenses for these at US$9 billion and US$1.4 billion PPP respectively in 2017.

Interpretation: The results of the economic evaluation demonstrate potential savings for the NHS and society. Achieving UHC for medicines reduces household expenses with health costs, health litigation, outpatient care, hospitalization, and mortality. An optimal private sector–public sector collaboration model with private community pharmacy accreditation is economically dominant with a feasible medicine price negotiation. The results show the potential to improve access to medicines by 25% for all income classes. This is most beneficial to the poorest families, whose medicines account for 76% of their total health expenses, with potential savings of lives and public resources.

Keywords: pharmacoecomomics, medicines policy, access to medicines, health inequalities, Universal Health Coverage (UHC), pharmacy funding models, Brazil

INTRODUCTION

Promoting access to cost-effective, safe, and quality medicines is a priority of public health policies (WHO, 2004). Medicines are consumer goods as well as essential products for health with a key position in economies and in health services. Medicine costs can have a strong and progressive burden on families as a consequence of the increasing costs of available treatments including, for example, cancer medicines in the United States and other essential medicines in developing countries where the cost of medicines can account for 60% or more of total healthcare expenditures (Cameron et al., 2009; Tefferi et al., 2015). Longer life expectancy as a result of new medicines, a higher prevalence of chronic diseases, and typically higher prices for new medicines especially those for cancer and orphan diseases, all contribute to increases in pharmaceutical expenditures in recent years (Howard et al., 2015; Luiza et al., 2016; OECD, 2017; Godman et al., 2018; Luzzatto et al., 2018). The higher prevalence of particularly chronic diseases puts pressure on public budgets to enhance access to medicines, including all essential medicines, exposing the weaknesses of how developing countries, like Brazil, fund and organize their services to distribute prescribed medicines to their citizens (MSH, 2012).

Many high-income countries have promoted health care as a right as part of their efforts to achieve universal health coverage (UHC) for medicines (WHO, 2004). The strategies adopted by high-income countries to fund and organize pharmaceutical services can differ from developing countries. Having said this, there is no universal access to healthcare for all in the US *versus* for instance Western European countries despite the US spending substantially more on health care as a percentage of gross domestic product (GDP) (OECD, 2017). Despite efforts across countries, access to medicines presents challenges for the public supply system in all countries, especially in developing countries. Medicine losses and shortages occur simultaneously with concerns with the quality of pharmaceuticals in several developing countries (Hassali et al., 2014; Fadare et al., 2016; Bochenek et al., 2017; Acosta et al., 2019), representing critical inefficiencies of public services resulting in increased patient expenditures in many countries as well as litigation in some countries where health is a constitutional right (PAHO, 2009; Castro et al., 2019; Nascimento et al., 2017).

Between 2001 and 2014, data from the World Bank showed a substantial increase in public and private health expenditures in many countries. In the Brazilian scenario, this data showed a five times increase in health expenditures (The World Bank, 2019). However, despite this increased funding, there are still concerns with the availability of essential medicines in the public healthcare system with no more than 62% availability of medicines in 2014 (Nascimento et al., 2017), although up from 47% in 2001 (Guerra Júnior et al., 2004). In addition, the lack of access to medicines in ambulatory care may increase treatment expenses for the national health systems as a result of unnecessary progression of diseases which may result in hospitalizations.

Due to historical reasons, pharmaceutical service organization in developing countries can have important differences from high-income countries. In some cases, developing countries finance and promote medicines access by using the public infrastructure of health care/medical units as dispensing sites and cover the costs for each component up to the dispensing of the medicine to patients. This is seen for instance in Malaysia and sub-Saharan Africa where care for patients in the public healthcare system is provided *via* primary healthcare centers or outpatient clinics which can cover the cost of medicines supplied (Rezal et al., 2015; Meyer et al., 2017; Nashilongo et al., 2017; Mbui et al., 2017; Mashalla et al., 2017). In contrast, high-income countries typically use private community pharmacies and cover the costs of the medicines dispensed plus a fee, which includes all logistic costs. In the public services model in Brazil, medicines are provided according to the level of care: basic component—medicines and supplies related to diseases treated in primary health care and specialized component—medicines and supplies for more complex diseases and patients treated by specialists in public and private outpatient services. In the case of specialty medicines, this lack of access can be particularly severe in developing countries as seen by the lack of biological medicines to treat patients with cancer and immunological diseases in Brazil, Central and Eastern European countries, and sub-Saharan African countries (Putrik et al., 2014; Jakupi et al., 2018; Atieno et al., 2018; da Silva et al., 2018; Baumgart et al., 2019; Wilking et al., 2019). Some high-income countries are also now facing difficulties with financing new medicine with continuously increasing prices despite limited incremental benefits for many new medicines (Malmstrom et al., 2013; Howard et al., 2015; Cohen, 2017). One issue that makes the model adopted by the NHS Brazil different from a number of other countries with UHC is that there is no limit on medicine expenditure by families, *i.e.* safety net. This is similar to for instance, Italy and Scotland where there is no copayment for any medicine prescribed and Sweden where there are no patient copayments after an initial limited amount (Godman et al., 2009; Garattini et al., 2016; Leporowski et al., 2018). While the Brazilian Institute for Geography and Statistics' (IBGE) real-world data shows annually the impact of medicine expenses among all income classes, the current theoretical and legal concept, based on constitutional provision, is that the National Health Service (NHS) could not impose a copayment for medicines or services (IBGE, 2010; IBGE, 2018). The adoption or not of copayment by patients in Brazil were addressed with the implementation of the NHS Federal program in 2003. The program hires private pharmacies and provides medicines with copayments but offers a very short list of medicines, targeting mostly cardiovascular diseases and diabetes.

Overall, the universal healthcare responsibility within countries including Brazil implies the obligation to provide health care using public resources as the primary source of funding. The methods of provision and payment used to achieve UHC may range from pure state services, amalgamation with public and private entities, as well as direct contracting of private providers or social organizations. Regardless of the type of organization and provision adopted, public or private contracted, it will be necessary to establish a system of payments. Whether the provider is public or private, the funding system should have the metrics to remunerate the service provider (pharmacies) to cover their costs. Other factors are the need to balance economic incentives and avoid cost escalation while at the same time promoting equitable access, delivering quality care and products, and ensuring citizens' satisfaction. The conceptual models for pharmaceutical payment systems include:

I. Payment for inputs/resources: all resources consumed to produce pharmaceutical services (HR, infrastructure, logistics, medicines, *etc.*);
II. Process Payment: types of procedures and health care performed;
III. Payment for Production: quantity and types of medicines supplied to patients;
IV. Payment by affiliated population: number of people registered in the health region of the provider;
V. Payment for Health Results: number of healthy or satisfied patients.

As mentioned, high-income countries typically follow the pay-per-production model where payments and pharmaceutical logistics are fully outsourced. The copayment and safety-net concepts in which households pay up to a preset threshold for medicines over a period are adopted in many countries including Australia, Canada, Denmark, England, Germany, Norway, Portugal, Spain, and Sweden (Pontén et al., 2017; WHO, 2019; Glover, 2017), with, as mentioned, some countries adhering to full, free access to reimbursed medicines (Garattini et al., 2016; Leporowski et al., 2018).

In 2017, the NHS in Brazil provided 247 medicines for outpatient medical specialties. These medicines are important due to their epidemiological impact and/or the cost that they represent for families (**Figure 1**).

Alternative strategies adopted by low and middle-income countries (LMICs) for public pharmaceutical supply include central medical stores, autonomous supply agencies, direct delivery systems to patients, and dispensing sites in medical centers/units. Consequently, there will be economic implications of the alternative scenario of the private sector–public sector collaboration model with private community pharmacies accredited by the NHS. Similarly to many developing countries, Brazil adopted a model for the organization, payment, and logistic provision of medicines that was almost completely state-owned. The public sector, in the three levels of management (municipal, state, and federal), adopted a model of payment for inputs/economic resources consumed.

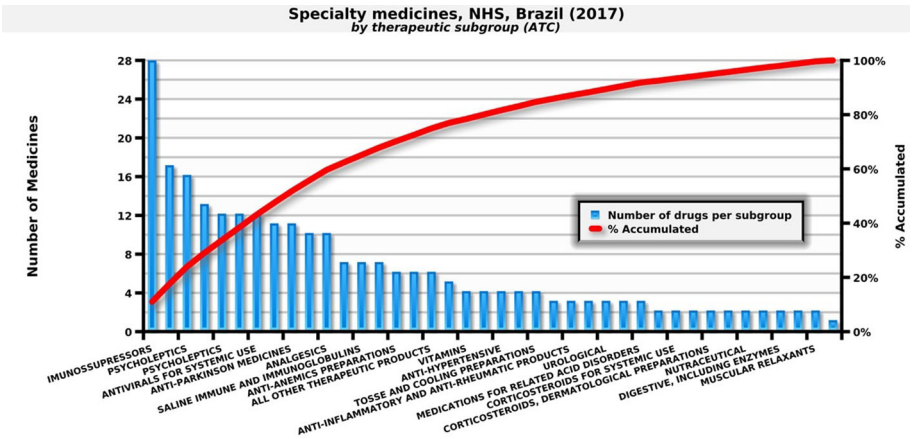

FIGURE 1 | Number of specialty medicines by therapeutic subgroup paid by the NHS. Source: self-elaboration, data available from the NHS (Brasil, 2018b).

The efforts of Brazil to achieve UHC for medicines resulted in increased public financing of medicines and their availability, ranging from <50 in 1999 to 62% in 2014 (**Table 1**), reducing avoidable hospitalization and mortality. However, the lack of access still remains in Brazil with still lower levels of access compared with other middle-income countries (Holst et al., 2016). Health benefits that have accrued include an increase of 13.8 years in life expectancy since the inception of the NHS in Brazil (IBGE, 2019). However, factors including inequalities in family income, insufficient financing, and cooperation between private and public sectors are still issues that need improvement as these can impact on the quality of life of the Brazilian population (Castro et al., 2019).

Consequently in this study, we will undertake an economic evaluation to understand the funding needs of the Brazilian NHS in a scenario of adopting a pharmaceutical service organization similar to that seen in many high-income countries, that is, hiring/accrediting private pharmacies to provide medicines access with public funds. As a result, we will seek to appreciably improve access to medicines in Brazil compared with the current situation. At the same time, keep to the concept of no limit on medicine expenditure among families as this is an important concept in Brazil.

TABLE 1 | Country income level and access to essential medicines (WHO, 2004).

Country income group	Median reported access level (%)	Minimum reported (%)*	Maximum reported (%)*
Low-income	60	10	93
Middle-income	85	30	100
Brazil 1999	<50	–	–
Brazil 2001 (Castro et al., 2019)	47	41	53
Brazil 2014 (Nascimento et al., 2017)	62	61	64
High-income	100	98	100

**The data from Brazil refer to the mean, and the values for minimum and maximum refer to the confidence interval (95%).*

METHODS

Overview

We performed an economic evaluation regarding the provision of medicines with public funds in two alternative scenarios: public pharmacies (NHS state-owned facilities) *versus* private pharmacies (NHS agreements). The analysis assumed the perspective of the NHS. We identified the types of resources consumed and the amounts and value of each item from Brazilian government data sources (Brasil, 2018b). All the monetary values were adjusted according to the purchasing power parity index of the World Bank (The World Bank, 2019).

Model of Pharmaceutical Services

We developed a model to evaluate alternative pharmaceutical service organization to provide access to medicines within public healthcare systems (**Figure 2**). The decision-tree model used inputs from a pharmaceutical service organization in Brazil for the medicines and supplies for outpatient medical specialties. We considered effectiveness in terms of medicine access as it is one of the goals of NHS funding, with citizens in Brazil having a right to health.

Litigation, direct expenses, hospitalizations, and death can be the consequences of a lack of access to pertinent medicines that can be used to cure, prevent and/or reduce the progression of both infectious and noninfectious diseases. Due to the difficulty in measuring the probabilities for each drug—247 in total—in relation to a given consequence, in our study we investigated and calculated the total cost of each of these outcomes (**Figure 2**) to provide insight into current expenditures for these items.

Availability of Data About Outcomes: Litigation, Out-Of-Pocket Expenses, Hospitalizations, and Death

In Brazil, NHS Federal expenditures on health litigation are mostly a result of citizens demanding medicines (Conselho

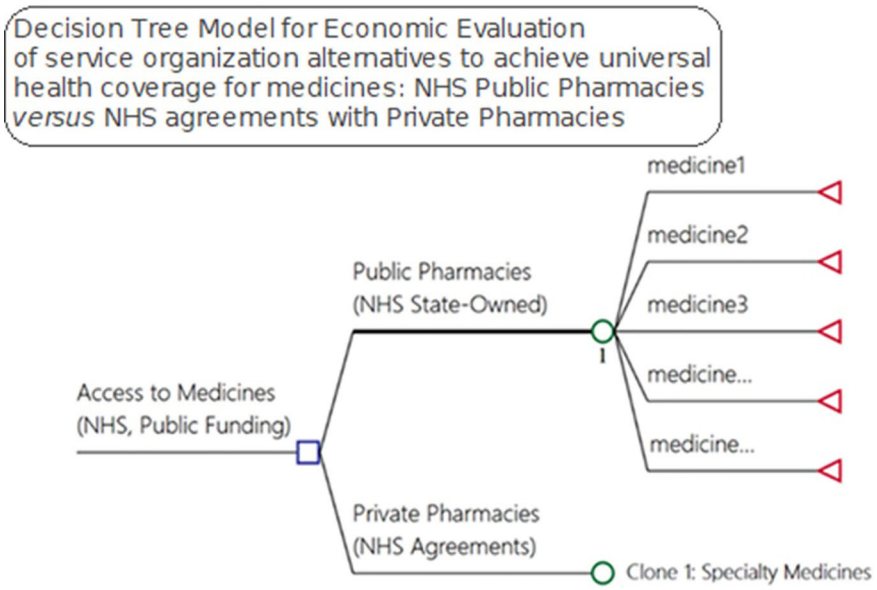

FIGURE 2 | Model for economic evaluation between pharmaceutical service organization alternatives for medicine access, NHS public pharmacies *versus* NHS agreements with private pharmacies—OECD medicines access model).

Nacional de Justiça, 2019; Machado et al., 2011). We performed a search of the Ministry of Health (MoH) website, available literature, and we contacted the officers at the Department Juridical Affairs of the MoH responsible for providing NHS technical–juridical information in cases of health litigation to gain robust data on the current status of medicine litigation in Brazil.

We obtained data on out-of-pocket expenses (household income and expenditures) on health and medicines from the National Survey by Household Sample (PNAD) for 2017 (IBGE, 2018) and from the last available dataset from Household Budgets Survey (POF) for the years 2008/2009 (IBGE, 2010) for urban and rural areas.

We obtained data related to specialty care with outpatient and hospital admissions due to conditions potentially treatable or avoidable with the use of medicines from Brazilian NHS databases from the frequencies of outpatient and hospital admission services and its costs (payments) for the period from January to December of 2017. Furthermore, we extracted from the National Mortality database (2017) the deaths from potentially preventable causes (Brasil, 2018b).

Resource Use

We identified the relevant costs incurred in providing medicine access for the current model of pharmaceutical services in Brazil. In the alternative scenario, all steps for procurement, logistics, and dispensing would be under a hiring agreement between the community private pharmacies and the NHS. The reimbursement happens for each medicine dispensed. The costs related to the management of the program that remain in the control of the NHS (public sector) are equivalent in both models (**Figure 3**).

Model Inputs

We performed a search of the available data in the MoH administrative databases to obtain details of the medicines dispensed and the amount paid in 2017 (monthly data) for the specialized component of pharmaceutical services. These medicines are of considerable importance because of either their epidemiological impact or their costs. Examples of such medicines include anti-TNF alphas for rheumatoid arthritis, insulins for diabetes, statins for cardiovascular diseases, antivirals for hepatitis, and medicines for schizophrenia (Andrieux-Meyer et al., 2015; Dos Santos et al., 2016; Marra et al., 2017; Barbosa et al., 2018; do Nascimento et al., 2018).

Due to lead times for procurement and logistics, we set the safety stocks in the public sector at four months, which we present as costs with immobilized assets accepting that this four months of safety stocks produces an opportunity cost. In LMICs where inflation and interest rates are usually higher than high-income countries, as seen in Brazil, there are rules recommending NHS managers to invest in low-risk funds when expenditures are not happening. *Logistics operation costs* are functions which include warehousing, inventory management, and transportation in bulk. In LMICs, this part of the logistic process may be executed using public facilities and public servants. To simplify the model, we considered that private companies hired by public administration would undertake bulk pharmaceutical logistics operations as is currently the case among the Ministry of Health and other large Departments of Health in the Brazilian States, which is also the situation in the State of

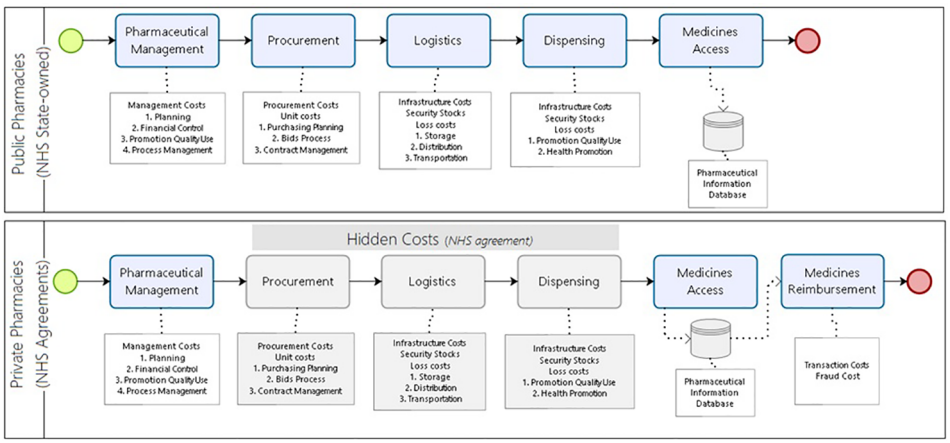

FIGURE 3 | Costs incurred to provide medicine access for the developing country model of pharmaceutical services.

Minas Gerais and Rio de Janeiro. In the logistic agreements made by these States and the Ministry of Health, the costs are usually established as a percentage of the volume of loads and their respective prices. We set the *costs with losses* due to obsolete medicines, those expiring, spoilage, wastage, and theft at five percent of the annual cost of the medicines purchased. This is because the information for pharmaceutical losses is currently uncertain both in the public or private sectors. Consequently, we adopted a wide interval in the sensitivity analysis to assess these influences in the different scenarios.

The scenario of private pharmacy hiring agreements for dispensing transfers the steps related to the procurement, logistics operations, and dispensing to the private sector. The NHS pays private pharmacies for access to each drug dispensed and must cover the cost of outsourced steps. The economic risks of these operations are implicit and under the responsibility of the private sector. All the parameters as a result of the literature searches, NHS databases, surveys of government websites and information provided by public authorities adopted as model inputs, are summarized in **Table 2**.

Dispensing and Maintenance Costs of Public Pharmacies by NHS

To develop the model, we considered public pharmacy operation hours as twelve hours of service per day, five days a week and twenty-two days a month. To establish these values, we surveyed the webpages of the twenty-seven Brazilian States of the NHS pharmaceutical dispensing services. For public employees, we considered 8 h per day and 40 h per week. This is because the NHS State pharmacies, which have the responsibility for dispensing specialty medicines, do not open on Saturdays and Sundays. We obtained the number of medicines dispensed per month and the other values of production of a typical public pharmacy for specialty medicines, in the NHS databases in the State of Minas Gerais. The costs related to the real estate were valued based on the cost per m^2 for renting from the national index of economic research (FIPE, 2019). The values of the public employees' salaries for Brazil were obtained from the market signals research station—EPSM (EPSM, 2017).

The average monthly costs of dispensing and maintaining an NHS public pharmacy are the result of the sum of all the resources spent on producing the service divided by the number of dispensing per month:

$$Average\ Cost\ per\ Dispensing = \frac{Resources\ Consumed}{number\ of\ dispensation\ realized\ in\ \ 30\ \ days}$$

Unit Cost of Medicines Purchased by NHS

We retrieved the unit cost of the specialty medicines provided by NHS from the official data bank of medicine procurement for the year of 2017 (Brasil, 2018c). This is the real-world price for the NHS as Brazilian public health authorities cannot currently make confidential price agreements under the law.

Unit Cost of Medicines in the Private Pharmacies

In Brazil, the National Pharmaceutical Market Authority (CMED) regulates the maximum prices for government and consumer purchases. This data is updated monthly by CMED and made available for public consultation on the government website (Brasil, 2018a). Using this information, we created a database with all prices for all the brands available for the specialty medicines. We used the price list released by CMED for September 2018.

We extracted the unit cost of each specialty medicine from the database created for all brands available in the Brazilian market for the selected medicines. The unit cost for private community pharmacies has been defined as the maximum medicine price for the government purchases (PMVG) situated in the first decile of all brands available. We inputted in the model parameters for potential market prices for NHS payment in the private pharmacies using the following rational that was previously adopted by the Ministry of Health initiative called "Aqui Tem Farmácia Popular do Brasil":

TABLE 2 | Parameters, base value, and intervals adopted as model inputs for pharmaceutical dispensing services NHS.

	Parameters	n	Cost US$PPP	Interval	Total	Source
	Medicines purchased by NHS	244	NHS Data	*		Brasil, 2018b
	Medicines costs private pharmacies	244	PMVG 0%	**		Brasil, 2018a
Dispensing and maintenance costs of public pharmacies by NHS	**Salaries and wages expenses**					
	Pharmacists, monthly salary	9	5,000	3,192–8,865	45,008	EPSM, 2017
	Attendants, monthly salary	92	2,268	1,570–4,015	208,647	EPSM, 2017
	Facilities structure expenses					
	Operation services hours	12 h/day; 5 days/week; 22 days/month				Survey
	Rent/property (real state value, m2)	1	60	54–65	60	FIPE, 2019
	Depreciation rate (equipment's, 5%)	1	172,467	155,220–189,713	172,467	Minas Gerais, 2017
	Utilities (telecom, energy, water)	1	25,000	22,500–27,500	25,000	Minas Gerais, 2017
	Security, cleaning services and supplies	1	15,000.00	13,500–16,500	15,000	Minas Gerais, 2017
	Office supplies	1	10,000	9,000–11,000	10,000	Minas Gerais, 2017
	Number of dispensing per month	44.000		11.000–88.000		Minas Gerais, 2017
	Number of medicines per patient	2.4		1.3–3.8		Cunha et al., 2002; Lima et al., 2017; Santos and Nitrini, 2004
	Costs immobilized assets	0.0971		0.0620–0.1373		Survey
	Logistics operation costs	4%		2–6%		
	Costs with losses	5% annual volume handled		2–40%		Minas Gerais, 2017
Benefits	**Costs with potential frauds in reimbursement**	2%		0.5–5%		Brasil, 2011
	Medicines availability NHS	65%		55–75%		Guerra, 2004; Lima et al., 2017
	Medicines availability Private Pharmacies	90%		85-95%		Guerra, 2004; Nascimento et al., 2017

**Consulted data from the acquisitions made in NHS during the year 2017.*

***The reference value: defined as the value of the brand at the 1st decile price, for government purchases without taxes (PMVG 0%, CMED).*

- *Minimum value*—cheapest brand between all medicines in the market for each drug;
- *Base value*—brand price in the first decile of all medicines in the market for each drug;
- *Maximum value*—brand price in the median of all medicines for each drug.

Monthly Treatment Cost

We estimated the monthly costs for each medicine by multiplying the unit cost by the number of pharmaceutical units required for a monthly treatment (30 days). For these estimates, we considered the number of pharmaceutical units needed for each treatment based on Defined Daily Doses (DDD) from the WHO Collaborating Centre for Drug Statistics Methodology (WHO, 2018). The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. In case information was not available in the ATC/DDD system, the maximum amounts permitted and authorized by the Ministry of Health for dispensing, according to the main indication recommended in the Clinical Protocols and Therapeutic Guidelines adopted in the NHS, were used to calculate the DDDs (Brasil, 2019).

We added to the monthly treatment costs the sum of the dispensing and maintenance costs in the public pharmacies, the logistic operation costs, and any losses per month. In the private model, the monthly treatment cost additionally included the percentage costs with losses from potential frauds in reimbursement as stated in audit reports (**Figure 3**).

Potential Benefits

The increase in the availability of medicines incorporated routinely into the Brazilian NHS should help reduce litigation and out-of-pocket expenses as well as subsequent hospitalizations and deaths (outcomes). The medicine access research reports (2004 and 2017) showed a 62% availability of medicines, while in the private pharmacies this was approximately 90%. We assumed an access rate in public pharmacies of 65%, ranging from 55 to 75%. For the private model, we assume 90% access, ranging from 85 to 95%.

Sensitivity Analysis

We performed a sensitivity analysis to test uncertainties arising from the model inputs. As the first step, we tested univariate variables to assess how the results might change. After testing each parameter individually, we evaluated the impact on results through probabilistic sensitivity analysis using Monte Carlo simulation.

RESULTS

NHS distributed approximately 21.4 million treatments in Brazil in 2017, spending eight billion dollars. Examples include immunosuppressant for rheumatoid arthritis, statins for cardiovascular diseases, antivirals for hepatitis, and mental health medicines used for schizophrenia (**Figure 4**).

The model estimated an incremental cost of US$3.1 billion (DPPP) in a scenario of no rebates over medicine reference prices for government purchases (PMVG) but with an increase in the average availability of medicines from 65% to 90% for citizens across the country and for all classes of family incomes (**Table 2** and **Figure 5**). The scenarios above 35% rebates put the alternative of hiring private pharmacies as dominant. Higher rebates are feasible and may lead to savings of US$1.3 billion (PPP) per year (**Figure 5** and **Table 3**).

Funding Demanded to Achieve Universal Health Coverage

To understand the funding demanded to achieve UHC for medicines, we analyzed the budget impact forecast scenario with 35.19% rebates over the first decile brand prices. In this scenario, we may see the estimated cost of hiring private community pharmacies. We estimate the incremental budget,

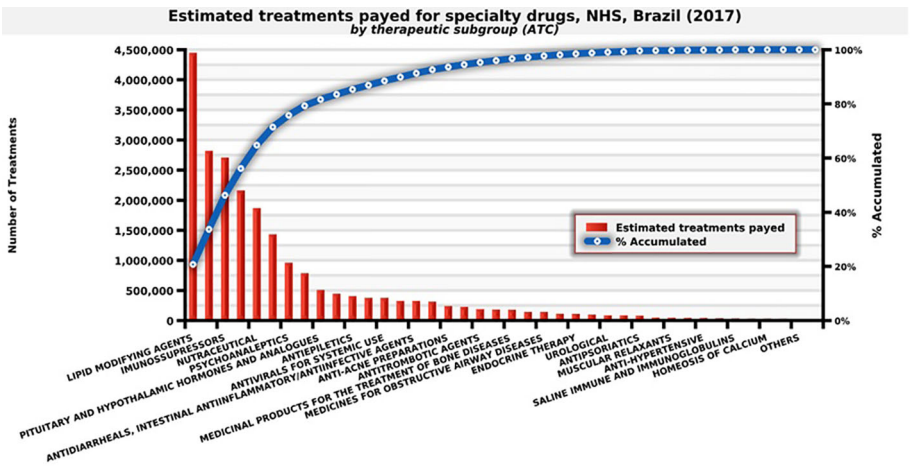

FIGURE 4 | Number of estimated treatments for each medicine provided by the therapeutic subgroup, NHS, Brazil (2017). Source: self-elaboration, data available from NHS (Brasil, 2018b).

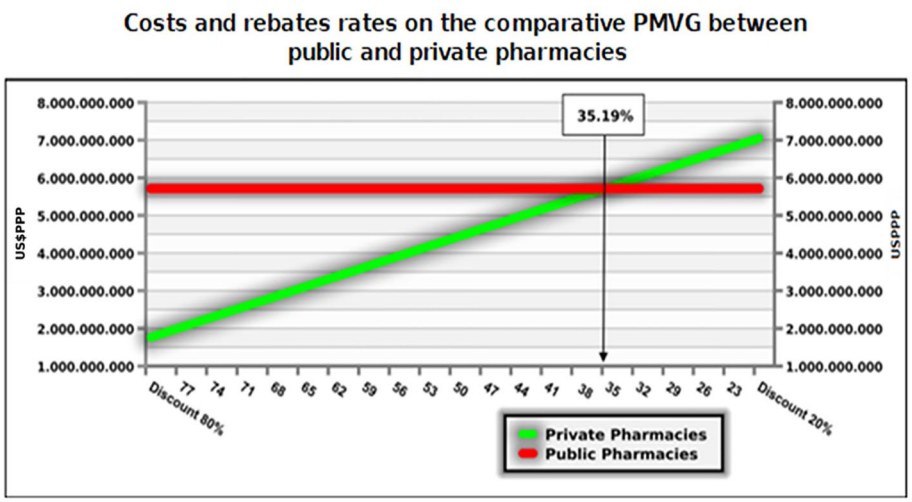

FIGURE 5 | Costs and rebates rates on the comparative PMVG between public and private pharmacies.

TABLE 3 | Forecast incremental cost in different rebate scenarios for distribution of medicines in private pharmacies.

Strategy	Cost (Billions US $PPP)	Incremental Cost (Billions US$PPP)
Forecast scenario: no rebate		
Public Pharmacy (State-owned facilities)	5,711,682,916.31	
Private pharmacy (NHS agreements)	8,812,681,695.98	3,100,998,779.67
Forecast scenario: rebate 30%		
Public Pharmacy (State-owned facilities)	5,711,682,916.31	
Private pharmacy (NHS agreements)	6,168,877,187.19	457,194,270.88
Forecast scenario: rebate 50%		
Public Pharmacy (State-owned facilities)	5,711,682,916.31	
Private pharmacy (NHS agreements)	4,406,340,847.99	(- 1,305,342,068.32)

considering that between the first and second years there would be a further 25% increase in access in the scenario of the NHS choosing to hire private pharmacies. The budget impact for the NHS would increase at a rate of 6% after that, which is the average growth of the last decade of the dispensing of these medicines in the NHS (**Table 4**). The impact of incremental funding is related with the access gain of 25% (second year) to move from payment for inputs of public dispensing to the private pharmacies contracting, and the incremental budget in five years would be US$4.8 billion PPP. We have yet to explore what would be the reduction in hospital/outpatient costs and lawsuits, with the yearly expenses for the NHS at US$9 billion and US$1.4 billion PPP, respectively in 2017.

Sensitivity Analysis

We perform the univariate sensitivity analysis on the variables with uncertainty and potential impact on the results. These included the monthly salary of pharmacists, the number of pharmacists per pharmacy, the number of medicines dispensed per month, the average number of medicines prescribed per patient, the unit cost of medicines, as well as the cost associated with logistic losses and losses due to reimbursement (**Table 5**).

The sensitive analysis scenarios demonstrated that the two most important parameters that might affect the incremental costs are the coefficient of variation of the unit costs and the cost associated with losses. Increased logistic efficiency of the NHS, with reduced losses, raises the incremental cost to hire private pharmacies by 5.1%.

Nevertheless, in a scenario of lack of control and increased losses, the incremental cost to hire private pharmacies would reduce by 58.9%. In a scenario of reduced unit costs by 65%, with

TABLE 4 | Funding demanded to achieve universal health coverage for medicines presented as budget impact analysis, estimate for five years forecast scenario with 35.19% rebates.

Year	Treatments		Access Growth	Budget Estimate Impact	Budget Estimate Impact
	Public	Private	(%)	Public Pharmacies	Private Pharmacies[b]
1	21,881,719.30	21,881,719.30	base year	5,711,682,916.31	5,711,683,192.33
2	23,174,852.21	27,352,149.13	25[a] + 6	6,049,223,355.86	7,139,603,991.57
3	24,544,404.75	28,968,565.26	6	6,406,711,254.25	7,561,529,559.43
4	25,994,893.03	30,680,505.93	6	6,785,325,430.57	8,008,389,452.70
5	27,531,100.10	32,493,616.29	6	7,186,314,382.00	8,481,657,198.57
Incremental Access		***18,249,586.52***		***Incremental Budget***	***4,763,606,055.61***

[a]25% is the incremental access between expected availability scenario of hiring private pharmacies. [b]The reference value: defined as the value of the brand at the 1st decile price, for government purchases without taxes (PMVG 0%, CMED), with a rebate rate of 35.19%.

TABLE 5 | Univariate sensitivity analysis of the parameters.

	Parameter	Base value	Interval	Variation of incremental cost (PPP$)
Public Pharmacies	**Monthly cost of pharmacist (salary, US$PPP)**	5,000.83	3,191.48	3,104,313,696.20
			8,865.24	3,093,918,801.60
	Number of pharmacists per pharmacy	9	1	3,109,142,800.33
			16	3,093,872,761.60
	Number of dispensing per month	44,000	11,000	2,902,559,701.36
			88,000	3,134,071,959.39
	Number of medicines per patient	2.4	1.3	3,045,028,783.23
			3.8	3,125,368,491.05
	Costs with losses	1.05	1.02	3,257,656,501.96
			1.4	1,273,325,352.95
Both	**Coefficient of variation of the Unit Cost**	1	0.35	1,042,354,439.25
			1.65	5,159,643,120.10
Private Pharmacies	**Costs with potential frauds in reimbursement**	1.02	1.005	2,984,393,133.56
			1.05	3,334,210,071.90

a larger share of generic/similar medicines, for example, there would be a reduction of the incremental cost to hire private pharmacies by 66.4%. Whereas, if there is an increase in the average unit cost due to lower supply/share of generic/similar medicines, this may produce an increase in the incremental costs to hire private pharmacies by 66.4%.

Model Limitations

Understanding that the lack of medicine access may have consequences including litigation, out-of-pocket expenses, hospitalizations, and death, we designed an ideal model to try and incorporate these parameters. However, the probabilities for each of 247 specialty drugs provided by the NHS in 2017 for these four consequences are difficult to measure. Consequently, in our study, we just investigated the total cost for each of these outcomes once the expenses for the NHS and families are linked to the lack of access, excluding premature deaths (**Figure 6**).

Potential Benefits

Data from the Family Budget Survey (POF) showed that the poorest Brazilian families medicines' expenditure was 66.5% of their total health spending (IBGE, 2010; Marra et al., 2017). The POF registered important differences between the distributions of household expenditures with healthcare and medicines concerning the family income distribution of the Brazilian population by total income class (**Figure 7**) (Sindusfarma, 2018). The data shows that the lower the income, the higher the impact of spending on medicines as a percentage of total family expenses on health. The poorest families, which represent 22.5% of the country, have a burden of more than 76% of their expenses on medicines in relation to their total health care costs, while in the upper levels of the Brazilian society this reduces to 34%.

The combined scenario of low availability of medicines and economic distress related to health expenses can lead to litigation against the NHS. As previously mentioned, in Brazil, NHS Federal expenditures on litigation are mostly due to citizens demanding medicines, corresponding to approximately 80% of the total lawsuits. In dollar amounts, as mentioned, the NHS currently spends approximately US$1.4 billion (PPP) per year on litigation. This is in addition to the costs associated with regular administrative claims for medicines received by the NHS (Conselho Nacional de Justiça, 2019).

In 2017, data from DATASUS indicate that the NHS in Brazil paid for more than 2.3 million hospital admissions and 5.6 million outpatient care procedures associated with procedures and complications potentially related to the treatments for which clinical protocols in the NHS exist. The care provided by the NHS\ for these procedures, as mentioned, costs approximately US $9 billion PPP in 2017 (**Figure 8**). The most demanded treatments were related to kidney problems, cardiovascular disease, infections and psychiatric treatment, for which there are medicines listed by the NHS for the control and a reduction in the worsening of the clinical conditions.

The last year with available data for mortality is 2016. The number of deaths from potentially preventable causes, including adequate clinical management and medicine usage, was more than 100,000 cases (**Figure 9**). Deaths related to hepatic, renal, cardiovascular and infection problems were highlighted, and most of these clinical conditions are treatable and/or preventable with medicines incorporated in the Brazilian NHS, which should be readily available.

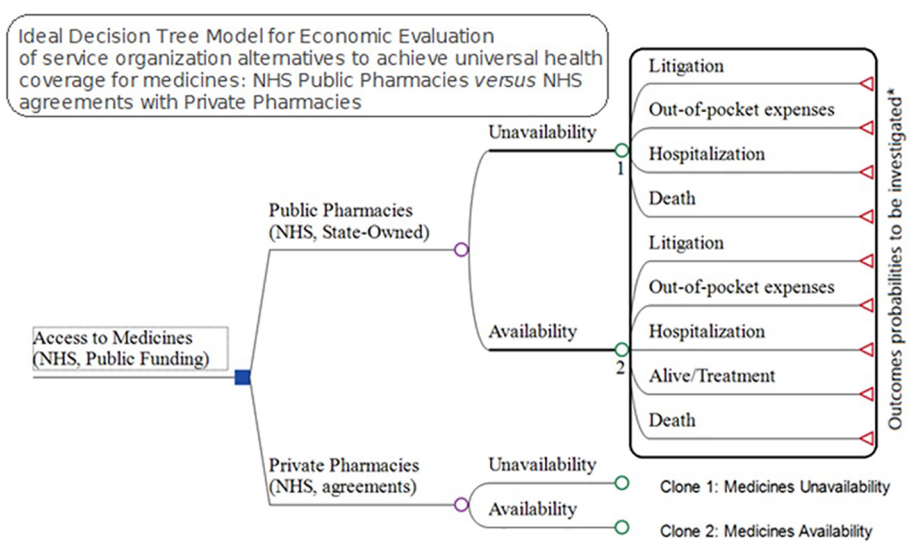

FIGURE 6 | Ideal Model for economic evaluation between pharmaceutical service organization alternatives for medicines access, NHS public pharmacies *versus* NHS agreements with private pharmacies.

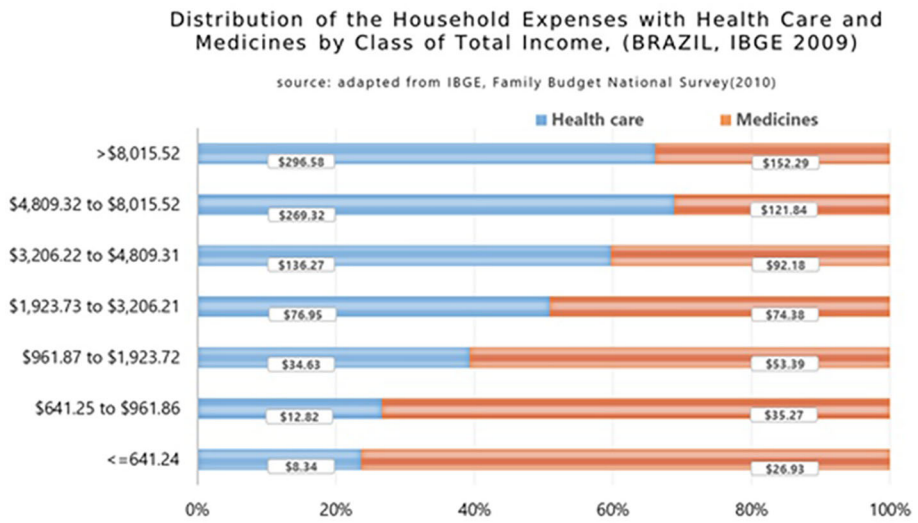

FIGURE 7 | Distribution of the household expenses with health care and medicines by class of total income in Brazil (2009) (Garcia et al., 2013).

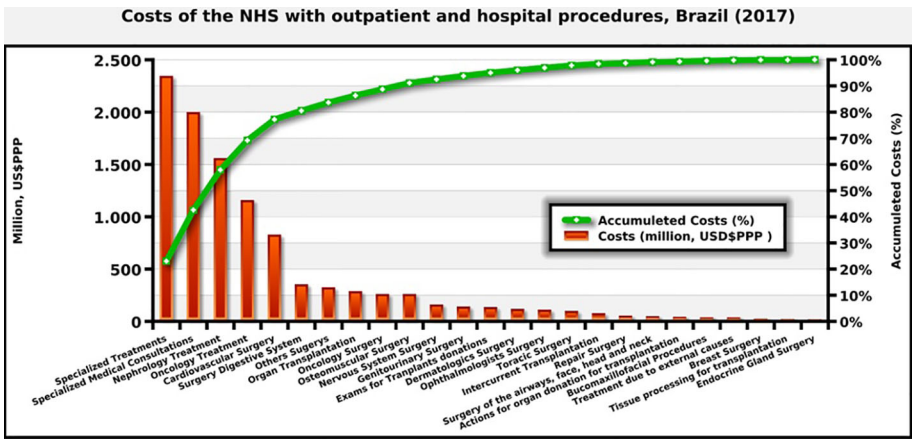

FIGURE 8 | Costs of the NHS with outpatient and hospital procedures in Brazil (2017).

Proposed Private Sector–Public Sector Collaboration for Pharmaceutical Service Organization

The optimal private sector–public sector collaboration looks to be the key to achieving UHC for medicines reducing subsequent avoidable hospitalization and mortality as well inequalities among families concerning household expenses. The resultant service organization (**Figure 10**) might consider the use of an information system and a simple workflow. It is important to preserve some of the NHS advantages of having the citizens geographically referred to the public health service centers in their neighborhood. The available health centers provide medical care, prescriptions, and authorization to obtain medicines in a private pharmacy of the citizen's choice. Pharmacists and pharmacies should work under the same information system and send invoices for payment to the appropriate government agency as typically happens in high income countries. The authorization system of the NHS would validate and reimburse the medicines (**Figure 10**).

DISCUSSION AND CONCLUSIONS

Despite important advances made in the implementation and improvement of NHS in Brazil, access to medicines remains a focus of inequality and health litigation. Insufficient progress

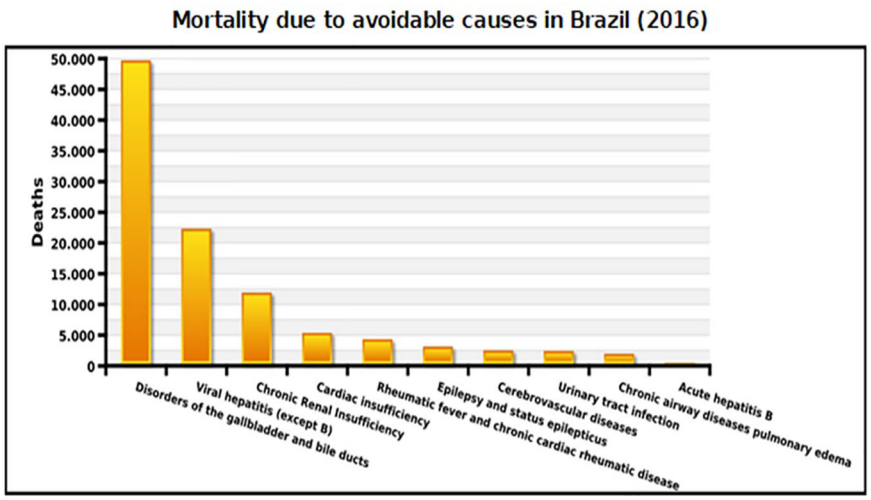

FIGURE 9 | Mortality due to avoidable causes in Brazil (2016).

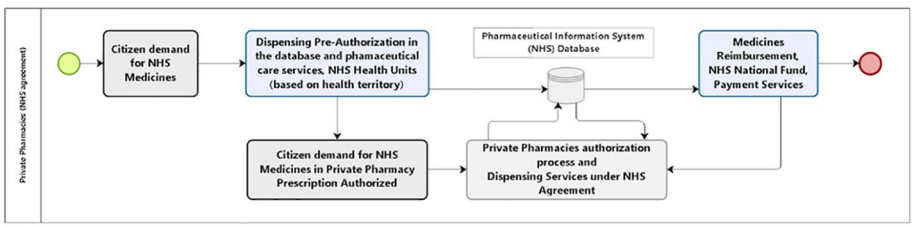

FIGURE 10 | NHS service model to provide access to medicines, private pharmacies agreements.

though has been made about the direct disbursement of the poorest families with pharmaceutical products over the years.

The total value of medicines purchased annually by the NHS should place it in a position of obtaining appreciable rebates. The scenarios above 35% rebates put the alternative of hiring private pharmacies as dominant, but higher rebates are feasible and may lead to savings of US$1.3 billion per year (DPPP) (**Figure 5** and **Table 3**). This study does not recommend the adoption of reference pricing for government purchases (PMVG with 0% tax) as a basis for NHS payment for dispensing. This is according to data from the Union of the Pharmaceutical Manufacturer Companies (Young et al., 2017) which state that in the Brazilian pharmaceutical market there is an average rebate of 41% over the unit cost of medicines. This can potentially be higher with more aggressive purchasing approaches. Reference pricing may reduce the size of the rebate alongside other concerns with reference pricing including appropriate comparator countries and their economic considerations including GDP (Young et al., 2017; Mahlich et al., 2019). There are also issues of transparency with reference pricing since list prices within countries typically do not include confidential discounts, which are now a key element of pricing negotiations for medicines across countries (Ferrario et al., 2017; Vogler et al., 2017; Maskineh and Nasser, 2018; Robinson et al., 2018).

Preventable morbidity and mortality due to a lack of access to medicines affects developing countries' economies such as Brazil. In addition to the social and economic consequences, the inefficiency of the model adopted leads to productivity loss for families, especially low-income families who are affected by economic crises and usually have to accept working conditions not protected by social security or labor legislation. It is possible that the consequences of this potentially preventable morbidity and mortality affect the economy as a whole. The seriousness of this framework implies an increase in costs for the NHS itself due to clinical complications and, finally, loss of quality of life for the citizens. It would be worth pointing out that the loss of citizens' quality of life alone would be reason enough to justify the improvement of public health policies and the reduction of inequality in access to medicines in the country.

As mentioned, the economic advantage in the private model occurs with a rebate rate of 35%. The new model proposal (**Figure 10**) considers the use of an information system and a

simple workflow. Citizens would still be referred to their health territory where they may receive medical care, prescriptions, and authorization to obtain prescribed medicines in the private pharmacy of their choice. Pharmacies would send the invoice for payment to the appropriate government agency. The authorization system of the NHS would subsequently validate and reimburse the medicines.

The implementation studies necessary to change the actual service models to provide access to medicines are complex, and the success or failure will rely on the strategies adopted. This implementation phase will demand specific studies which were not the focus of this paper. Overall, we believe the results of this economic evaluation robustly demonstrate the benefits of the introduction of an optimal model of collaboration between public and private sectors. The current model of pharmaceutical services provided by NHS Brazil produces inequality, shortages of medicines especially for chronic diseases, and jeopardizes other health policies and household income. The model used in many high-income countries with accredited private community pharmacies appears more economical alongside competent price negotiations for medicines which we believe is feasible. The results also suggest that the inclusion of private community pharmacies in NHS has the potential for improving access to medicines by 25% across all income classes with the greatest benefit to the poorest families.

Overall, we believe that the results presented in this article can result in new health policies and help to reduce inequalities in access to medicines in Brazil, with potential savings in lives and public resources through the negotiation of prices practiced in the Brazilian market. In addition, the study helps support decision making by managers by allowing them to evaluate different scenarios within the Brazilian context. We will be monitoring these developments in the future.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/ **Supplementary Material**.

AUTHOR CONTRIBUTIONS

All authors contributed to the planning, analysis, and interpretation of data, and preparation and approval of the final version of the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2020.00370/full#supplementary-material

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Addressing Health Care Disparities: A Radical Perspective and Proposal

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This paper begins by rethinking the sociological theory that social conditions are fundamental causes of health disparities and that controlling disease ironically increases or creates them. While usually true, the radical proposal of non-profit health care and pharmaceutical development could ameliorate health disparities if a nation like Canada or a region like the EU looked to radically different but successful models such as the Drugs for Neglected Diseases *initiative*. It uses what could be called *entrepreneurial collaboration for public health markets* and inverts intellectual property to *public health IP* to maximize health gain instead of profits.

Keywords: health disparities, inequality, prescription drugs, access, intellectual property, non-profit

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INTRODUCTION

This essay of ideas and the sociological imagination begins by providing a new perspective on the famous studies on social conditions underlying health care disparities and on the paradox that controlling disease can create or increase such disparities. It then discusses dysfunctions of current drug development that increase disparities through high priced, patent-protected new medicines. As a radical proposal, the essay turns of the Drugs for Neglected Diseases *initiative* (DND*i*) as a working, successful model of a non-profit, virtual collaborative that researches, tests, gains approval, manufactures, and distributes clinically superior medicines at low cost and for wide access, thus reducing health care disparities. This model is illustrated by how DND*i* has developed highly effective drugs to eradicate Hepatitis C and created an example of markets to maximize public health rather than to maximize profits. Unlike other proposals to delink R&D from costs, DND*i* stands the power of patents and IP rights on their head to guarantee low prices and reduce health disparities. More work needs to be done to understand how these innovations actually work and how a theory of moral markets for public health could be developed.

Despite efforts to minimize them, health disparities plague the United States, Canada, the European Union, and regions of the world beyond. A landmark study by Link and Phelan (1995) showed that social conditions underlying health disparities are fundamental causes of diseases, not just in the US but globally. Ten years later, Phelan and Link (2005) explicated a paradox: controlling disease through costly interventions creates or increases health disparities, as people with more knowledge, money, and beneficial social connections have greater access and ability to harness medical advances and treatments than those with less. They cited evidence from the United States and Europe; but this too is a global pattern, especially for middle and lower-middle countries, where income inequalities are often even greater. For example, costly new drugs that control diseases create disparities because poorer states, subareas, and poorer individuals are less able to afford them (Iyengar et al., 2016). Costly medicines crowd out other health care services. Unequal access to needed but patented, expensive medicines exacerbates existing disparities among disadvantaged populations.

Might it be possible to control diseases without creating or increasing disparities? Could the paradox be resolved? Understanding this paradox has important implications for the kind of institutional strategies that could control disease without creating or increasing health disparities.

Let us begin by taking the fundamental or radical global perspective that all peoples have a right to effective health care and the best health possible. In fact, whole societies can organize themselves to ameliorate social conditions and maximize health and access to health care. Olafsdottir (2007) effectively illustrated this in the *Journal of Health and Social Behavior* by contrasting the social, economic, and moral conditions developed in Iceland with those in the United States. Through a constellation of acts, programs, and financing, Iceland has developed a pro-family, pro-female set of programs, while providing free, high-quality education through a university degree; universal, high-quality health care; strong pro-work provisions, and wages; robust public services and services for children and adults at all ages; and government efforts to minimize the role that markets play in providing these services. As a result, health disparities are minimized. By contrast, the United States provides only some of these services, though states vary widely along some dimensions. As a result, the percent living in poverty is much greater in the U.S., income inequality is 50% greater, female participation in the labor force is less, and women's pay is a lower percent of men's pay than in Iceland. Infant mortality is three times greater in the US, and happiness about living standards is lower. Access to effective health care is not a right in the U.S., though again, some states like California and cities like San Francisco are working hard to make it so.

Olafsdottir's study indicates that social conditions as fundamental causes of disease and health disparities can be significantly mollified and even transformed into fundamental contributors to reduced health disparities and better physical and mental health. In health care, controlling disease need not create health disparities, at least not nearly so much as is evident in a neoliberal, market-based, inegalitarian society. In theory, the paradox of creating or increasing health disparities when controlling disease need not exist. Some nations actually stand this paradox on its head: they give priority to treating those who are most disadvantaged and most ill. Challenging the "inverse care law"[1] requires constant vigilance and re-dedication.

DYSFUNCTIONS OF CURRENT DRUG DEVELOPMENT

Because health is a social or societal good, it is part of social justice and the meaning of a just society. A universal right to health care is also part of social and global justice, but one especially frustrated by putting the research, development, and sales of prescription drugs and vaccines into the hands of pharmaceutical companies. Over the decades, especially through the development of the pharmaceutical part of the Food and Drug Administration (FDA) in the United States, (Hilts, 2003) but also in Europe and the development of the European Medicines Agency (EMA), industry leaders have worked closely with politicians and government officials to develop a constellation of laws, practices, precedents, and institutions that minimize a focus on unmet health care needs, particularly among the poor, and maximize a focus on developing newly patented products for clinically minor variations and rare diseases (Light, 2007, 2010, 2015; Lexchin and Light, 2012). As a government-backed monopoly, patenting allows companies to charge about 50 times manufacturing costs for huge gross mark-ups on what they characterize as new, innovative medicines that they pay regulators to review (Light, 2006; Gagnon and Lexchin, 2008).

Contrary to common belief, this bald conflict of interest results in regulators approving drugs with minimal testing for clinical effectiveness or for adverse reactions (Light, 2010). This pattern lies at the center of the Risk Proliferation Syndrome. One in every four new drugs results in adverse reactions serious enough that the regulators who approved them as safe issue their most severe warning or have the drug removed from the market (Lexchin, 2012; Light et al., 2013). For priority drugs that are reviewed on an accelerated basis, that risk has risen to one in every three new drugs. Over years of independent evaluations, Prescrire found that among drugs approved, nearly twice as many are harmful enough to be regarded as not acceptable as the number found to offer a clinical advantage over existing drugs. On the effectiveness side of approvals for drugs, independent review experts conclude that 85–90% of new drugs are little or no better than existing drugs (Lexchin et al., 2003; Lexchin, 2011; Lexchin and Light, 2012). Massive marketing to physicians and patients, which companies spend more on than on research, successfully promotes these new minor variations as better and desirable (Gagnon and Lexchin, 2008). The marketing drives the Risk Proliferation Syndrome, leading to about 130,000 deaths a year in the US from prescription drugs taken properly, plus another 60,000–80,000 deaths from overdoses and misuses. The opioid crisis is a recent example of this Risk Proliferation Syndrome that has been in force for years (Light, 2010). In Europe, over 200,000 deaths from properly prescribed drugs and 20 times those numbers in hospitalizations from serious adverse reactions occur—about 4 million hospitalizations in Europe (Gøtzsche, 2013). The most frequent treatment of adverse drug reactions is to prescribe another drug, which introduced its own adverse risks.

The high costs of newer drugs, patented for profits through government-protected prices, increase inequalities of access, and health disparities and thus contribute to Phelan & Link's paradox that controlling disease may increase health disparities. Increasingly, the costs of new medicines are threatening entire health budgets and crowding out curative services (Iyengar et al., 2016). This leads to rationing, often by income. It seems time to consider a radically different way to construct research, development, manufacturing, and sales in order to reduce health disparities by addressing real health needs at low cost. Such an approach may seem utopian but is actually worked out and in operation now.

[1]The inverse care law holds that health care is inversely related to need. Those who need services least get the most, and those in greatest need get the least.

THE DRUGS FOR NEGLECTED DISEASES *INITIATIVE* MODEL

Over the past 15 years, the Drugs for Neglected Diseases *initiative* (DND*i*) has developed a non-profit, public-private, virtual collaborative that is guided by principles and embodied in practices that lead to research, development, testing, and manufacturing of more effective medicines to treat patients and populations of greatest need at low cost and thus reduce health disparities (DNDi, 2019). Principles of the DND*i* model include: putting patient needs, not profits, at the heart of R&D for public health; making sure (through using patents and licensing rights to maximize public health rather profits) that better medicines are affordable and available in the communities who need them most; using open, transparent collaboration to harness the best applied science from public, academic, private sources; networking globally on "the broadest possible sharing of research knowledge and data" to facilitate scientific exchange and research capacity; and piloting new approaches to innovation for a more effective, equitable pharmacological research systems. Central to new approaches is establishing intellectual property policy around pro-access licensing terms in contractual agreements on a non-profit basis. While DND*i* has focused on neglected diseases in lower-income countries in the global South, it may serve as a model for nations or regions like the EU that wish to develop high-quality, low-cost better drugs in ways that reduce health disparities. We will start with the background of DND*i* and its development.

A seminal publication in 2001 showed that over a period of 25 years, only 1.1% of new drugs were approved specifically for neglected diseases, despite the fact that these diseases represented 12% of the global disease burden (MSF, 2001). From 2000 to 2010, that figure rose only to 4%. The report, *Fatal Imbalance*, provided the evidence needed to advocate for action and change, within and beyond the global health community. It embodied new approaches and alternative R&D models to address market and policy failures, notably by Doctors Without Borders or *Médecins Sans Frontiéres* (MSF) (MSF, 2001).

MSF used some of its Nobel Peace Prize money to cofound DND*i*, the Drugs for Neglected Disease *initiative* as a non-profit, collaborative organization, driven by patient needs and dedicated to developing more effective medicines for serious but economically neglected tropical diseases such as malaria, sleeping sickness, and Chagas disease. Its core partners consisted of five public sector institutions; one humanitarian organization, MSF; and one international research organization, the UN Development Program. The five public sector institutions were the Oswaldo Cruz Foundation from Brazil, the Indian Council for Medical Research, the Kenya Medical Research Institute, the Ministry of Health of Malaysia and France's Pasteur Institute (DNDi, 2014).

Through collaborations and partnerships with a score of pharmaceutical and biotech companies, over 50 universities and research institutes, and North-South projects, DND*i* orchestrated the development, testing, and manufacturing of six new treatments at low cost for a fraction of what pharmaceutical companies claim their R&D costs (DNDi, 2014, 2019). It has also overseen research for 12 new molecular entities (NMEs) and orchestrated 25 clinical trials for a fraction the cost reported by commercial pharmaceutical companies. These six new treatments, 12 NMEs and pivotal trials cost altogether about $200 million, about what a major company reports spending on a single phase of one drug.

This work has involved more than 125 staff in eight regional offices and over 350 collaborations in 43 countries. DND*i*'s non-profit public health projects have recruited staff and brought together research materials, and scientific know-how from nearly 20 pharmaceutical and biotechnology companies and over 50 universities and research institutes. North-South and South-South technology transfer projects and three disease-specific clinical research platforms were formed to strengthen research capacity in neglected disease-endemic countries. With its partners, DND*i* has conducted 25 clinical trials from Phase I to Phase IV implementation and pharmaco-vigilance studies, enrolling over 33,000 patients. The studies were carried out in compliance with international standards, despite often in remote and unstable areas. Suppose a constellation of states or a regional government like the EU decided to establish a non-profit, vertically and horizontally linked collaborative to undertake drug research, developing, trialing, and manufacturing. Might it cut down on patenting by largely minor innovations for profits and refocus on the public's health? Might it invert the relationship between controlling disease and health disparities? Is DNDi an example of what (Mazzucato, 2013) might call an *entrepreneurial collaboration* as an extension of the entrepreneurial state?

An Illustration: Eradicating Hepatitis C

The growing epidemic of hepatitis C and its co-infection with HIV is growing and already causing about 400,000 deaths from HCV-related disease. Its prevalence is highly skewed toward lower -income populations and countries and disadvantaged groups within nations (DNDi, 2014; Unitaid, 2017b). Major advances known as DAAs, or direct acting antivirals, discovered largely through public funding but also by high mark-up firms, have recently revolutionized treatment. Instead of years of treatment with toxic side effects, patients are cured within a few months, with few adverse reactions. Based on patents and related rights in commercial markets, however, companies have charged up to $1,000 a pill and threatened the national budgets of even wealthy nations (Iyengar et al., 2016).

By contrast, DND*i* and its parent, Doctors Without Borders/*Médecins Sans Frontières* (MSF) started researching and testing selected combinations of newer and existing DAAs that fill genotypic gaps and are effective even in persons with HIV or HCV (Unitaid, 2017a). They are producing pan-genomic pills for patients and whole populations. They license to qualified low-cost manufacturers and construct what I think should be called "*markets for public health*," using prices 100 times lower than in affluent, commercial markets as part of population-based campaigns (DNDi, 2018a). The nature and organization of such markets warrant further analysis.

Key to DND*i*'s methods are the roles of earmarked or special monies (Zelizer, 1994) from several partners and on an international scale. In medical and economic sociology, we need to draw on the very creative work of anthropologists like Jane Guyer to reconceive the deep inner life of currencies, especially in health care (Guyer, 2012; Wilkis, 2014). DND*i* also develops national public health markets on the "demand" side so that markets become more viable on both sides—greater risk and disease awareness, better products and more effective delivery (DNDi, 2017). How DND*i* oversees and orchestrates both the supply and demand sides of a public health market (which have very different cultural issues) warrants further study.

Since DND*i* oversees the construction of integrated, networked pre-markets for development and then markets for population-based public health, its strategies are of great interest to large states like the US or China and to regional governments like the EU. For-profit health care corporations as well as private non-profit and public institutions are involved. Theoretically, DND*i* is doing what pharmaceutical market theory says is impossible. The construction of such health care markets, their organization, ethics, and governance have wide implications for reducing health disparities elsewhere.

Markets for public health have existed for a long time; but their logic, values, organization, and structural features have not been sufficiently theorized or studied (Chorev et al., 2011). What is the coinage of the realm? What investments are being made, by whom, and for what kinds of returns? Should gain and loss measured in terms of population health gain and loss, like QALYs or DALYs? If there is a long latency period, as with reducing the risk for cervical cancer or hepatitis C or HIV, should a substantial discount rate be applied? Regardless of the answer to this question, is the goal of this kind of market increased labor force participation, productivity, and reduced health disparities, rather than profit?

The current example of Hep-C and the breakthrough of new DAA drugs has special relevance to addressing global health inequalities today (DNDi, 2019). It addresses a major problem in recent decades of new medicines that have the ability to reduce inequalities in a population's health but are priced under patent protection so that inequalities by income are exacerbated rather than reduced. To take the current example, patents and IP entanglements aside, DND*i* and MSF have shown through independent clinical trials that cost much less than big-pharma commercial trials, that *everybody* with Hep-C could afford these drugs with a cure rate of 94–96% and costs about 1% of posted prices in the United States. By contrast, monopoly pricing, and legally induced inequality have been worsened by companies proliferating minimally innovative, secondary patents, such as patenting new uses, new combinations, and a separate patent for how a given drug decomposes as it travels down the digestive tract (I-MAK, 2018). Resulting "patent thickets" stifle competition and innovation, block access and human rights, and extend monopoly rights for years.

PATENT RIGHTS FOR PUBLIC HEALTH

Theoretical and empirical studies have challenged many aspects of the standard patent claims made by companies, which hold that patents are necessary to reward the large risks and costs of research for new, "innovative" drugs with monopoly prices and defenses against competitors for a sustained period (Gøtzsche, 2013; Light et al., 2013; Gaffney et al., 2018). In response, theoretical models to delink research costs from prices have been developed (Cohen, 2002; Kapczynski et al., 2005; Outterson, 2006; Petryna, 2006; Correa, 2008, 2014; EFM't Hoen., 2009; Biehl and Petryna, 2013; Lemmens, 2013; Outterson et al., 2016; UN, 2016).

A number of complementary organizations and initiatives are addressing patent proliferation and monopoly pricing [e.g., (I-MAK, 2018)]. Nearly all of these aim to move as rapidly as possible to generic production and low costs by eliminating or circumventing patents. DND*i*, however, uses patent and licensing powers to *guarantee low prices and wide access* at low profits (DNDi, 2019). How they accomplish this is now well-known and needs further study. One might call this *patenting and IP for public health*. It uses IP and patenting rights to maximize public health gain rather than profits. This is a concept that warrants the combined interests of experts in global ethics and global health injustices. MSF and DND*i* use monopoly rights to guarantee low prices and foster competition through non-exclusive licenses, thus putting markets for public health into practice (DNDi, 2018a).

The most advanced new market being constructed to increase uptake if DAAs and reduce Hep-C is in Malaysia (DNDi, 2018b, 2019). It illustrates how important is a creative and dedicated "buyer," like the Ministry of Health in Malaysia. Markets for public health differ radically from markets studied by economic social scientists and are designed to elevate the position of the most ill and disabled in the hierarchy of lives, rather than the most affluent and resourceful [(Fassin, 2018):124].

In conclusion, health disparities need not be exacerbated by advances in medicine. Through models like DND*i*, researchers, key actors on the demand and supply sides of health care markets, providers and suppliers can come together in joint collaborations, as is already happening in DND*i* -led markets for public health. Conceptually, one needs to broaden current theories and studies beyond commercial markets, because their foundations, cultures, concepts of "buyers" and "sellers," and organizational features can provide insights into a more humane society, where "buyers," "sellers," and "consumers" work together to achieve shared, health-promoting ends. Developing the theory of markets for public health, with empirical evidence, and understanding their organizational and cultural complexity could lay the foundations for a new generation of virtual collaborations to reduce health disparities. Studies could provide the basis for how economic social scientists, welfare economists, moral philosophers, and international leaders for greater health justice conceptualize and address the inequalities of current health care markets.

DATA AVAILABILITY STATEMENT

All datasets generated and analyzed for this study are included and cited in the article/supplementary files.

AUTHOR CONTRIBUTIONS

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

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Pathopolitics: Pathologies and Biopolitics of PrEP

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This paper unveils the pathologies that are produced and sustained by the pharmaceutical industry, specifically by Gilead Sciences, Inc. Broadly defined, pathopolitics is the politics of treating and/or reproducing pathologies. This paper examines pathopolitics in the context of PrEP, or *pre-exposure prophylaxis,* an antiretroviral medicine that prevents HIV transmission. Although Gilead promises to prevent a pathology through PrEP, it reproduces social and biological pathologies by exposing certain people to higher risks of infections and diseases, thus epitomizing the operating logic of the pharmaceutical industry: that life is protected only insofar as it offers surplus economic and social value. This essay raises three fundamental sets of questions: (1) What are the techniques and mechanics of pathopolitics? (2) How does the pharmaceutical industry produce and exploit surplus value? (3) What is the nature of the relationship between the pharmaceutical citizenship and pathopolitics?

Keywords: PrEP, HIV, pathologies of power, Corporate Social Responsibility (CSR), Gilead Sciences, Inc., biopolitics

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INTRODUCTION

"Contemporary biopolitics is *risk politics.*"
—Nicholas Rose (2001, 1: emphasis original)

Following the beginning of the epidemic in the 1980s, HIV and AIDS have become a central field of biopolitical interventions and biomedical surveillance. Informed by a pseudo-scientific homophobia, the biopolitics of HIV has targeted less the ending of the epidemic than disciplining gay men and curing them of alleged pathological practices. Halperin (2015, p. 206) notes that by the end of the 1980s, epidemiologists considered changes in the sexual behaviors of gay men as the "most profound modifications of personal health-related behaviors ever recorded." The fear of AIDS of course played a crucial role in this. The Western public health rhetoric, likewise, has often disciplined deviant sexualities by spreading the fear of HIV transmission (Tewksbury, 2003; Holmes and O'Byrne, 2010). The same fear is adamantly kept alive today to surveil and extract profit from gay men's bodies, HIV+ or not (Race, 2009). In 21st century, "biopolitics becomes bioeconomics driven by the search for what Catherine Waldby (2002) has termed 'biovalue': the production of a surplus out of vitality itself" (Rose, 2001, p. 15).

The convergence of biopolitics into bioeconomics and the subsequent extraction of value out of "vitality itself" was only possible as a result of a radical transformation of the meanings of health, disease, and risk. With developing medical technologies, "our increased knowledge about nutrition, disease, and medicine," Dean wrote, "has not produced a greater sense of security but, on the contrary, a heightened sense of risk" (2009, p. 62). Dumit (2012, p. 1) too noted.

> "Health in America today is defined by a double insecurity: never being sure enough about the future—always being at risk—and never knowing enough about what you could and should be doing. Paradoxically, the insecurity continues to grow despite there being an equal growth in the amount of medicine consumed each year—as if the more we know, the more we fear; and the more we fear, the more preventive actions and medications we need to take."

Dumit (2012) also called our attention to how the pharmaceutical industry redefined (surplus) health to create new markets and generate demand for new medicine. Health today means not preventing diseases but reducing risk since everyone is assumed to be "inherently ill." Being inherently ill hits gay men close to home, for they have long been conceived and have conceived themselves as always already sick, even before the epidemic.

Since 2012, the pervasive commodification and regulation of queer sexualities and bodies has taken a new form with the expansion of the use of antiretroviral medicine for HIV negative people. The new definition of health as risk prevention requires that one is "PrEPared" all the time, as many gay men like to put it on the social media. This, Thomann (2018) argues, indexes the pharmaceuticalisation of the neoliberal sexual actor, as self-responsible as self-interested and rational, who is encouraged to respond to HIV risk pre-emptively through PrEP, trade name Truvada, an antiretroviral (ARV) medicine manufactured by the transnational pharmaceutical company Gilead since 2004. Since 2012, it has been used as pre-exposure prophylaxis, the scientific term from which the more common, more euphonic, and market-friendly abbreviation "PrEP" is derived. Truvada alone, when taken daily or as otherwise recommended, is more than 99% effective in providing protection against HIV (Grant et al., 2010; Anderson et al., 2012).

In this essay, I focus on the biopolitics and pathologies of PrEP. Foucault developed his ideas on biopolitics that first appeared on the first volume of *The History of Sexuality* during a series of lectures gathered under the name of *Society Must Be Defended*. There he explained, "Biopolitics deals with the population, with the population as a political problem, as a problem that is at once scientific and political, as a biological problem and as power's problem" (2003, p. 245). By biopolitics, I specifically refer to (a) governance of bodies in the name of health and (b) management of life chances, that is, manipulating who will be protected from and exposed to risk. Medical anthropologist and physician Paul Farmer chooses the phrase *pathologies of power* to describe this latter function of biopolitics invested in determining "who will suffer abuse and who will be shielded from harm" (2003, p. 7).

I offer the term *pathopolitics*[1] to draw attention to the pathological nature of biopolitics under the pharmaceutical industry. The leading actor of pathopolitics is the pharmaceutical industry, commonly known as the Big Pharma, whose *raison d'etre* is curing pathologies, even though it survives through the reproduction of both biological and social pathologies. Pathopolitics is essentially biopolitics enacted by the pharmaceutical industry; in other words, it is a particular way of dealing with the population as a political and medical problem that needs to be distinguished from biopolitics writ large. Instead of relying on governmental or non-governmental techniques of managing life and death, pathopolitics operates primarily through corporate strategies of risk distribution.

Pathos in ancient Greek means, among other things, suffering. Therefore, pathology (*pathos-logia)* by definition signals suffering and pathopolitics can be defined in terms of ending and/or perpetuating pathologies as well as the suffering they cause. Paradoxically, the contemporary pharmaceutical industry prevents some pathologies while reproducing others—indeed, sometimes it produces certain pathologies precisely to treat others. Like biopolitics, pathopolitics makes live, lets die, and makes die, but in a slightly different fashion. Administering enough or too much medicine into bodies or depriving bodies of the necessary medicine is how pathopolitics determines who will be exposed to and protected from risk. While biopolitics can produce death in numerous distinct ways, death under pathopolitics will only take the shape of a disease or a pathology, which can mostly be prevented.

There are essentially two problems with the pharmaceutical industry and its pathopolitics: on the one hand, it penetrates too deeply into people's lives and bodies and turns them into a not-so-fictitious capital. The human body and its biological functions are made into physical assets that keep producing profit as long as they are alive (and, in our case, aroused). In this instance, the omnipresence and omnipotence of the pharmaceutical regime is what renders it extremely violent. On the other hand, the problem is its absence: the pharmaceutical regime is not equally concerned about populations whose medicalization does not promise an inexhaustible source of profit. The violence occurs in this case not from being subjected by/to pharmaceutical regimes but from being ignored/erased by them. Pharmaceutical (mis)management of bodies is a double-edged sword invested in the "overtreatment of some and undertreatment of others" (Tomes, 2016, p. 2). The phenomenon is also carefully documented in *Global Pharmaceuticals* by Petryna et al. (2006) who described the constitutive contradiction of pharmaceutical markets in terms of *access* vs. *excess*.

Instead of looking at how PrEP intervenes in the prevention of pathologies as has been done abundantly by public health and HIV experts, I examine pathologies that are produced and sustained by the pharmaceutical industry in tandem with widespread structural inequalities. To accomplish this, I raise three interrelated questions: (1) What are the techniques and mechanics of pathopolitics? (2) How does the pharmaceutical industry produce and exploit surplus value? (3) What is the nature of the relationship between the pharmaceutical citizenship and pathopolitics? In response to these questions, I argue that although Gilead Sciences, Inc. promises to prevent a pathology through PrEP, it reproduces social and biological pathologies that expose certain people to higher risks of infections and diseases. This happens in three fundamental ways: by setting exorbitant drug prices, halting generics, and relocating pathologies to developing countries. Here, I also claim that PrEP lays bare the

[1]I would like to thank Susan Craddock for offering the term "pathopolitics" to conceptualize my work on PrEP and Gilead; David Valentine, Dominique Tobbell, and Aren Aizura for their most helpful feedback; and, Nicholas Greatens for his extraordinary editorial skills. I also have to thank Karen-Sue Taussig for drawing my attention to the previous invocations of the term pathopolitics. The first instance is Mariella Pandolfi's use of the term in 2008 (see Allen, 2012) while analyzing the intertwined nature of humanitarian aid and military intervention in the case of NATO's bombardment of Serbian forces during the Kosovo War. The second is a recent dissertation (see Huber, 2017) exploring "the increasingly politicized nature of the cultural representation of emotions in contemporary American culture." Although in both instances Foucauldian biopolitics is what inspired the authors' use of pathopolitics, I am employing the term with completely distinct purposes that are not inspired by either of its previous uses.

constitutive failure, or the operating logic, of the pharmaceutical industry: life is only worth protecting from risk as long as it can offer surplus value. Finally, I make the case that uncritical advocacy and consumption of a drug in the name of health or pleasure can inadvertently reproduce pathopolitics, for it will invisibilize the unjust—or, to put it differently, pathological—mechanics through which risk is distributed.

In this article, I interpret the violence enacted by pathopolitics on those undertreated as an instance of slow violence, so normalized, pervasive and pernicious that it rarely makes into news. Nixon (2011) employs the term slow violence to account for the environmental damage both on nature and human life, which is readily ignored because it is neither spectacular nor instantaneous. As a result of slow violence, people are perpetually debilitated—living each day without necessary medications or care brings them one step closer to illness. Slow violence brings slow death, which Berlant notes, "shapes our particular biopolitical phase: mainly, people do live in it, just not very well" (2007, p. 780). To paraphrase Foucault, the question is if the pharmaceutical industry's objective is essentially to make live, how can it let die? (2003, p. 254).

PREVENTING HIV AT THE COST OF $24,000

"With its vested interest in biological catastrophism, neoliberalism is similarly intent on profiting from the 'unregulated' distribution of life chances, however extreme."

Cooper (2011, p. 11)

When it comes to the production and sale of ARVs, Gilead is the largest and richest company and Truvada is one of its most important sources of profit, bringing in more than US $ 3 billion each year (Langreth and Brown, 2019). The development of new and better ARV medicines led Gilead to create alternative markets for its old compounds to extend patent protection (Spieldenner, 2016), which is commonly known as "evergreening." Truvada has been a part of anti-retroviral treatment of HIV since 2004. Later, in 2012, it was approved by the Food and Drug Administration (FDA) as PrEP. It consists of Emtricitabine and Tenofovir, which together inhibit the replication of HIV and thereby controls its growth. The first successful PrEP trials (iPrEx) were initiated in Peru and Ecuador in 2007, and were extended to Brazil, South Africa, Thailand, and the U.S. In 2010, the first set of results demonstrated that Truvada provides protection from HIV infection by up to 99% when taken daily (Grant et al., 2010; Anderson et al., 2012). For public health authorities this was a harbinger of a new era in HIV prevention and for many in the queer community it heralded a sexual revolution, which offered the chance to say goodbye to condoms, which is not necessarily antithetical to the principles of public health and HIV prevention (Brisson et al., 2019; Rojas Castro et al., 2019). Three decades after the AIDS epidemic, gay and trans people were once again able to enjoy sex without latex barriers and with virtually no risk of HIV transmission. This found widespread criticism from influential figures of the early AIDS movement such as Larry Kramer and Michael Weinstein, the president of the AIDS Healthcare Foundation. While the former considered PrEP as an erasure of the history of AIDS and the end of the fight against HIV (Healy, 2014)[2], the latter suspected an ominous increase in the transmission of sexually transmitted infections (STIs) (Ryan, 2017).

Gilead, who spent more than 100 million dollars in 2017 alone on advertising Harvoni, a Hepatitis C medicine, spent merely several hundred thousand dollars per year on promoting PrEP (Fitzsimons, 2018). This considerably small-scale marketing strategy of Gilead can be interpreted on two registers: first, as I will mention in more detail below, Gilead sought to portray PrEP as a public health intervention and not a commercial tool. Second, gay men, public health experts, and government agencies took it on themselves to popularize PrEP. In 2014, the CDC suggested half a million of uninfected Americans should go on PrEP as an HIV prevention strategy. In 2019, Gilead, the producer of Truvada, announced in its publicly accessible second quarterly earning results that more than 213,000 Americans are on PrEP and the numbers are rapidly growing. Nevertheless, PrEP uptake has counterintuitively been slow in spite of its often-cited (by Gilead and CDC) public health potentials and it remains inaccessible to those who need it most (CDC., 2019). Truvada for PrEP in the US costs approximately $24,000 per year plus the expenses of visits and obligatory tests every 3 months. The exorbitant prices are commonly justified by citing the expenses of research and development even though "after tax deductions only about 1.3 percent of the money that the industry spends actually goes into basic research, the type of research that leads to new medications" (Lexchin, 2018, p. 2). Moreover, the research necessary for the discovery of new drugs is usually undertaken by universities or governments and funded by philanthropic organizations or the NIH. The Democratic congresswoman Alexandria Ocacio-Cortez brought to public attention in May 2019 that the research that enabled the use of Truvada as PrEP was publicly funded through taxes[3]. Following is an excerpt from the testimony of Dr. Robert Grant, who is the leading scientist of the first successful PrEP trial:

> I believe that the root cause of low PrEP access is the high price of the medication. PrEP can be manufactured and distributed, including a profit, for about $6 per person per month. Gilead charges more than $2,100 per person per month, a 35,000% markup. Gilead's prices continue to increase: Gilead has increased the price of Truvada 76% since I published evidence of PrEP efficacy in 2010, using US government funding. You might hear that "no one pays" the list price after discounts. This is not true [. . .] In my experience, public health officials are reluctant to promote PrEP in their jurisdictions because of the high price of PrEP medications (House Committee on Oversight and Reform, 2019).

[2]It is reported that Larry Kramer later changed his opinion on PrEP and recognized its potentials, while still being unapologetically critical of Gilead.

[3]According to an investigative report published in 2016, Gilead avoided paying almost $10 billion in taxes thanks to untaxed offshore profits (Merle and Johnson, 2016).

McKenney et al. (2017) demonstrated PrEP drug costs must be reduced to be a cost-effective and efficient prevention method. Along the same lines, Patel et al. (2017) noted insured people are four times as likely to use PrEP compared to the uninsured. Doblecki-Lewis et al. (2017) too pointed out that white people and people with health insurance are more likely to use PrEP. The biggest obstacle in providing PrEP for all is the absence of generics in the US (although they can be ordered from abroad). Gilead substantiates the popular belief that Big Pharma, infamous for morally questionable marketing techniques like patent interference and evergreening, has blood on its hands when it comes to generics. In 2018, the FDA published a list of pharmaceutical companies blocking the production of generics. Gilead secured a place on the list for preventing generics of Truvada among a few other medicines (FDA, 2018). Moreover, the company is accused of reaching agreements with potential generic manufacturers behind closed doors to halt generics (Rowl, 2019). When the unethical and rapacious actions of Gilead hit the fan, the company eventually announced the introduction of generic PrEP in the US in 2020. Nevertheless, the patient groups and activists are not thrilled about the news since Gilead will share the patent with a single manufacturer, Israel-based Teva, one of the pharmaceutical companies accused of fueling the opioid crisis in the U.S. (Lovelace, 2019). This is naturally not expected to result in a significant decrease in the price of Truvada due to the continuing monopoly over the patent. The timing of this announcement is highly suspect too: first, the patent of Truvada is already going to expire in 2021. Second, at the time of this writing, Gilead obtained approval for another medicine, Descovy, as PrEP (Fitzsimons, 2019). The company has been sued in the past few years for intentionally deferring the use of Descovy until Truvada's patent expires, even though the former is proven to be less toxic. This crystallizes the fundamental mechanics of pathopolitics: not only does Gilead perpetuate pathologies and suffering by making life-saving drugs inaccessible as a result of high prices and lack of generics, but also it openly causes those who take its drugs to suffer easily preventable life-threatening side-effects. This is a crucial point for one of the central claims this paper makes: in the next section, I will discuss how human life is protected only insomuch as it promises financial returns. Nonetheless, the intentional delaying of Descovy makes clear that even those whose lives can be capitalized are expandable within pathopolitics.

According to the data provided by the U.S. Department of Health & Human Services, populations disproportionately affected by HIV are gay men (and especially gay men of color), people of color, queer and trans people (of color), and IV substance users. Notwithstanding, studies showed those that are disproportionately affected by HIV also have greater difficulties accessing PrEP (and, treatment too): IV drug users (Guise et al., 2017), young transgender women (Wood et al., 2017), black men who have sex with men (MSM), transgender women (Hoots et al., 2016; Garnett et al., 2018), and male sex workers (Underhill et al., 2014) reported higher barriers to access PrEP. These studies reported that disparities in PrEP uptake stem from mistrust in the medical system, lack of information, limited awareness, lack of universal health care and high prices of pharmaceuticals. In 2017, after receiving widespread criticism by activist groups like ACT UP, Gilead broke the silence and finally admitted the racial disparities in the use of PrEP. The numbers shared by Gilead disclosed that the white population makes up 27% of new HIV incidents but 75% of PrEP users; whereas African-Americans and Hispanics respectively make up 44% and 23% of new cases but only 10 and 12% of PrEP uptake (Levin, 2017). Another set of results was released in March 2018:

> In 2015, there were approximately 1.1 million Americans who could potentially benefit from PrEP: 500,000 African Americans, 300,000 Latinos, and 300,000 whites. However, analysis of available data on PrEP prescriptions finds that 7,000 prescriptions were filled at retail pharmacies or mail order services for African-Americans [that is, only 1%] and only 7,600 for Latinos [3%] during a similar time period (September 2015–August 2016) (CDC., 2018).

On the other hand, today women represent only 11.4% of current PrEP consumers (no racial or ethnic data is provided) (Levin, 2017). Although Gilead claims a growing increase in PrEP uptake, a set of recent studies still point out significant racial and gendered disparities (Golub, 2018; Kuehn, 2018; Caponi et al., 2019; Jenness et al., 2019).

These numbers would be confusing for someone who has recently watched Gilead's TV ads or visited Gilead's social media campaign *HealthySexuals*. Both are saturated with the images of queer people of color (POC), operating within a framework of public health and centering them as the targets of HIV **prevention**[4]. In a statement on its TV ads Gilead declared, "When developing this campaign, it was important to us that the materials feature a diverse group of individuals who are representative of the communities most impacted by HIV, including young Black and Latino gay men, as well as cis-gender and transgender women" (Fitzsimons, 2019). What Gilead misses is that although PrEP is advertised as targeting primarily queer POC, inclusion and outreach take more than online visual **representation**[5,6]. Gilead's original PrEP strategy was to portray it as an essential public health tool not a "commercial opportunity" as expressed by Gilead's spokesperson Cara Miller in 2015 (Chen, 2015). Today, Gilead is heavily invested in advertising PrEP, yet, as an example of its marketing genius that disguises commercial gains under the roof of public health, the company says, "TV advertising is a natural evolution

[4]Gilead's new TV ad for Descovy is called "Prep Up, Step Up." The meticulous performance of inclusivity that started with the first TV ad on Truvada, entitled "I'm on the Pill," continued with the new marketing campaign showcasing a trans woman of color, gay men of color, and a drug queen.

[5]I personally participated in marketing research for Gilead's existing and future webpages twice in 2018. Both times, I was shown real and animated images of POC and asked my opinion on the accessibility and attractiveness of the visuals as well as the information provided.

[6]The company proudly underlines that it has invested $100 million in community-based organizations to support HIV prevention awareness (Tindera, 2018). Based on my research in Turkey, I can say that if the nature of its investment is in any way similar to its philanthropic operations in Turkey, those millions of dollars are spent less on actually strengthening communities than on the production of what can be a called a community-to-pharmacy pipeline. In Turkey, Gilead's support of local HIV organizations more often than not aims at reaching out to HIV+ persons who are not yet diagnosed to put them on treatment.

of efforts to educate people about risk factors and what they can do to protect themselves" (Tindera, 2018).

I would like to go back to the *HealthySexuals* to raise a few urgent questions. HealthySexuals is a web platform created by Gilead, although the visitors, unless they scroll all the way down where they can spot Gilead's logo, would not notice the origin at first sight since the corporate identity behind the platform is carefully veiled to make it more user friendly. The platform invites everyone to "find [their] healthysexual side" and informs them that "there are things everyone can do to help protect their sexual health." The homepage welcomes visitors with a brief, minute-long video, where PrEP is only mentioned toward the end of it, probably to avoid to be registered by visitors as an aggressive advertisement. The HealthySexuals supposedly gives the message of protection and its sole purpose is to provide information on sexual health, which, to the trained eye, is just another way of advertising. What the HealthySexuals campaign is not capable of asking—so I will ask for Gilead—is what does it take to be healthy? Is PrEP enough if one cannot even afford healthy food and basic medical care? The HealthySexual campaign encourages people to "be sexy and healthy" and to "talk healthy," fetishizing health as a commodity required to be sexually attractive while, at the same time, pretending as though being healthy is simply a personal choice.

The individualization of responsibility not only for health but also for risk (Thomann, 2018; Nicholls and Rosengarten, 2019) is a conspicuous example of how pharmaceuticalization and neoliberalism are inextricably intertwined. In reference to the popular PrEP campaign implemented in the NYC in 2015 that encouraged gay men of color to "stay sure" and "play sure," Thomann (2018) discussed the pharmaceuticalized neoliberal sexual actor who must assume exclusive responsibility for his sexual health. Consequently, responsibility, when located in the individual, is avoided by public and private institutions. What HealthySexuals campaign points out is yet another way in which the neoliberal pharmaceutical regime creates pathologies through depoliticization of health. Whereas biopolitics is about politicization of health, pathopolitics is about its depoliticization. Being able to price a medicine at about $2,000 per bottle requires an understanding of health that is not rooted in social justice or politicized. Under pathopolitics, health is treated as a product of free-market whose purchase is up to the individual's discretion. In order to cover up its complacency in the unequal distribution of health, Gilead puts the burden of being healthy on the individual or offers nominal assistance. The most popular strategy it employs to distort the reality of how it reproduces pathologies is commonly known as Corporate Social Responsibility.

Philanthrocapitalism: Saving the World Through Corporate Social Responsibility?

Amidst all the criticisms directed toward Gilead's outrageous pricing policies, two things remained stable: the increase in Gilead's earnings (Owens, 2019) and the global recognition for its corporate social responsibility. The pharmaceutical giant is extremely proud of its success in "promoting global health" and does not shy away from branding itself as a global health super hero. Gilead dedicates a meticulously curated section to "responsibility" on its official website, placed at the very upper center, where it catches the eye before anything else. The social responsibility initiatives include *Compass Initiative*, a 10-year, $100 million partnership with community-based organizations working to combat the HIV/AIDS epidemic in the Southern United States; *HIV Age Positively Initiative*, supports programs that may help improve quality of life and health for aging PLWHIV; *US Patient Access,* helps patients to access Gilead therapies accessible for uninsured individuals and those who need financial assistance; *Developing World Access*, supports the developing world to fight against HIV/AIDS and viral hepatitis usually by funding regional organizations and cheap generics produced by Indian companies to be exclusively used in low-income countries; and, *Corporate Contributions*, an example of which is Gilead Fellowship awarded to non-profits, patients advocates, and medical researchers. Gilead is also the first pharmaceutical company to join the Medicines Patent Pool whose vision is "a world in which people in low- and middle-income countries (LMICs) have rapid access to effective and affordable medical treatments and health technologies" through voluntary licensing and patent pooling. The company whose 2019 revenue was a little more than $22 billion and whose total worth is around $70 billion prides itself endlessly on having spent $300 million only in cash donations and for being chosen the leading corporate funder 4 years in a row for helping to address HIV/AIDS epidemic by Funders Concerned About AIDS (Gilead Impact Report, 2017).

In the U.S., Gilead offers limited opportunities for uninsured people and people who are insured but have to pay co-pays. On the popular Facebook group *PrEP Facts: Rethinking HIV Prevention and Sex,* created by Damon Jacobs, a self-proclaimed *PrEP warrior* dedicated to mainstreaming PrEP, one can find numerous posts by gay men sharing their happiness with the Gilead Co-pay Assistance Program (or CAP, from which I also benefit to avoid monthly co-pays for my ARV medicine). Only those who are privately insured are eligible for CAP and can benefit from up to $7,200 annual help with drug coverage. It must be noted that this is a common practice among drug manufacturers—I am personally enrolled in two other co-pay programs offered by Jannsen and ViiV. Sadly, Medicaid participants are not eligible for Gilead assistantship. Although states that have expanded Medicaid cover Truvada for PrEP, the co-pays and other treatment-associated costs—transportation, visits etc.—can still be a huge burden for many. As Allen et al. (2017) observed, "insurance alone may not translate into access to health care" as substantial barriers exist even for the insured due to patient-level (family/work barriers), provider-level (perceived discrimination etc.), and system-level (coverage, financial, and access barriers) factors.

Ecks (2008, p. 178) convincingly exposed that strategic mechanisms such as assistance programs are inherently insufficient and employed to "distract from less obvious market mechanisms" that create the need for assistance programs in the first place. The drug donations and assistance programs have been also criticized for justifying monopoly, not being sustainable or reliable, and for pharmaceuticalizing disease

and depoliticizing health (Rajan, 2017, p. 190). Žižek (2006) opines that the real evil of corporate responsibility is hidden in its ability to offer a fictitious moral action without structural transformation. Notwithstanding, as though the solution was to offer more financial assistance, on July 2018, Gilead raised the annual limit on the CAP from $4,800 to $7,200, which was widely celebrated by the PrEP-warriors.

The good news came right before Gilead announced a potential price increase of 4.9% for Truvada (Rivas, 2019), which barely found any coverage within the mainstream LGBQT media outlets. What did attract attention was the deal reached with Gilead following Donald Trump's State of the Union Address in February 2019, where he pledged to end HIV in the US (The Lancet HIV, 2019). According to the agreement, which came a few months after the US government sued Gilead, Gilead is to donate 2 million bottles of Truvada per year for up to 11 years. The donated bottles will be distributed by a new federal program called Ready, Set, PrEP—yet, the patients will still be responsible for paying for the regular blood tests and medical visits. This seemingly beneficent step taken by Gilead was rightfully called an "empty gesture" by a 2019 Lancet Editorial, which concluded, "The donations from Gilead [. . .] are on the surface positive steps, but they will not close the gap in the number of people at risk and the number of people on PrEP sufficiently to counter the inequity in access to this proven public-health intervention." Besides, the CDC suggests there are 1.1 million people in the US right now who could benefit from PrEP and the amount donated would cover <200.000 individuals. In a context far away from the US, Whyte and her colleagues' work on Uganda revealed that price cuts by the big multinational pharmaceutical companies, action research programs, donor support, and even the production of cheaper generics are never sufficient to provide universal access to ARV (Whyte et al., 2006). Without significant regulation of drug prices, access to medicine will never be universal neither in the U.S. nor in Africa and that it was never meant to be.

"It is sadly ironic," Susan Craddock (2017, p. 58) wrote in her latest book, "that pharmaceutical companies might now profit socially if not financially from the disease burdens they helped create through their own strident pursuit of pharmaceuticals with hefty financial returns to the neglect of public health." The quote from Craddock reveals what is at the heart of pathopolitics: the pharmaceutical industry contributes to the emergence of pathologies it claims to cure. If the unreasonable pricing of medicine is how the pharmaceutical industry perpetuates suffering nationally, the prevention of access to generic medicine is what globalizes suffering. The 1995 TRIPS (Trade Related Aspects of Intellectual Property Rights) Agreement signed by the World Trade Organization is the quintessential reason behind the worldwide lack of access to generic medicine. The last step of the Uruguay Round of the General Agreement on Tariffs and Trade (GATT) was TRIPS whose mastermind was the U.S. government and the pharmaceutical lobby. It was the same pharmaceutical lobby of 41 companies who pressed charges against South African Government in 1998 and criticized president Nelson Mandela for trying to universalize ARV access through generics. TRIPS is causing hundreds of thousands of people to suffer numerous illnesses and face death. Hickel (2012, p. 526) argues, "The bulk of Swaziland's present AIDS burden can be directly attributed to constraints imposed by the TRIPS agreement and the resistance of the WTO and pharmaceutical companies to changing it."

When it comes to Gilead's CSR, there are two critical questions to be answered: Why aren't generics made available to U.S. patients and why does Gilead provide cheaper generics or donate medicine abroad? In response to the second question, Ecks (2008) claims some medicines are never meant to be affordable in the Global South. While losing the chance to exploit potential local medical markets, pharmaceutical companies win two other battles by donating medicine: they protect their good image and maintain the higher prices in the Global North (Ecks, 2008, p. 177). In essence, through drug donations and third-party generic agreements, not only will Gilead enjoy control over the locally produced drugs (Ecks, 2008) but it may partially prevent or delay any backlash from poor countries, which, as Melinda Cooper (2011) suggests, might end up igniting the public in the U.S. as well. Besides, Gilead might be rightly concerned about the lack of access to treatment in Africa. HIV/AIDS in Africa is a global concern and turning a blind eye to this would simply be a bad marketing strategy for the company who owns most of the patents on ARV medicine. One of the most important functions of CSR is to transform the conventional monstrous, greedy image of pharmaceutical companies. Or, as Fortune's *Change the World* list claims (Anderson-Minshall, 2016), Gilead can simply be a force for good (note the irony here).

As for the absence of generics for the U.S. citizens, Gilead's partners in crime are the insurance companies for profiting from the lack of universal healthcare and the U.S. government for failing to implement a functioning healthcare system. When Daniel O'Day, the CEO of Gilead Sciences, was asked during the congressional hearing to explain the lack of generic PrEP in the U.S., he gave as pretext "the government's willingness and ability to pay, market dynamics, and the structure of insurance markets specifically related to drug delivery" (HIV Prevention Pill, 2019). O'Day went on justifying the exorbitant prices on the grounds that Medicaid insurance covers Truvada for PrEP as though it does not create an immense burden on the taxpayer, who paid for the PrEP research in the first place. This pervasive normalization of lack of free healthcare and its domination by the insurance industry deceivingly moves the discussion away from those factors and agents that make it possible for the reign of the pharmaceutical companies. The insurance industry is among the principal actors who impeded the implementation of compulsory healthcare during the early 20th century (Hoffman, 2001). "American values" and capitalist market dynamics must also be accounted for here as state-sponsored healthcare was widely attacked based on its "un-American" nature that goes against the principles of free market (Hoffman, 2012). The most striking aspect of O'Day's response is how he verbalizes a dangerous open secret when he mentions "the government's willingness to pay." Examples such as Brazil, South Africa, and Turkey make clear that the pharmaceutical regime is not stronger than people and their lives when the governments take the necessary actions to put citizens' needs before the profit of pharmaceutical companies. As corrupt as it is, the system is not broken. It "works quite well at what it is

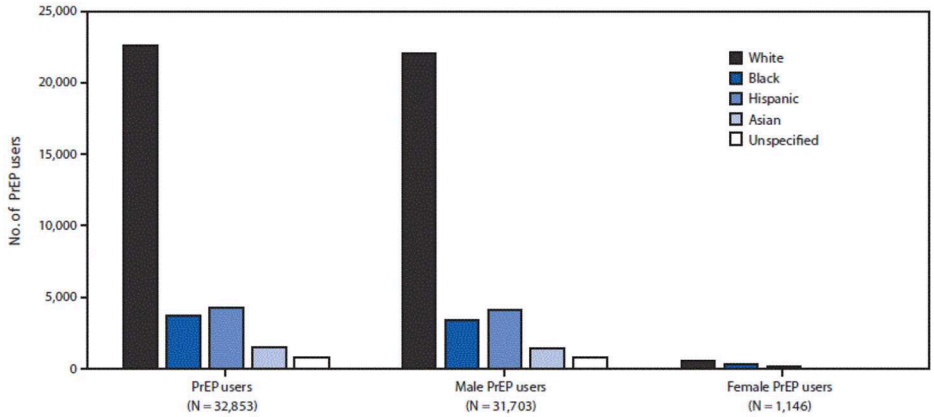

FIGURE 1 | Number of PrEP users by sex, race/ethnicity-IQVIA Longitudinal Prescription Database, United States, 2016. Adopted from Huang et al. (2018).

designed to do—provide a good return on investment" (Tomes, 2016, p. 416).

The question is whether "global corporate citizenship is not a brake in free-wheeling capitalism, but rather a strategy of extending and accelerating it by new means" as provocatively suggested by Ecks (2008, p. 178) or whether "the seemingly contradictory goals of ethical action and profit incentive are not mutually exclusive" as incisively pointed out by Craddock (2017, p. 57). Rajan too wrote that "ethics can be potentially opposed to surplus value but also deeply tangled within its logic" (2017, p. 21). According to him, ethics are not irrelevant but inherent to the extraction of value as it is materialized in the idea of corporate responsibility. Although Rajan is hopeful about the embrace of ethics by corporations and writes "one could envisage a value that is not just defining of capital but (in its ethical registers) also an alternative normative framework to capital," he is well cognizant that "corporations are perfectly capable of enfolding these concerns into their own value-generating enterprises" (ibid).

TO SWALLOW OR NOT TO SWALLOW: PHARMACEUTICAL CITIZENSHIP AND PATHOPOLITICS

> "Being poor, being black, being of color puts your life at risk. Your health is compromised when you do not have the external resources to support a life in all of its contingencies. And then of course, you are deemed responsible for your own ill health, for your own failure to look after yourself better. When you refer to structures, to systems, to power relations, to walls, you are assumed to be making others responsible for the situation you have failed to get yourself out of. 'You should have tried harder.' Oh, the violence and the smugness of this sentence, this sentencing."
>
> Ahmed (2017, p. 238)

In a piece called *chemical condoms* written in response to mainstreaming of PrEP, Preciado highlights the purpose of PrEP is not to improve consumers' life but to exploit them by creating an illusion of freedom [from fear] and liberation [from condoms] (2015). In contrast, I argue that the purpose of PrEP is precisely to improve consumers' life as long as they are able to consume and generate profit. The pharmaceutical industry cares about human life insofar as it produces a surplus value that can be extracted to accumulate wealth. In the words of Rabinow and Rose, pharmaceutical companies seek to "develop and maximize targets for pharmaceutical markets and other health-care interventions [. . .] in the name of the maximization of quality of life" (2015, p. 317). It follows that only those bodies that can be transformed into profit-making machines deserve a quality life, as is shown below. On the other hand, having one's life quality maximized comes with its own costs. "There exist biopolitical [or, pathopolitical] side-effects (in addition to physiological ones) to mass compliance with pharmaceutical mandates" (Dean, 2015, p. 234). In return for the protection the pharmaceutical industry offers, it expects full cooperation which necessitates complicity in distributing and relocating pathologies.

Figures 1, **2** provide evidence that when it comes to PrEP what is at stake is not so much public health as it is profit (as well as pleasure). PrEP is disproportinately enjoyed by white gay men and celebrated for eliminating the need for condoms. In the words of Race (2009, p. 15), PrEP is "emblematic of a broader technology of power that converges on embodiment, consumption, and pleasure in the name of health." The popular Facebook group mentioned earlier, *PrEP Facts*, is a perfectly suitable platform to follow the trends on PrEP use. With over twenty thousand members from all over the world but mainly the U.S., the posts on the page can be gathered under two broad categories: posts made by members who need guidance to access PrEP and stories about sexual liberation achieved a result of saying goodbye to condoms without fear (Race, 2018). One of the most common activities in the group is to create polls to see who is still using condoms and who is only practicing bareback (condomless) sex. The results always lean toward the latter. One

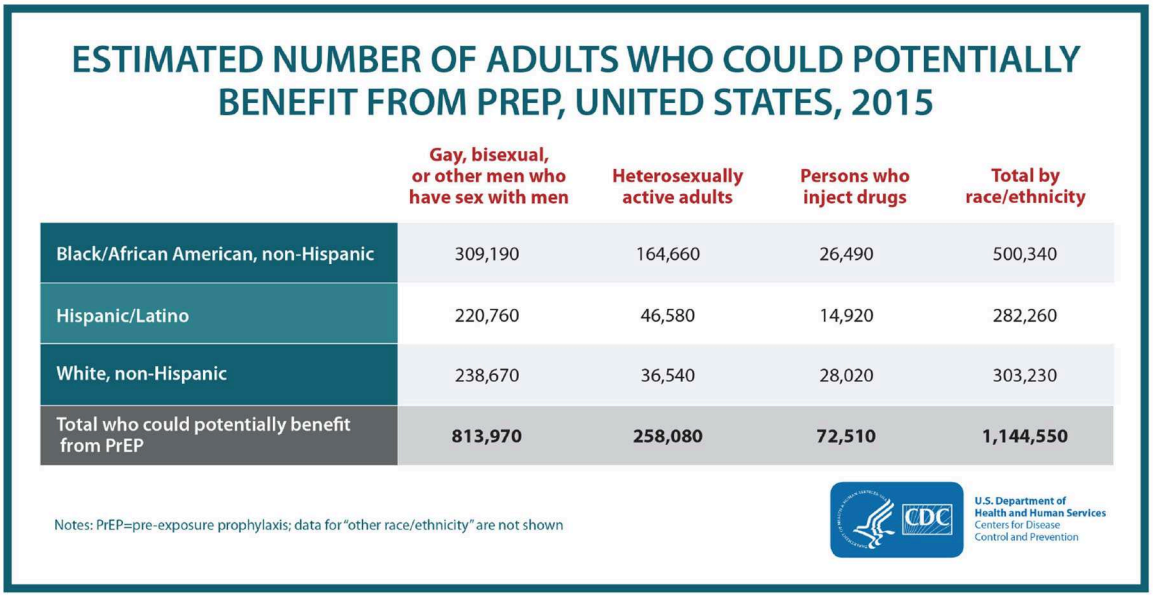

FIGURE 2 | "HIV prevention pill not reaching most Americans who could benefit—especially people of color." Retrieved from https://www.cdc.gov/nchhstp/newsroom/2018/croi-2018-PrEP-press-release.html.

particularly attention-grabbing post was about a gay man asking others' opinion on whether PrEP provides enough protection to fulfill his fantasies of being a "cumdump," where multiple men ejaculate inside the same person. This post was welcomed by others who enthusiastically assured him that the beauty of PrEP comes from its ability to make one's fantasies come true[7].

Duggan (2003, p. 50) defined homonormativity as "a politics that does not contest dominant heteronormative assumptions and institutions, but upholds and sustains them, while promising the possibility of a demobilized gay constituency and a privatized, depoliticized gay culture anchored in domesticity and consumption[8]". The homonormative gay man is the henchman of the neoliberal state: he is an exemplary citizen because he protects social norms rather than questioning them. He is an indispensable part of the workforce, a zealous supporter of consumerism, and is patriotic. Ironically, it was the AIDS epidemic that gave way to an epidemic of assimilation. In conjunction with public health discourses and prevention technologies, gay men are made into "proper" healthy citizens, who are monogamous, ideally married, or practice only safe-sex and remain HIV- at any cost (Davis, 2002; Keogh, 2008; Gonzalez, 2010; Robinson, 2014). Thanks to their surplus economic and biopolitical value, they have taken their place among those whose lives matter and shall be protected, even at the cost of others. As Collins (2009, p. 467) wrote "homonormativity—like heteronormativity—is an exclusionary process; inclusion is for select bodies—white, middle-class, consumerist, Western, and often gay male bodies who have access to the consumer "freedoms" of the West." In Stefan Ecks' words, the homonormative gay man is the most desirable citizen under the framework of "pharmaceutical citizenship" which not only

[7]I would like to open a parenthesis here to mention my purposes to evoke the figure of cumdump, which terrorized both the heterosexual and gay communities during and after AIDS crisis. The exchange of bodily fluids, especially that of sperm, is still pathologized in the context of public health, denying the crucial importance of carnal pleasure to people's lives. Although there is virtually no aspect of gay men's sex lives that is not yet thought to be destructive both for the self and for the community, the abandonment of condoms has especially been panic inducing for almost four decades now. I use cumdump as a provocative example precisely to point out PrEP's ability to allow the materialization of fantasies and uninhibited practice of pleasures. I am in no way against the intensification or proliferation of sexual pleasures through PrEP. When I was first diagnosed with HIV, I found infinite emotional and sexual comfort in knowing that my partner could use PrEP. I still find a lot of comfort when I have sexual interactions with strangers who are on PrEP. But, this is not about me and how I find pleasure in the presence of PrEP. This is about the political potentials of pleasure. Bodies and pleasures, said Foucault (2003), are the only sites wherein which resistance to biopower is possible. If, in this essay, pleasure appears to be overdetermined by biopower, it is because I do not believe that pleasure stands outside the realm of biopower: that is, pleasure can resist biopower precisely because it operates within not outside. While critiquing the pathopolitics of PrEP, I would also like to consider the ironic ways in which PrEP can provide radical queer alternatives to normative sexual practices. Besides, I would be contributing to the biopoliticization of PrEP should I argue that it must only be used in the name of health by those who need it, distributing pleasure on a racial basis. I would be happy to see PrEP becoming a real "party drug" one day—that is, accessible to all and not only a privileged few. The unintended moral tone of my argument, therefore, does not stem from a critical stance toward pharmaceutically intensified pleasure, which can effectively disturb the cultural associations between condomless sex and self-destruction (Race, 2018). Rather, it stems from the nature of pleasure obtained through PrEP that is at once exclusionary and discriminatory. That is, pleasure, as politically subversive as it might be, comes at a cost, which is the reproduction of pathopolitics.

[8]Even while discussing how homonormative citizens expand the reach of pathopolitics, it must not be forgotten that the potential to subvert homonormativity still lies in the figure of cumdump, who resists to be domesticated and disciplined, even when on PrEP (or, maybe, because on PrEP).

determines who has the right to access medicine but also operates in a feedback loop such that those who take the medicine become more fully citizens (Ecks, 2005, p. 241). Thanks to PrEP, gay men can now enjoy condomless sex without risking HIV or losing their citizenship privileges.

Even though the original conceptualization of homonormativity puts a lot of emphasis on the intimate relations between queer subjects and state institutions such as military and marriage, what I want to call attention to is another set of relations and practices quintessential to the operations of the pharmaceutical regime. Queer citizens today extend the realm of homonormativity to the uncritical consumption of pharmacological discourses and products, therefore, contribute to pathopolitics. Gay men's contribution to the extraction of surplus value is not limited to their consumption and labor. Neither can it be reduced to their enthusiastic advertisement of PrEP, which is claimed to be the most effective form of pharmaceutical advertising (Elliot, 2010). They also produce infinite value through what Preciado (2013, p. 36) calls *masturbatory cooperation*: every excitation and every ejaculation achieved on PrEP extends the reach of biopower and the revenue of pharmaceutical industry. White gay men's HIV negative cum is not wasted knotted up in latex condoms in the garbage, but, rather turned into a profitable asset through PrEP, circulating not only between bodies but also in the pharmaceutical market. Already engaged in an intimate relationship with the state, the homonormative citizen opens the doors of his bedroom to the pharmaceutical regime and invites it to be a part of and enjoy the most intimate bodily moments. And, he does so willingly without being coerced by the state. "It is not power infiltrating from the outside," said Preciado, "it is the body desiring power, seeking to swallow it, eat it, administer it, wolf it down, more, always more, through every hole, by every possible route of application" (2013, p. 208). In this consensual encounter between the body and power, both of them find pleasure in penetrating and being penetrated.

Pathopolitics does not only determine who gets to live disease free but also who gets to enjoy sex without risking HIV infection. When it comes to women, trans persons, people of color, sex workers, substance users, and HIV+ people who are not on medication, their orgasms are not equally valuable or lucrative. Preciado writes: "the new hegemonic subject is a body (often codified as male, white, and heterosexual) supplemented pharmacopornographically (by Viagra, coke, pornography) [. . .]" (2013, p. 48). To this description, I would add that a new hegemonic subject is the white gay man who is supplemented by PrEP. The security and protection provided by PrEP is nothing new for the homonormative subject who benefits from all the material and immaterial advantages of being privileged. "When a whole world is organized to promote your survival, from health to education, to the walls designed to keep your residence safe, to the paths that ease your travel, you do not have to become so inventive to survive," wrote Sara Ahmed (2017, p. 237) powerfully in another context. You do not need to be inventive to survive; if not the state, then the pharmaceutical companies will find a way to keep you alive, so long as you keep producing profit. This is by no means to deny the problems even the homonormative subject can face. "Privilege does not mean we are invulnerable: things happen; shit happens. Privilege can however reduce the costs of vulnerability; you are more likely to be looked after" (Ahmed, 2017, pp. 237–238). Even though not heterosexual, he is still cared for and made to live by the same system that condemns marginalized people to slow and not-so-slow violence and death. PrEP is only another piece of the larger puzzle, extending economic, political, and social safety into corporeal satisfaction and biological security. It is through such improvements the bare flesh becomes a fully abled social subject, blurring the lines between bios (qualified, meaningful life) and zoe (unqualified, bare life) (Agamben, 1998). It is not the life alone that matters anymore; it is a particular way of life—a more sexual, more aroused, more commodifiable and marketable one, where bodies are more fuckable. It is less about bare life than it is about bareback sex.

Lastly, the final question is what kind of sufferings and pathologies are produced in the making of some bodies more biosecure and sexually attractive? To put it another way, whose suffering made the consumption of PrEP possible? The pharmaceutical industry complex does not simply cure pathologies; instead, it relocates them. The prevention of HIV for the citizens of the Global North might mean exposing the disposable bodies of the Global South to increased risk of HIV. One could say some are sacrificed so that others can enjoy more pleasurable and less risky sex. The pharmaceutical industry produces global casualties by recruiting "treatment-naïve" populations found in resource-poor countries, where trial recruitment and conduct is less costly and less time-consuming due to insufficient regulations and monitoring (Petryna, 2006). The first PrEP trials in Cambodia, funded by NIH and Gates Foundation and not by Gilead[9], were conducted with sex workers. Nevertheless, they were halted in 2004 by the Cambodian Prime Minister. Among the reasons that incited widespread demonstrations by small local HIV and queer activist groups were inadequate prevention counseling, a lack of pre- and post-HIV test counseling, non-provision of services for those who seroconverted during the trials, insufficient data about the long-term effects of tenofovir for HIV- people, and the inadequate involvement of target populations in the research design and implementation. As the activist groups made clear, "participants take all of the risks and get little [if any] of the benefits" (Singh and Mills, 2005). In 2005, trials in Cameroon were canceled due to similar concerns about lack of counseling. Yet, local activists this time made an astonishing claim about participants being intentionally exposed to risk of infection (ibid). Unlikely though it sounds, the case of Cameroon uncovers a constitutive failure of global health and randomized drug trials. Researchers most often find themselves trapped between meeting ethical standards and obtaining "desired" scientific outcomes (Adams, 2010). Obtaining the most profitable

[9]Note that Gilead's presence is always noteworthy within drug trials even though they are not funded by it. The company still provides the drugs for the trials, whose research teams include Gilead's own researchers.

outcomes, although not necessarily the most scientific ones, might at times require manipulation of the data (Dumit, 2012). It may too require giving placebos—as is the case in PrEP trials—to members of poor marginalized populations and watch them become infected with HIV. Years after the first PrEP trials, the trend of outsourcing human subjects has remained the same. Among the countries where the succeeding trials were conducted are Kenya, Uganda, Thailand, Botswana, Peru, Ecuador, and Zimbabwe, most of which suffer from the absence of universal access to ARV treatment. It must be noted that the ethical issues with PrEP trials are hardly only about the outsourcing of research participants. In an article entitled The Cost of Science, Patton and Kim (2012) question the ethics of PrEP trials altogether. They argue that PrEP trails used the limited resources for pharmaceutical interventions instead of community support and divested resources from people who already live with HIV. Patton and Kim also strongly defend that neither were trial results transferable to the U.S. nor they were able to prove enough efficacy for the use of women (which was ignored for the benefit of MSM). Their most controversial point is on the potential misinterpretation of data, which might have obscured how PrEP can do more harm than good.

CONCLUSION

As I was finishing this essay, the COVID-19 pandemic hit the world, which like any other modern epidemic or pandemic meant disaster for those affected and business for those who profit from disasters. Disaster capitalism can be observed at its worst when human life is at stake. Gilead was among the first scavengers who rolled up their sleeves to benefit from the pandemic. One of Gilead's broad-spectrum antiretroviral medicine, Remdesivir, also developed with US government funding, promised hope against the novel Coronavirus (Fang and Lerner, 2020). As a result of high demand, on March 23rd, Gilead announced it would stop providing emergency access to Remdesivir. Following the announcement, the drug was given orphan status by the FDA within the same day (ibid.). Orphan status, which gives the manufacturer the exclusive control of the drug and its pricing, is reserved for drugs used to treat rare diseases that affect fewer than 200.000 individuals. However, due to a loophole, popular drugs can enjoy orphan status if they earn it before the disease reaches the threshold. This was the case with Remdesivir and it visibly increased Gilead's stock price in a matter of hours (ibid). The story of Remdesivir is but an example of how much can a drug company value profit over life during extraordinary circumstances. The only thing that separates this story from others is that on March 25th, following widespread public outcry, Gilead surprisingly announced it will seek to rescind orphan drug designation for Remdesivir (Lerner, 2020). There is a limit, an invisible line, the pharmaceutical industry sets for itself to judge how much of greed is too much. It turns out it is not yet too much to exclude 48% of global population—including low- and middle-income countries—from the geographical scope of the voluntary licenses Gilead provides for the production of Remdesivir's affordable generics (Baker, 2020). Neither has the limit been breached yet when Gilead was blocking generics and setting unaffordable prices for a life-saving Hepatitis C drug, Sovaldi, only a few years ago (TAG, 2015).

Gilead is but one example of countless other pharmaceutical companies that pit the right to health and life against the right to make profit. The monopoly over patents bestows drug companies with no public accountability the monopoly over the distribution of risk. Instead of relinquishing the monopoly, the companies would rather donate drugs or provide aid, which they then call corporate social responsibility. Writing about Novartis' resistance to renounce its monopoly over the anti-cancer medicine Gleevec in India, Rajan expressed, "The limited responsibility of corporatized philanthropy sits comfortably with an idea of Responsibility Ltd. It is a form responsibility that is completely appropriable and appropriated by the interests and instruments of global capital" (2017, p. 238).

Pathopolitics, as I argued in this essay, is the corporate politics of strategic distribution of pathologies and suffering. Drug companies develop and manufacture technologies to be used to remedy or prevent pathologies. Nevertheless, they strengthen the existing pathologies, or create new ones, by making these technologies accessible only to a few. Through unjust pricing policies and aggressive control of generics, the companies aggravate pathologies and the suffering they cause. In addition, the suffering of some has increasingly become the necessary condition for the treatment of others. The pharmaceutical industry is producing pathologies for certain populations precisely to cure or protect others, who promise financial returns. PrEP unveils the way in which the distribution of pathologies is determined by how much surplus value individuals can offer. One of the questions this article sought to raise is whether those of us who use drugs to prevent pathologies are to a certain extent complicit in pathopolitics, which does not so much do away with pathologies as it relocates them to other parts of the world, away from where they can be seen or heard. What PrEP lays bare is that health and sexual pleasure might come at a cost: the uncritical advocacy and consumption of a medicine that is by nature exclusionary and discriminatory might inadvertently reinforce pathologies, social and biological.

Given that pharmakon means both poison and cure, the central paradox of pathopolitics lies in how the pharmaceutical industry sometimes poisons so as to cure: it promises to treat not only the existing pathologies but the ones it helped create. The way it does that is called Corporate Social Responsibility, which aims to balance two sides of pathopolitics. As the case of Gilead reveals CSR functions akin to putting a cheap band-aid on an infectious wound in need of medical attention—under the bandage, the infection will keep spreading to the point where it could become lethal or cause the mutilation of a limb. Pathopolitics, hence, is not kept in balance by CSR but, rather, turned more destructive, more pathological.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

AUTHOR CONTRIBUTIONS

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

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CONCEPTUAL ANALYSIS
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Access to Medicines, Access to Markets

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This article explores some uses by the pharmaceutical industry of language from the "access to medicines" movement in global health, sometimes for goals almost completely opposite to those of the movement. Important in the context of extremely expensive treatments, the industry draws on the idealistic discourse around access to medicines to create a very specific continuity between the needs of the Global South and its own marketing needs. By focusing on "access," the industry can promote the opening up of markets in relatively wealthy countries with important public or highly regulated payers.

Keywords: access to medicines, access to markets, pharmaceutical industry, marketing, drugs

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AN OPPORTUNITY AND A PROBLEM FOR PHARMACEUTICAL COMPANIES: SKY-HIGH PRICES

In May of 2019, Novartis won FDA approval for Zolgensma, a gene therapy for spinal muscular atrophy, a group of rare, degenerative and often-fatal conditions. The agency approved the one-time treatment for patients under 2 years of age who had a particular mutation in the SMN1 (survival motor neuron) gene (Bosely, 2019). Zolgensma attracted some attention for being one of very few approved gene therapies, one of only two then available in the US. But it attracted considerably more attention as a result of its price: slightly more than US $2 million for a treatment, setting a new record for a drug!

That might look like a record that a company would not want to hold, but Novartis didn't appear concerned. The record had changed hands many times over the previous decade, a decade that started with sticker shock at treatment prices of a mere US $100,000, amounts that shortly became commonplace. For example, the cancer drug Provenge was priced at US $93,000 in 2011, a price that led to low sales because physicians and hospitals were concerned about being reimbursed (Fuerstein, 2011). In the pharmaceutical industry, the 1990s and 2000s were marked as the decades of blockbuster drugs—earning more than US $1 billion in a year—for widespread use. The 2010s, by contrast, were the (first?) decade of extravagantly priced drugs for narrow use.

Clearly, sky-high prices for drugs are attractive for pharmaceutical companies. Equally clearly, they present the problem that customers, including different kinds of insurers, may not be willing to pay for those drugs. It is not a foregone conclusion that anybody will pay $100,000 for a treatment, let alone $2 million. Over the past decade, as they have introduced higher and higher prices, companies have had to work on solving this problem.

In the case of Zolgensma, the record price had been thought through. As a one-time treatment, the US $2 million is about the same as 5 years of successful treatment with a competing drug, Spinraza, made by Biogen. Given the precedent that Biogen had established, Novartis's pricing was somewhat less bold than it looked. Moreover, at the broader level, some of the rhetorical work to address the problem had already been done. Most US private insurance plans and Medicaid will cover Zolgensma's cost for at least a subset of the small number of spinal muscular atrophy patients. For the US insured patients, the question of access to this medicine has already been at least partly

answered, as has the question of access to this market for Novartis.

In addition, Novartis announced plans to donate, through a lottery, 100 doses of Zolgensma per year to children outside the US. The geographical choice is interesting, because it recognizes that Zolgensma's price puts it out of the reach of almost everybody. This lottery program accomplishes a number of things at once. It allows Novartis to claim that it is promoting access to medicines, while hiding from Zolgensma's prize market, insured patients in the US, the lower prices Novartis might be forced to charge elsewhere (see Ecks, 2015 for analysis of an analogous case). And the lottery will likely generate some valuable advertising for the treatment in Western Europe and elsewhere—and some mobilization of patient groups to get it covered by public and other insurance plans.

I should note that there was a potential glitch in the approval process. Although results from the clinical trial of 68 children were positive, it was found that the company originating the drug, AveXis, had manipulated or falsified data from animal testing. Neither Novartis nor AveXis revealed this fact until 1 month after FDA approval (FDA, 2019). Their failure to report the manipulated data was potentially consequential. The FDA (FDA, 2019) wrote in a press release another month later: "The agency will use its full authorities to take action, if appropriate, which may include civil or criminal penalties." Two AveXis employees were fired, but it is unclear exactly how the FDA has acted. The animal data concerns were serious enough that the FDA ordered a halt to a later study, though they didn't affect approval. An AveXis spokesperson said that the data problems had been fully explained to the FDA and didn't affect "the medicine itself" (Bosely, 2019).

With approval, some cases covered, and a lottery program on the way, Novartis could consider the most immediate issues of access to be dealt with—and indeed, almost 100 infants, earning the company revenue of US$160 million, were treated in the financial quarter immediately following availability in the US (Dunn, 2019).

The lottery for Zolgensma is only one focused face of Novartis's efforts at access. The company has developed programs for a number of its other expensive drugs (e.g., Ecks, 2015). Most prominent at the moment is probably its "Novartis Access" program, which offers 15 drugs for non-communicable diseases at a rate of $1 per month, in a number of countries in sub-Saharan Africa, Central America, Southeast Asia and Central and Eastern Europe (Novartis, 2020). Many of those drugs are either on or are competing with drugs on the World Health Organization's (WHO) "Model list of essential medicines" (WHO, 2019). Novartis Access is the flagship of the company's "Social Business" unit, and can boast of hundreds of thousands of treatments per year. The evidence for effects of Novartis Access on the ground is mixed (Rockers et al., 2019), though there is no doubt that it is a public relations success.

Novartis's efforts to get approval for Zolgensma, its promoting and pricing of the treatment in the US, its program of donating a small number of treatments outside the US, and its Novartis Access program, can be seen as different approaches to access. While these approaches are genuinely different, they also occupy the same terrain. The pharmaceutical industry has adapted to the discourse of access to medicines, and has adopted some of the key terms of that discourse to its own ends.

THE ACCESS TO MEDICINES MOVEMENT

Greene (2011) insightfully asks, how did a discourse around "essential drugs"—later "essential medicines"—arise and become dominant? Why did *drugs* become essential? Greene's answer has many parts, and I will skip to a central feature of it. Although there were antecedents, the WHO's first publication of a "model list of essential drugs" (in WHO, 1977, p. 20–33) is the key event that shaped debates around what was essential and what not. This particular list was born in the context of a conflict between low-income countries and multinational pharmaceutical companies over the cost of drugs, and followed a call for a shift in the production of drugs to members of the Non-Aligned Movement (Greene, 2011, p. 17). The objects—drugs—at the center of the conflict thus became elevated in importance, to the point of being made "essential." Clearly, the problem of access to medicines is implicit in the publication of a list of essential medicines, but it took two decades to come to the fore, and to be generalized.

We can see dramatic growth in use of the phrase "access to medicines," beginning in the second half of the 1990s (**Figure 1**). Moreover, the applications of the phrase become narrower at about that time, more focused on the problem of drugs for treating life-threatening conditions that are unaffordable, especially in developing countries. In terms of more academic interest, Google Scholar and Google Ngram show essentially the same pattern of results.

The growth in the use of the phrase reflects activism and debates around the essential drugs concept, but in the form of an access to Medicines movement sparked by the TRIPS (Trade-Related Aspects of Intellectual Property Rights) Agreement. The story of TRIPS, including the central role of a number of large pharmaceutical companies in the design of TRIPS, has been well told many times (e.g., Drahos, 1995; Sell, 2001; Matthews, 2003). In the early 1980s, a group of companies successfully put intellectual property at the top of the US trade agenda and helped to design not only international agreements, but also a very successful strategy for convincing other countries to sign onto them. Prominent in that group of companies were representatives of the pharmaceutical industry: the Advisory Committee for Trade Negotiations, formed in 1981, was chaired by the CEO of Pfizer, Ed Pratt, and its 1986 successor, the Intellectual Property Committee, consisted of 13 large companies including Pfizer, Bristol-Myers, Johnson & Johnson, and Merck, making pharmaceuticals the largest of the industry sectors represented on the committee; the chemical, computer, automotive, aerospace, and communication industries also were represented. These committees designed a strategy that combined the building of coalitions with non-US companies, forceful bilateral pressure to link intellectual property and other trade, and finally multilateral agreements built on those bilateral pressures. The result was the 1995 TRIPS Agreement, which has formed the basis for new intellectual property laws in countries around the world.

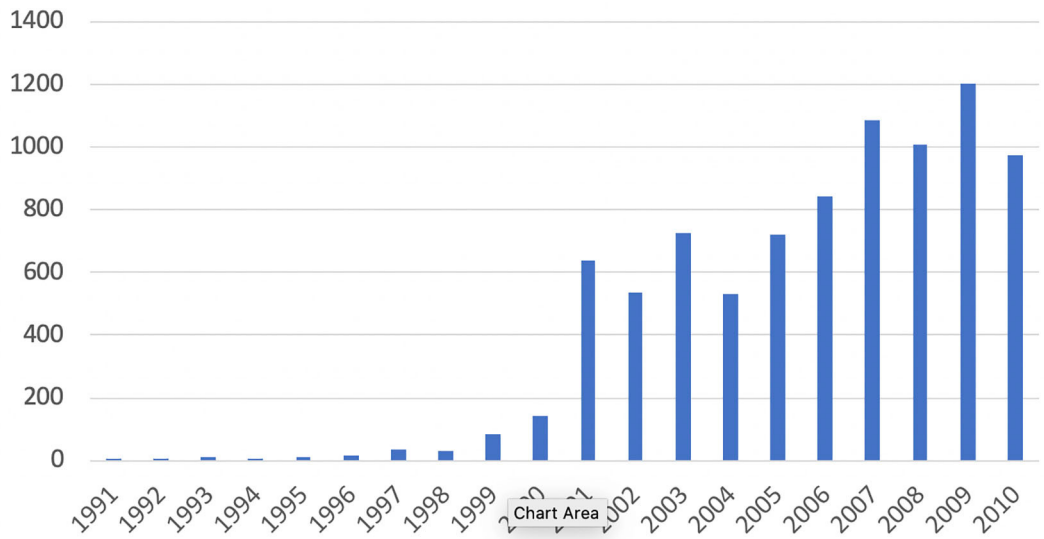

FIGURE 1 | Articles mentioning "access to medicines," 1991–2010 (*Factiva* database, search performed 19 June 2020).

Effectively, TRIPS extended a version of a new and strengthened US intellectual property law to many parts of the globe.

In the wake of TRIPS, a campaign for access initially involved the Consumer Project on Technology, Health Action International, and Médecins Sans Frontières though expanding to include a number of other organizations (Sell, 2001). A notable event was the Conference on Increasing Access to Essential Drugs in a Globalized Economy, taking place in 1999 in Amsterdam; the conference issued a statement that connected TRIPS and the immense challenges of global health, and calling on the World Trade Organization to establish, at its upcoming meeting in Seattle, a standing working group to address the issue (WHO, 1999). TRIPS and "access to medicines" were so strongly linked that in the early 2000s almost all of the most prominent discussions of access also referred to TRIPS or to patent protection. The most immediate concerns that linked the two were about antiretroviral treatments, given the HIV/AIDS crises in sub-Saharan Africa, Southeast Asia and Brazil. The concerns were realized when, for example, the US government used all of its legal power to try to intimidate South Africa into repealing its legislation allowing compulsory licensing of generic HIV/AIDS drugs (Sell, 2001, p. 501ff). When the US government withdrew from the confrontation, the pharmaceutical industry attempted legal action on its own, but also backed away in the face of domestic protests. Individual companies relented, and adjusted their pricing of the drugs in different countries. "Access to medicines" was a public relations mess for the pharmaceutical industry in the early years of this century (e.g., 't Hoen, 2003). The industry recognized this, and immediately engaged in damage control, trying to reframe the problem as arising because of a regrettable combination of their high research and development costs and poverty in the Global South (e.g., Cochrane, 2000). Within a few years, though, companies were systematically setting up access programs to try to clean up their image messes (Greene, 2011, p. 25–26).

Setting the context for the discourse on access to medicines, the World Health Organization's current highest-level webpage on the subject begins: "Nearly 2 billion people have no access to basic medicines, causing a cascade of preventable misery and suffering" (WHO, 2020). The statement continues:

> Good health is impossible without access to pharmaceutical products. Universal health coverage depends on the availability of quality-assured affordable health technologies in sufficient quantities. … Efforts to improve access to medicines are driven by a compelling ethical imperative. People should not be denied access to life-saving or health-promoting interventions for unfair reasons, including those with economic or social causes (WHO, 2020).

As this suggests, the conflict and the issue have not gone away. And it is also possible that, like lists of "essential medicines," conflicts about "access to medicines" make drugs in general all the more prominent in discussions about global health. But unlike "essential medicines" or possible alternatives such as "affordable medicines," the focus is on *access*, a concept with some flexibility.

ACCESS MATTERS TO PHARMACEUTICAL COMPANIES

Clearly, the pharmaceutical industry, which makes few of its products affordable in poor countries, is one of the central problems, perhaps *the* central problem, identified by the access

to medicines movement. As a result of the large public relations challenges, pharmaceutical companies have developed a number of programs to improve public relations by making some products available to some populations at relatively low costs. The Novartis Access program mentioned above is one, but every major company has multiple such programs, blunting some of the effect of the access to medicines movement.

However, the industry also has made positive use of some of the language of access to medicines: not to laud its access programs or to advocate for better healthcare in poor countries, but as part of efforts to convince payers in wealthy countries to cover expensive drugs, to cover more patients for their drugs, and to cover them more quickly. The industry has picked up the ideals and the discourse around access, and has applied those to situations in which it can most profit.

For example, in a report on "Access to new medicines in public drug plans," the industry lobby group Innovative Medicines Canada goes so far as to lead by citing its former opponent the WHO:

> According to the World Health Organization (WHO), access to medicines and vaccines is a key component to a quality health system. There is no doubt that innovation in medicines and vaccines has made a significant contribution to improving health outcomes in Canada and around the world. It is therefore important for Canadians to know the state of access to new medicines in their country, relative to comparable countries. The goal of this study is to measure access against international benchmarks in order to drive improvements to access here at home (Innovative Medicines Canada, 2016, p. 1).

Here, selectively adopting the language of access to medicines allows this industry association to make the case that Canadians could be better served. Only 37% of new medicines were reimbursed across all provinces (public drug plans are run by individual provinces, not the Federal government), and most involved some "reimbursement conditions." Even excluding smaller provinces, only 59% of new cancer medicines and only 23% of biologics were covered. There is an average wait time of 449 days between drug approval and the beginning of reimbursement. On almost every one of the report's metrics, Canada places poorly among comparator countries, and readers can only conclude that there is a serious problem of access to medicines in the country.

The Association of the British Pharmaceutical Industry's website also draws attention to access: "For every 100 patients that get a new medicine in its 1st year of launch in other parts of the EU—including France and Germany—just 21 patients in the UK get access. There is also significant variation across the UK when it comes to accessing different types of medicines" (ABPI, 2020). The German Medicines Manufacturers' Association (BAH) has a report on "Sustainable access to medicines in Europe" (BAH, 2017). Unlike the Canadian and UK reports, this one generously focuses on patient access to medicines outside Germany, arguing for increased harmonization of regulations and new trade deals—for example with the UK following Brexit.

Important in the background here is the rise of health technology assessment (HTA), used in many jurisdictions to rationalize (especially) the public provision of healthcare services and treatments. Among other things, HTA does cost-benefit analyses of drug treatments, and in some places these analyses translate almost directly into decisions about which drugs are funded systematically. Across Europe, for example, there are national HTA agencies. The kinds of evidence assessed by these agencies are broadly similar, and their roles are similar, though there are significant differences in the agencies' analyses and how they are applied (Angelis et al., 2017).

Nonetheless, "[i]n recent years, access to essential medicines has become an issue even in the wealthiest parts of Europe. In particular, the proliferation of high-priced medicines has pushed the issue of access to new medicines high on the policy agenda of all European countries, including in high-income economies" (Vogler et al., 2017). As a result, though HTA establishes the baselines for healthcare systems' funding of drugs, there are multiple and various alternative access schemes (Löblová et al., 2019). Often as a result of lobbying, unapproved drugs may be funded for "compassionate use," or "off-label" or more particular schemes, and approved drugs may be made available through special funds or on a putatively trial basis awaiting further evidence of effectiveness. When they don't manage to land their products on public formularies, it is in pharmaceutical companies' interests to encourage or lobby for some kind of alternative access scheme.

Patient advocacy organizations (PAOs) have often been excellent vehicles for promoting specific ideals of access in wealthy countries (O'Donovan, 2007), and over the past few decades pharmaceutical companies have become increasingly aware of the value of PAOs as such vehicles (Sismondo, 2018). In forming alliances, PAOs are likely to cede some control over the uses of their efforts and the public articulation of their interests, though they may still get meaning and value from their actions (see, e.g., Klawiter, 2008). Of relevance here, specific groups of patients may have strong interests in promoting high-priced drugs, when, for example, companies provide the drugs to those groups for free or at a greatly reduced price—through a special access program (e.g., Ecks, 2015). Some single-disease PAOs have been important allies in companies' efforts to secure quick regulatory approval for specific new drugs, even when the data is equivocal.

Thus companies generously fund PAOs, hoping to align interests. For a 2018 news story on payments to PAOs—now a well-reported phenomenon—a spokeswoman for the company said that "Bristol-Myers Squibb is focused on supporting a health care environment that rewards innovation and ensures access to medicines for patients. The company supports patient organizations with this shared objective" (Kopp et al., 2018). Today, patient voices are represented in almost every controversial drug approval process, and they are speaking the language of access.

When the UK government commissioned an "Accelerated Access Review," the reviewers heard from a large number of patients and PAOs, and, at least as represented in the review, they were overwhelmingly in favor of streamlined approvals for

some classes of drugs (Accelerated Access Review, 2016, see also Muscular Dystrophy UK, 2015). The resulting Accelerated Access Review program was indeed tasked with bringing innovative treatments to patients more quickly; it was initially headed by the former CEO of GlaxoSmithKline, Andrew Witty, then 6 months out of his previous position (Jefferson, 2017). It appears that today's PAOs formed around one or a cluster of debilitating or life-threatening diseases are very likely to advocate in favor of early approval of new drugs, or even compassionate use for substances that have not yet been approved—on the latter, pharmaceutical companies can even reasonably claim to be more conservative than patients and PAOs (e.g., Pharmaphorum, 2014).

Of course, some of the PAOs involved are even more closely connected with the pharmaceutical industry than they reveal. I provide a lengthy example. In 2017, the prominent health newsletter *STAT News* published an op-ed by Dr. Robert Yapundich (2017), a neurologist, who argued that sales reps should be allowed to discuss "off-label" uses of drugs—uses for which the drugs aren't approved. This, he said, drawing on anecdotes about patients, would allow him to better help his patients. Yapundich's bio mentioned that he was a member of a US group called the Alliance for Patient Access. Another newsletter, HealthNewsReview (2017a), quickly noted that Yapundich had accepted a considerable amount—more than $300,000, as it turned out—from the drug industry, and hadn't noted the conflict of interest. Embarrassed by these and other revelations, *STAT News* withdrew the article.

Although the name, Alliance for Patient Access, suggests a PAO, it is officially an organization of physicians. The physicians who sit on the organization's Executive include some of the industry's most highly paid key opinion leaders, including Dr. Srinivas Nalamach, who received $800,000 from drug companies between 2013 and 2015, in connection with the promotion of opioids and drugs to treat the side effects of opioids (HealthNewsReview, 2017b).

In addition to not reporting his conflicts of interest, Yapundich had neglected to mention that the article was drafted for him by a public relations firm working for the Alliance (HealthNewsReview, 2017c). Yapundich stood by the article, though he acknowledged that the ghostwriters had either fabricated or made mistakes about some details of the anecdotes. It turns out the Alliance for Patient Access is actually operated by the public relations firm that commissioned the ghostwritten op-ed, and that the Alliance is supported primarily by membership dues paid by pharmaceutical companies and trade associations. So, what is superficially a patient organization is officially a physician organization and is effectively a pharmaceutical industry organization—or at least a creature of the industry. It is unsurprising, then, that the Alliance for Patient Access opposes limits on drug costs, even though high costs clearly affect patients' access to drugs. For example, in the midst of a public outcry over steep drug price hikes, the Alliance for Patient Access wrote a blog post on the need for a "comprehensive dialogue," especially focused on how insurers should cover full costs of drugs (Alliance for Patient Access, 2015). When discussions at a United Nations panel on access to medications turned to exorbitant costs as a result of patents, the Alliance wrote a blog post on how patents make access possible (Alliance for Patient Access, 2016).

As we've already seen, strong intellectual property laws tend to create monopolies that allow for very high prices. Nonetheless, there is no shortage of PAOs willing to advocate in favor of patent protections for pharmaceuticals, in the name of increased innovation. In response to discussions on a United Nations panel, which pointed fingers at drug patents as key culprits in keeping needed drugs expensive and out of the hands of patients, fifty PAOs wrote to then-Secretary of State John Kerry, to support the US government's strong defense of the patent system. Some of those organizations might have been acting as a result of hopes for magic bullets, and some might have been acting purely as creatures of the pharmaceutical industry: the Global Alliance for Patient Access, a spin-off project of the US Alliance for Patient Access, was one of the signatories (Global Colon Cancer Association, 2016).

The access to medicines movement, including the organizations that began it, continues in its efforts to contribute to global health by advocating and acting for the affordability of important drugs, especially in the Global South, and to oppose intellectual property regimes that stand in the way of those efforts. In this case, activists in the movement have been able to remain independent of the pharmaceutical industry and its actions.

But with newer groups like the US and Global Alliances for Patient Access, the motivations behind the original access to medicines movement have been turned on their heads. The pharmaceutical industry is arguing, using supposed patient advocacy organizations as its mouthpieces, in favor of unfettered access to consumers in wealthy countries, as well as higher prices and stronger intellectual property regimes. The companies are busy rhetorically establishing a very specific continuity between issues in the Global South and the North, a continuity that can be made precisely because of the extremely high prices that the companies want to charge.

ACCESS TO MARKETS

But nothing in the adoption of the access discourse should be surprising. From the point of view of the industry, patients' access to medicines is essentially the same as companies' access to markets, though the value of drawing attention to them is very different.

The American Marketing Association (2017) has a broad concept of marketing, defining it as "the activity, set of institutions, and processes for creating, communicating, delivering, and exchanging offerings that have value for customers, clients, partners, and society at large." In the "marketing era" (Applbaum, 2004) captured by this expansive definition, products and services don't simply arrive at a marketplace to be sold. In the ideal case, every step in the trajectory of manufacture, advertisement, transportation, sale, delivery and consumption will have been shaped by every

other step. In the context of the pharmaceutical industry, the American Marketing Association's definition would include anything that pharmaceutical companies do to get their products into consumers' bodies. As a result, not only is patients' access to medicines conceptually linked with companies' access to markets, but the work that companies do to increase access to medicines is part of their marketing of those products.

In a short article for pharmaceutical marketers in Europe and the UK, insider Colin Wright provides a view of market access that firmly links it to access to medicines. He starts with a definition: "Market access is the process to ensure that all appropriate patients who would benefit, get rapid and maintained access to the brand, at the right price" (Wright, 2012, emphasis removed).

Similarly, a survey of UK industry employees working on market access produced a very similar definition of the term: "Ensuring patients receive appropriate treatment at the right time and right price, working with the local/regional NHS and their processes based on value" (Bradley, 2017). Marketer Craig Bradley writes: "Essentially, there is a need for interested stakeholders to work together to develop a system that is fit for purpose in recognizing innovation and allowing patient access to new treatments that can demonstrate value. The main issue is making sure that patients are able to access innovative new treatments." As he notes, this is operationalized by the UK Pharmaceutical Marketing Society as: "Principally market access involves preparing a positive environment which supports uptake of your product and demonstrating the 'value' of your product to the range of customers who influence uptake. Strategically, market access is about packaging data in the right way, for the right customer at the right time" (PM Society 2020). Access to medicines and access to markets are linked, or even fused.

On the expansive view of marketing above, regulatory approval itself—whether accelerated or not—is a crucial element of access. Approval represents the first possible date for market access, though in most cases there is a delay. In his article on market access, Wright (2012) provides a chart showing the average number of days between "marketing authorization" and "patient access" for a number of European countries—ranging from zero days in the case of the UK and Germany to 392 days in the case of Belgium. The chart is quite similar in content and form to ones in the Innovation Medicines Canada report on "access to medicines."

After regulatory approval, then, pharmaceutical companies have to work with payers, respecting their processes and identifying the value that a new drug can offer. In launching a drug, companies are "preparing the brand for the market, preparing the company for the brand." But this is a matter of "value communication," and in particular is a matter of identifying "improved health outcomes: outcomes that reflect the correct endpoints in eyes of payers." And thus market access needs to focus on patients. Wright emphasizes points that would be at home in many treatments of access to medicines: "Benefit must be expressed relative to Standard of Care.… Preferably, it would be expressed in real-life settings to show how the new medicine performs in more naturalistic environments, which reflect the value that will be delivered in real life." And, there is no one-size-fits-all solution, as the "market access process must link the requirements at global level, which guide the clinical development process, to the needs at local country level" (Wright, 2012, emphasis removed; also Proctor and Silvey, 2017). Again, access to medicines and access to markets are linked.

And thus, Joseph Jimenez, CEO of Novartis can say: "Innovation doesn't just mean developing new drugs. So innovation also, in our minds, includes new business models that can improve access to medicines to people around the world" (Novartis, 2015). This is a way of speaking that makes perfect sense in the context of deep concerns with access to medicines/access to markets.

AUTHOR CONTRIBUTIONS

SS did the research, planned, and wrote the manuscript.

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The "Square Box": Therapeutic Equivalence as a Foundation of the WHO Model List of Essential Medicines

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Every two years, the World Health Organization (WHO) updates its Model List of Essential Medicines, intended as a guide for countries to adopt or adapt in accordance with local priorities and treatment guidelines, for the development of national essential medicines lists. When more than one therapeutic option is available for a given indication, the WHO Model List often includes a single medicine as representative of a group of equivalent and interchangeable medicines. The representative medicine of that group is listed with an accompanying 'square box' symbol. The intended purpose of the square box is to highlight pharmacological classes or groups of medicines for which countries, institutions and health professionals can assume homogeneous therapeutic efficacy and safety and select the most appropriate single medicine based on price, local availability, and acceptability. Though this concept of therapeutic equivalence within a therapeutic class has been endorsed by most authoritative textbooks of pharmacology since *Goodman & Gilman's The Pharmacological Basis of Therapeutics* and evidence-based guidelines, marketing forces have often made claims on individual drugs to distinguish them beyond relevant differences shown by reliable evidence: this has generated the concept of "me-too drugs" with its double meaning—*i.e.*, market latecomers differing minimally from products preceding them and whose marketing budgets have significant opportunity costs, or medicines which may be useful to substitute for equivalent products in the event of shortages. The square box concept is applied in the context of a comprehensive list: therapeutic equivalence or interchangeability cannot always be easily established. Different interpretations have been applied to different groups of medicines over the 40+ year history of the Model List. This paper presents the concept of the square box, provides key examples and guidance on how square box listings should be practically interpreted in the development and implementation of national essential medicine lists, considers the applicability of a square box listing concept to biologic medicines and proposes that an updated review of the square box concept and listings is warranted.

Keywords: WHO model list of essential medicines, medicines selection, therapeutic equivalence, interchangeability, biologic medicines

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INTRODUCTION

Markets are filled with thousands of medicines: many are similar pharmacological analogs (so-called "me-too drugs"), offering little, if any, additional clinical benefit in comparison. The expression "me-too" in the field of medicines was first introduced by Goodman in the 1950s and was popularized during the Golden Age of pharmacotherapy, when hundreds of new chemical entities were studied and eventually approved. Describing a medicine as a me-too has a double meaning, that of a "*market latecomer which often differs trivially from earlier products and that the billions of dollars spent marketing these me-too products could be spent in better ways*" (Lee, 2004) but also as medicines which "*may be useful when equivalent drugs can replace each other in the event of shortages*" (Aronson and Green, 2020).

It is thus important to have a mechanism to facilitate the selection of a limited number of essential medicines from the plethora of pharmaceuticals available on the global market. Controlling the number of medicines deemed essential will deliver both healthcare and economic advantages: to facilitate rational prescribing and use by providing more focused information, to enable better value procurement through tendering and competition leading to lower costs for individuals and health systems and to improve access (Hogerzeil, 2004).

The WHO Model List of Essential Medicines was first published in 1977 and has since been recognized as a revolution in public health; introducing the notion that some medicines are more important than others ('t Hoen et al., 2014). WHO defines essential medicines as those that satisfy the priority health care needs of the population, which are intended to be available in functioning health systems at all times in adequate amounts, in appropriate dosage forms, with assured quality, and at prices individuals and the community can afford (WHO, 2011). Medicines are added to or removed from the Model List on the advice of the WHO Expert Committee on Selection and Use of Essential Medicines, an independent, multidisciplinary group of medical and pharmaceutical experts responsible for reviewing medicines and making recommendations to the WHO Director-General. The Expert Committee is convened every two years to evaluate applications proposing additions, deletions, and changes to medicines on the Model List. It is required to make its recommendations having given due regard to disease prevalence and public health relevance, evidence of clinical efficacy and safety, and with consideration of comparative cost and cost-effectiveness (WHO, 2020a).

The Model List is intended as a guide and reference standard for countries for the development of national and institutional essential medicine lists that together with other medicines' policy actions, empower countries to progress towards universal health coverage and affordable access to safe, effective, and quality-assured essential medicines and health products.

Establishing a limited list of essential medicines is particularly important in low- and middle-income countries, where total health expenditure is more limited and medicine expenditure constitutes a larger proportion of total health expenditure, compared to high income countries (Lu et al., 2011). Investments in medicines should pay worthwhile returns in terms of additional clinical benefit and deliver value for money. In low-, middle-, and high-income countries alike, the costs of many medicines are becoming prohibitive, and policies to improve the efficiency of pharmaceutical spending are increasingly important (OECD, 2010). Square box listings build on the fundamental principal of limited selection. They are intended to give countries scope to select a medicine from within a pharmacological class that best suits local needs based on availability and resources (WHO, 2020a).

Against this background, countries, irrespective of income level, are creating or updating national essential medicines lists, guided by the work done by WHO at the global level. However, countries frequently face uncertainties when undertaking national essential medicine selection, including how to interpret square box listings on the Model List, and determine the alternatives that can be considered therapeutically equivalent. Providing more explicit information on therapeutically equivalent medicines within the square box listings on the Model List can serve to address these uncertainties, better informing and supporting national decision-making.

The aim of this review is to provide guidance for decision-makers to interpret square box listings on the WHO Model List in developing and implementing national essential medicine lists. It also considers the applicability of square box listings to biologic and biosimilar medicines as a mechanism to stimulate competition, reduce cost, and increase access to these therapies.

HISTORY OF THE SQUARE BOX CONCEPT

The concept of a single medicine being included on the Model List as a representative of a broader group of clinically or therapeutically equivalent alternatives has been in place since the first Model List was published in 1977. Listed medicines to which this early concept applied were accompanied by an explanatory note stating "*Listed as an example of this therapeutic category: choose cheapest effective drug product acceptable*" (WHO, 1977). The square box symbol itself (□) was first introduced into the Model List in 1983 when it was determined that therapeutically equivalent alternatives could be represented by a single medicine, so distinguished by this symbol (WHO, 1983). At that time, this was one of the few special symbols that could be used by typographies around the world, ensuring global understanding of the Model List. By 2002, with a relatively large number of medicines on the Model List with a square box listing (n = 113), the Expert Committee recommended a review of medicines listed with a square box, noting some confusion and inconsistency with regard to the application of the concept and implications for its definition (WHO, 2002). Following consideration of the review in 2003, the Expert Committee made a series of recommendations to retain or remove square boxes and modified the explanatory description of the square box symbol on the Model List:

> *"The square box symbol is primarily intended to indicate similar clinical performance within a*

pharmacological class. The listed medicine should be the example of the class for which there is the best evidence for effectiveness and safety. In some cases, this may be the first medicine that is licensed for marketing; in other instances, subsequently licensed compounds may be safer or more effective. Where there is no difference in terms of efficacy and safety data, the listed medicine should be the one that is generally available at the lowest price, based on international drug price information sources. Therapeutic equivalence is only indicated on the basis of reviews of efficacy and safety and when consistent with WHO clinical guidelines. National lists should not use a similar symbol and should be specific in their final selection, which would depend on local availability and price."

This description remains unchanged to date.

The square box is not used to indicate bioequivalence of multisource pharmaceutical products containing the same chemical compound. Bioequivalence of pharmaceutical products is determined by national regulatory authorities and may differ between jurisdictions. The Model List is constructed using the international non-proprietary names of medicines and does not differentiate by proprietary names. Generic substitution between bioequivalent pharmaceutical products is considered acceptable for medicines on the Model List.

TABLE 1 | Square box listings on the 2019 Model List in numbers.

	Number	Examples/comments
Total listings with a square box	108	– 93 unique medicines or fixed-dose combinations – 89 on the core list, 19 on the complementary list
Unrestricted square box*	84	Examples: – simvastatin (representative of statins) – omeprazole (representative of proton pump inhibitors) * some unrestricted listings have reference to acceptable alternatives in the technical report of the meeting where recommendations were made, but these alternatives are not specified in the list.
Qualified square box	24	Examples (specified alternatives): – enoxaparin (nadroparin, dalteparin) – erlotinib (gefitinib, afatinib)
Small molecules	103	Examples (specified alternatives): – bisoprolol (atenolol, metoprolol, carvedilol) – morphine (hydromorphone, oxycodone)
Biological medicines	5	Examples (specified alternatives): – adalimumab [certolizumab pegol, etanercept, golimumab, infliximab (including biosimilars)] – erythropoiesis-stimulating agents [epoetin alfa, beta and theta, darbepoetin alfa, methoxy polyethylene glycol epoetin-beta (including biosimilars)]
Entries without a square box but with named alternatives	14	*e.g.* cycloserine (terizidone), propofol (thiopental), rituximab (quality-assured biosimilars)

CHARACTERISTICS OF CURRENT SQUARE BOX LISTINGS

There are currently 108 entries (involving 93 unique medicines or fixed-dose combinations) on the 2019 Model List that carry a square box symbol (WHO, 2019). These entries appear in the Model List either as "unrestricted" listings, or they are "qualified" by a note specifying the acceptable alternatives. In some cases, there is reference to acceptable alternatives in the technical report of the Expert Committee meeting where specific square box recommendations were made, but the alternatives are not referenced in the list *per se*. An additional 14 entries do not carry a square box but include annotations indicating acceptable alternatives. Square box listings apply to both small molecules and biologic medicines (**Table 1**).

Unrestricted Square Box Listings: All Medicines Are Equal

The majority of square box listings on the 2019 Model List are unrestricted. That is, there is no qualifying note in the list to limit the choice of medicine within the pharmacological class. In these cases, the square box indicates that all medicines within the same pharmacological class can be considered therapeutically equivalent and interchangeable. The representative listed medicine is usually the one for which there is the best or more evidence for effectiveness and safety.

The Model List relies on the Anatomical Therapeutic Chemical (ATC) classification to define medicines within the same pharmacological class. The ATC classification is a 5-level system that classifies medicines according to the anatomical system upon which they act, and their therapeutic, pharmacological and chemical properties. The first level includes fourteen anatomical and pharmacological groups, which are subdivided at the second level into pharmacological or therapeutic groups, at the third and fourth levels into chemical, pharmacological or therapeutic subgroups, with the fifth level being the individual chemical substance (WHO Collaborating Centre for Drug Statistics Methodology, 2020). The ATC classification and the defined daily dose (DDD) assignment are useful tools to identify medicines within pharmacological classes and inform medicine selection decisions at country, institution, or prescriber levels.

Current examples of unrestricted square box listings include proton pump inhibitors (PPIs) for peptic ulcer and gastro-esophageal reflux disease and HMG CoA reductase inhibitors (statins) for hyperlipidemia and prevention of cardiovascular disease, represented on the Model List by omeprazole and simvastatin, respectively. These listings should be interpreted to mean that PPIs and statins have similar clinical performance within their pharmacological classes and represent a group of medicines from which countries can select the most appropriate for their national lists. The ATC classification structures for PPIs and statins are illustrated in **Table 2**. The individual medicines at the fifth ATC level represent options for country-level selection.

However, there are some instances where unrestricted square box listings have reference to acceptable alternatives in the technical report of the meeting where recommendations were made, without this recommendation being reflected in the list *per se*. This has the disadvantage for users of the Model List of requiring reference to the historical meeting reports. For example, in 2009, intravenous ibuprofen was included in the Model List with a square box for the management of patent ductus arteriosus in preterm infants. In making this recommendation, the Expert Committee recommended that indomethacin was an appropriate alternative, yet this is not explicit in the list (WHO, 2009). Instances such as this give rise to uncertainty for country-level decision makers and warrant revision as qualified square box listings to increase clarity and eliminate inconsistency.

Qualified Square Box Listings: When Some Medicines Are Better Than Others

Over 20% of square box listings on the 2019 Model Lists are qualified by a note to indicate that acceptable alternatives are limited to specific medicines. These qualifying notes are recommended by the Expert Committee for a variety of reasons: when there is evidence to suggest within-class differences between medicines (*e.g.*, opioid analgesics) or when there is more limited clinical evidence for some medicines in the class. Qualified square box listings more clearly inform and support rational, evidence-based medicine selection decisions at institution or country level, assist with tendering and procurement processes, and tacitly discourage use of unspecified agents, which would be based on untested assumptions about equivalence in terms of efficacy and safety.

For example, the 2015 addition to the Model List of enoxaparin with a qualified square box listing limits alternatives for low-molecular-weight heparins (LMWHs) to nadroparin and dalteparin, based on the supporting evidence (WHO, 2015). Different LMWHs have been directly compared in a limited number of studies, mostly exploring benefits for venous thromboembolism (White and Ginsberg, 2003). Enoxaparin, nadroparin, and dalteparin are the only LMWHs with evidence in the prevention of venous thrombosis after surgery, as well as for treatment of acute coronary syndromes and venous thromboembolism, the indications for which they are included in the EML. The absence of sufficient evidence on the relative efficacy of other agents in this pharmacological class in conditions other than prevention or treatment of venous thrombosis drove this decision by the Expert Committee.

Similarly, in 2017, the Expert Committee recommended the addition of erythropoiesis-stimulating agents to the Model List for treatment of anemia in patients with chronic kidney disease requiring dialysis, with a qualified square box listing, limiting alternatives to epoetin alfa, beta and theta, darbepoetin alfa, and methoxy polyethylene glycol-epoetin beta (WHO, 2017). The Expert Committee further recommended that their respective biosimilars were also acceptable alternatives based on evidence of therapeutic equivalence and safety of switching to biosimilars from the reference products. Peginesatide, a synthetic erythropoiesis-stimulating agent was not included as an accepted alternative due to serious post-marketing safety concerns that led to its withdrawal from the market in several countries (Hermanson et al., 2016).

In some cases, the square box is used to indicate interchangeability, based on therapeutic indication, of medicines with different pharmacological properties but considered to be therapeutically equivalent alternatives. This use of the square box is only seen in circumstances where comprehensive reviews of efficacy and safety support a conclusion of therapeutic equivalence and when use of the medicines is consistent with recognized clinical guidelines. In such circumstances, the listing is always qualified. However, determining therapeutic equivalence in such circumstances is complex. These cases require detailed and comprehensive review of clinical data on comparative effectiveness and safety and are uncommon. For example, methadone for use in opioid substitution therapy, was added to the Model List in 2005 (WHO, 2005). A square box is included with this listing, along with a qualifying note to identify buprenorphine as an alternative. While methadone and buprenorphine differ in their pharmacological properties, they were considered appropriate therapeutic alternatives for use as substitution therapy for opioid dependence based on the available evidence.

TABLE 2 | ATC classification structures for proton pump inhibitors and statins.

ATC level	PPIs	ATC code	Statins	ATC code
1: Anatomical main group	Alimentary tract and metabolism	A	Cardiovascular system	C
2: Therapeutic subgroup	Drugs for acid related disorders	A02	Lipid modifying agents	C10
3: Pharmacological subgroup	Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD)	A02B	Lipid modifying agents, plain	C10A
4: Chemical subgroup	Proton pump inhibitors	A02BC	HMG CoA reductase inhibitors	C10AA
5: Individual chemical substance	omeprazole	A02BC01	simvastatin	C10AA01
	pantoprazole	A02BC02	lovastatin	C10AA02
	lansoprazole	A02BC03	pravastatin	C10AA03
	rabeprazole	A02BC04	fluvastatin	C10AA04
	esomeprazole	A02BC05	atorvastatin	C10AA05
	dexlansoprazole	A02BC06	cerivastatin	C10AA06
	dexrabeprazole	A02BC07	rosuvastatin	C10AA07
	lansoprazole, combinations	A02BC53	pitavastatin	C10AA08
	rabeprazole, combinations	A02BC54		

APPLICATION OF THE SQUARE BOX CONCEPT TO BIOLOGIC OR BIOTHERAPEUTIC MEDICINES

There is increasing availability of biologic medicines on pharmaceutical markets, many of which are associated with a significant budget impact to health systems. Biosimilar medicines are versions of originator products approved by regulatory agencies that can be manufactured after the originator product patent expires. By virtue of their complex, biological production methods, biosimilar medicines cannot be considered identical to their reference counterparts in the same way that generics of small molecule medicines are considered identical to their reference counterparts (Weise et al., 2014). It has also been noted that each batch of a reference biological is not 'identical' to previous or subsequent batches—"*as 'non-identicality' is a normal feature of biotechnology that has to be controlled by tight specifications of critical product attributes, within current technical and scientific limitations (inherent variability)*" (Schneider, 2013). Indeed, the promotion and use of biosimilars have given rise to concerns and been the subject of intense debates. However, biosimilars are approved following the same standards of pharmaceutical quality, safety, and efficacy that apply to all biologic medicines, and they can reach the same clinical effect in given clinical settings.

Since 2015, the number of biologics on the Model List has increased, raising the question of how the square box concept should apply to biologic and biosimilar medicines. The 2019 Model List includes erythropoiesis-stimulating agents, enoxaparin, human insulin, filgrastim, leuprorelin, pegaspargase and monoclonal antibodies adalimumab, nivolumab, rituximab and trastuzumab (WHO, 2019). Several of these medicines are listed with a square box. The square box introduces the opportunity at country level for biosimilar versions of these medicines to be procured along with the reference products, or as alternatives. It has been applied when a biosimilar has been shown not to have clinically meaningful differences from the reference product in terms of quality, safety, and efficacy and should be considered to be therapeutically equivalent for national or institutional selection and procurement purposes. The availability of alternative biosimilar medicines also creates increased choice for patients and clinicians.

It is expected that with increasing availability of biosimilar medicines, prices will fall, as has been the experience with the prices of small-molecule medicines with the introduction of generics. Cost-efficiencies can potentially be achieved through increased market competition, which facilitates the treatment of a greater number of patients and adds further sources of supply, potentially reducing the likelihood of shortages (NHS England, 2019). However, in 2019, the Expert Committee expressed concern that to date, availability and access to biosimilars of some essential medicines (*e.g.* rituximab) have been limited. To address this, the Expert Committee recommended WHO to consider expanding its medicines' prequalification program to include biosimilars of medicines listed on the Model List, such that they are routinely evaluated along with the reference counterparts (WHO, 2019).

Switching from a reference biologic product to its biosimilar or between biosimilar medicines remains a matter of debate in clinical practice (Faccin et al., 2016). The issue of interchangeability and switching between therapeutically equivalent biologic and biosimilar medicines is important for wider access and to foster market competition. The stringent regulatory criteria and the need for providing a comprehensive data package have often been claimed as putting unnecessary burden and cost on the development and licensing of biosimilars, thus leading to delay in the availability of alternatives. On the other hand, these criteria are meant to provide a sufficient level of evidence to reduce patients' and health care professionals' concerns about the use of biosimilars. Pre-marketing trials and post-marketing drug-utilization data help to consolidate not only the therapeutic equivalence of two products, but also the safety of switching from reference to biosimilar medicines (Ebbers et al., 2012; D'Amore et al., 2016; CADTH, 2017).

Most biosimilars have been approved after switching patients that have been previously treated with either an originator or a biosimilar medicine. Finally, it should be emphasized that many originators have become biosimilars of themselves due to modifications and improvements in their manufacturing processes after their approval and along the product life cycle (Schneider, 2013). A 2011 study analyzed the quality profiles of market-sourced darbepoetin alfa, rituximab, and etanercept between 2007 and 2010, identifying changes in relevant molecular attributes over time. The tested products remained on the market with unaltered labels, indicating that the changes were not expected to be associated with an altered clinical profile and were thus considered acceptable by health authorities (Schiestl et al., 2011).

IMPLICATIONS FOR THE MODEL LIST FOR THE 2021 UPDATE

Square box listings on the Model List were last reviewed in 2003. An updated review is therefore warranted. In 2021, the Expert Committee will be asked to consider a proposal to revise the definition of the square box concept and the related jargon. "Square box" is a term that lacks both clarity and consistency in its use—a critical flaw for any technical term if it is to be globally understood. The Committee will also be asked to review the existing square box listings and determine the specific alternatives for country-level selection. How best to present square box listings to provide the greatest clarity for countries regarding therapeutically equivalent medicines is important to support informed decision-making about pharmacological class effects.

To clearly indicate appropriate alternatives for therapeutic equivalence, applications for new medicines will need to provide evidence for the medicines deemed to provide equivalent clinical benefits. Applications will also be required to consistently and preferentially use the "qualified" square box listing option. Following this approach, the Model List will continue to recommend a representative medicine for classes of medicines where the Expert Committee accepts therapeutic equivalence. Recognized therapeutically equivalent medicines will be included

in the listing in a dedicated field, providing more clear information to support countries in their national selection, tendering, and procurement processes.

The release of an electronic version of the Model List in 2020 (the "eEML") has introduced the ability to easily and clearly indicate the specific therapeutic alternatives recommended for all medicines listed with a square box, effectively allowing all square box listings to be qualified (WHO, 2020b). This will overcome inconsistency in recommendations and address the uncertainty experienced by country-level decision makers in interpreting some listings with a square box symbol in the traditional print version of the list.

Recently, the Model List has adopted inclusion criteria for quality-assured biosimilars of listed biologic medicines in order to support both their therapeutic equivalence and potential interchangeability. Efforts to identify and address the issues and barriers to interchangeability of biologic medicines to improve access and affordability are also warranted. This includes tackling new approaches to develop, license, and monitor biosimilars to improve efficiency, accelerate access, and reduce uncertainties about their use. It is also relevant to explore different types of switching—from an originator product to a biosimilar (or *vice versa*) or between biosimilars—and if there are implications in terms of efficacy, safety or immunogenicity issues. Recommendations issued by the Expert Committee might target which medicines can be identified as alternatives, how the switch can be implemented (*e.g.* prior to the start of a biological treatment or during prolonged treatment) and policies related to interchangeability. For instance, there are multiple levels at which switching can be enacted: by the physician, by the pharmacist, or by the healthcare system (Barbier et al., 2020). Recommendations could clarify cases in which the switch should be under the responsibility of the treating physician, cases in which the patient can safely switch among biologic and biosimilar medicines (*e.g.* insulins), and cases in which the switch is automatic (*i.e.* without consulting the prescriber). Automatic switching might allow for optimal allocation of resources, given the potential or actual associated cost-reductions (Jensen et al., 2020).

CONCLUSIONS

This review aims to clarify the interpretation and practical application of square box listings of essential medicines to better inform decision-making for national essential medicine lists. The Model List continues to evolve with time, with new medicines regularly considered for inclusion to meet changing public health needs. In 1983, quality information about medicines was scarce and its access very limited; four decades later, prescribers face an overflow of information which mixes biased and low-quality studies with relevant evidence. Additionally, a plethora of me-too medicines have entered the market, many of them without showing clear differences in efficacy or safety over the competitors, yet often at higher costs. Finally, the appearance of biologic products and their biosimilars has changed some paradigms of the chemical medicines and worsened the affordability of essential medicines at country level. Therefore, it is timely to perform an updated review of the square box concept, definition and listings at the next update of the Model List in 2021.

Within this panorama, guidance provided by WHO through the Model List on therapeutic equivalence within a pharmacological class and interchangeability of medicines will support countries to make evidence-based informed choices and avoid listing redundant me-too products with the same efficacy and safety profile. In the case of biological products, the inclusion of biosimilars on the Model List as therapeutic alternatives to reference biologics can serve to improve affordability of otherwise expensive treatments being considered for inclusion on national essential medicines lists by stimulating market competition and introducing opportunities for better value procurement. Utilization studies of access and use policies of medicine classes would enable a better understanding of the impact of the therapeutic equivalence and interchangeability, helping countries to better respond to the strategic opportunities and challenges being faced.

AUTHOR CONTRIBUTIONS

BC, LM, and NM contributed to the conceptualization of the review. BC, LM, and AF researched and wrote the manuscript. NM was the Secretary of the WHO Expert Committee on Selection and Use of Essential Medicines between 2015 and 2020 and an employee of the World Health Organization, Geneva, Switzerland, at the time of writing of this paper. All authors contributed to the article and approved the submitted version.

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REVIEW
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Global Mental Health and Pharmacology: The Case of Attention Deficit and Hyperactivity Disorders in Brazil

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Global Mental Health (GMH) is the field of study, research, and intervention, which aims at improving access to mental health worldwide. It is based on the global burden of disease research program and on the existence of a large "treatment gap" between the need and availability of mental health services, displaying individual and social costs of undiagnosed and untreated mental disorders, especially in low- and middle-income countries (LMIC). Few academic publications in Brazil dialogue directly with the field of GMH, although several issues drawn from its agenda have been the subject of mental health policies in the country. Brazil can be classified as a middle-income country with a well-structured national health system. This system is oriented toward primary health care, which integrates both community mental health services and the broader health care network. The debate between GMH advocates and critics has unearthed old controversies in psychiatry such as universality or cultural specificity of mental disorders, their expressions, and their relationship with social and economic factors. We intend to examine how these controversies reverberate in the Brazilian mental health scenario, taking as an illustration the debates around Attention Deficit Hyperactivity Disorder (ADHD) in the country. ADHD discussions oppose those who argue that the condition is underdiagnosed and undertreated, and those who claim that there is overdiagnosis and overtreatment and thus, medicalization of childhood. This article presents the current status of the Brazilian mental health literature on ADHD, with emphasis on tensions around diagnosis, prevalence and interventions. Our aim is to highlight how the differential in discourse shapes the debate on ADHD in Brazil and how this may contribute to the GMH agenda. This goal will be undertaken in three steps. First, we will briefly examine studies around GMH and ADHD. Secondly, we address Brazilian studies on this theme, considering the specificities regarding the constitution of the mental health field. Finally, we will examine the debate of treatment gap vs. medicalization in the country in order to underscore the potentials and limitations of each perspective.

Keywords: global mental health, attention deficit and hyperactivity disorder, medicalization, methylphenidate, treatment gap, child and adolescent mental health

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INTRODUCTION

Global Mental Health (GMH) is a field of study, research and practice, which aims at improving access and ensuring equity in mental health care for all people in the world (Patel and Prince, 2010). GMH researchers highlight the existence of a treatment gap in mental health around the globe and promote strategies to address the situation (Chisholm et al., 2007; Jacob et al., 2007; Patel et al., 2007; Prince et al., 2007; Saraceno et al., 2007; Saxena et al., 2007; Patel, 2012).

The GMH agenda has also raised important criticism especially from transcultural psychiatrists and anthropologists. Overall, such objections outline the biology vs. culture controversies and denounce the neglect of social, political, and economic processes associated to mental health diagnostics, treatments, and research (Summerfield, 2012; Clark, 2014; Kirmayer and Swartz, 2014; Ortega and Wenceslau, 2020).

Attention Deficit Hyperactivity Disorders (ADHD) are among the mental health conditions singled out by GMH research and interventions (Kieling et al., 2011; Patel et al., 2013, 2018; Ordóñez and Collins, 2015). The issue of accessibility to pharmacological treatments for ADHD raises important questions for GMH. Estimating prevalence for the condition is one of the aspects to be considered. Early detection and diagnosis are believed to be central for management of ADHD cases (Flisher et al., 2010). Researchers have examined the obstacles to achieve this goal in low- and middle-income countries (LMIC), such as limited resources and lack of mental health specialists, and have proposed that diagnosis and treatments may be achieved by raising awareness and empowering community health care teams, educators and school counselors along with other lay agents in the community (Flisher et al., 2010).

There are strong controversies between those who advocate that ADHD remains globally prevalent but undiagnosed and inadequately treated (Polanczyk et al., 2007; Flisher et al., 2010) and those who understand that it is a social construct, reflecting the advancement of both US psychiatry and the pharmaceutical industry (Singh et al., 2013; Conrad and Bergey, 2014; Mills, 2014; Conrad and Singh, 2018). GMH initiatives highlight the neurobiological nature of the disorder and promote the access to psychostimulants and other pharmacological agents in LMIC (Flisher et al., 2010). Assuming the universal, neurobiological nature of the condition that would affect equally all individuals across cultural contexts and nations justifies the scalability and generalizability of the use of psychostimulants as well as the exportation of Western psychiatric expertise and standardized care packages to the Global South (Mills, 2014). Critics argue that such strategies privilege one-size-fits all interventions, leaving aside difference markers such as gender, race, or culture. The result is the rapid expansion of diagnosis and pharmaceutical treatments–what has been called the "McDonaldization of children's health" (Timimi, 2010; Mills, 2014). Although we sympathize with those perspectives, they frequently hide deep differences and important negotiations in the way individual countries have engaged with ADHD. While some countries have rapidly accepted the US biomedical model and consequently have diagnosed and treated with psychostimulants large parts of their children and adult population, other countries, like Brazil, have challenged and rejected biomedical models (Smith, 2017).

Controversies around ADHD play in different ways across diverse national configurations and should be considered when promoting GMH strategies for the condition. Moreover, there are still few studies that focus on the provision of evidence-based care for this population in LMIC. Most investigations center around pharmaceutical treatment strategies originally implemented in high income countries (Patel et al., 2013, 2018; Ordóñez and Collins, 2015) and set aside local histories, perspectives and approaches (Smith, 2017).

The specifics of the different national contexts impact a global agenda for ADHD (Smith, 2017) and are seldom addressed from a social science perspective. It is not possible to make generalizations about the phenomenon without the risk of reducing the dynamics, manifestations and results associated with its dissemination (Conrad and Singh, 2018).

Thus, ADHD is an interesting case to examine social and structural processes that permeate the transmission of psychiatric diagnoses and treatments, as well as their differences across national contexts. Literature on the issue draws on two key-concepts from social sciences, medicalization and globalization (Singh et al., 2013; Conrad and Bergey, 2014; Smith, 2017; Conrad and Singh, 2018). In this sense, ADHD illustrates the overarching globalization of a medicalized category (Conrad and Singh, 2018).

This article examines how global issues and controversies in global (mental) health take specific forms within particular socioeconomic, political and historical contexts focusing on the debates surrounding ADHD in Brazil. The national history of ADHD in the country discloses the influence of social, political and cultural factors in the framing of diagnosis and treatments. The debates around the condition in Brazil are also distinguished by tensions between those who argue that the condition is underdiagnosed and undertreated, and those who claim that there is overdiagnosis and overtreatment and thus medicalization of childhood.

This article presents the current status of the Brazilian mental health literature on ADHD, with emphasis on tensions around diagnosis, prevalence and interventions, organization of care and health policies. Our aim is to highlight how different discourses shape the debate on ADHD in the country and how they can contribute to the GMH agenda. This goal will be accomplished in three steps. First, we will briefly examine studies around GMH and ADHD. Next, we will address the Brazilian studies on this subject, considering the specificities of the constitution of the mental health field. Finally, we will critically analyze the debate over treatment gap vs. medicalization in the country in order to examine potentials and limits of each perspective.

The contrast between these two perspectives regarding ADHD (treatment gap or medicalization) can display assumptions about mental disorders as universal biological conditions or as social constructs, which limit the dialogue and proposals for this population. GMH strategies highlight the notion of treatment gap as evidence of the existence of a portion of the world population living with mental distress and without access to health care (Jacob et al., 2007; Patel et al., 2007; Saxena et al., 2007). Children

and adolescents are among the most affected, and ADHD is one of the conditions recognized by GMH to contribute to this gap. Although the care and inclusion of children and adolescents living with mental distress should have urgent attention, it is also essential to understand how this index (treatment gap) is used in specific contexts and what effects it may have.

Moreover, ADHD has been one of the main entities studied by medicalization scholars (Singh et al., 2013; Conrad and Bergey, 2014). In this sense, it is important to examine the different configurations involved in the expansion of the diagnosis globally and the role played by diverse movements, such as GMH, and the debates they raise (Clark, 2014; Conrad and Bergey, 2014).

GLOBAL MENTAL HEALTH AGENDA FOR ADHD

Childhood and Adolescence Mental Disorders and Global Mental Health

The objectives of Global Mental Health include producing knowledge about mental health from a global perspective, promoting research and evaluation of mental illness and care strategies, mitigating the treatment gap, ensuring access, and equity in mental health care and advocating for the rights of people with mental disorders and their families at a global level (Chisholm et al., 2007; Jacob et al., 2007; Patel et al., 2007; Prince et al., 2007; Saraceno et al., 2007; Saxena et al., 2007; Patel and Prince, 2010; Patel, 2012).

To achieve these goals, GMH supporters stress the role of community mental health services and primary care facilities, and favor evidence-based, collaborative interventions that are responsive to local characteristics and scalable to broaden the access to mental health care (Chisholm et al., 2007; Jacob et al., 2007; Patel et al., 2007; Prince et al., 2007; Saraceno et al., 2007; Saxena et al., 2007).

Since its emergence in 2007, GMH researchers have produced a significant amount of empirical studies focused on low- and middle-income countries (LMICs), especially those in sub-Saharan Africa and Southern Asia. Conversely, there is a tendency in these studies to prioritize various conditions, such as depression, psychotic, and stress-related disorders, but with limited attention to contextual and socio-demographic aspects (Misra et al., 2019).

GMH initiatives have revitalized old controversies in psychiatry around the universality or cultural specificity of mental disorders. Critics of GMH argue that it promotes a Western, biomedical model of illness and treatments as well as the expansion of the Pharma industry; neglects practitioners of traditional therapies; disregards cultural influences on cause, course and outcome of mental disorders, as well as explanations for mental distress; medicalizes suffering and ignores social and economic determinants of mental health (Summerfield, 2012; Clark, 2014; Kirmayer and Swartz, 2014; Ortega and Wenceslau, 2020). GMH advocates have refuted such criticism and stressed their engagement with local communities and attention to context and culture in the design of the interventions. Furthermore, they have also underlined the deep influence of social sciences and cultural psychiatry in their methods and principles and their strong concern for human rights (Patel, 2014).

Mental disorders in childhood and adolescence, especially ADHD, constitute an interesting case to examine controversies around GMH and how these are instantiated differently across the diverse national contexts. There is an important treatment gap for these disorders as well as those victims of abuse and neglect, particularly in LMICs, where 90% of the world's children and adolescents reside and represent 50% of the local population (Kessler et al., 2007; Collins et al., 2011; Gore et al., 2011; Kieling et al., 2011; Barry et al., 2013; Patel et al., 2013; Ordóñez and Collins, 2015). According to the literature, mental disorders account for the higher burden of disease in children and young people, including developmental disabilities (such as intellectual disability and autism), emotional disorders (mainly anxiety and depression), and disruptive behavioral disorders (ADHD and conduct disorders), with lasting lifelong impact in terms of health and employment options, as well as to health systems (Patel and Prince, 2010; Kieling et al., 2011; Patel et al., 2013; Ordóñez and Collins, 2015).

Strategies to address both treatment and research gaps in child and adolescent mental health are equivalent to those aimed at adults, for they involve the adoption of a perspective that incorporates life-course and system-wide approaches, as well as evidence-based initiatives (Collins et al., 2011; Kieling et al., 2011; Ordóñez and Collins, 2015; Orr and Bindi, 2017). GMH professionals propose complementary pathways to overcome these barriers. Early diagnosis, increased awareness of family members and education professionals, development of collaboration among schools, social care and the legal system, and skilled mental health professionals are believed to be key features for addressing mental disorders and granting individuals access to quality mental health care (Flisher et al., 2010; Kieling et al., 2011; Barry et al., 2013; Patel et al., 2013).

Clinical and Epidemiological Features of ADHD

ADHD is classified as a neurodevelopmental disorder within psychiatric and GMH literature (Flisher et al., 2010; American Psychiatric Association, 2014; Insel, 2014; Ordóñez and Collins, 2015). Brain developmental studies have contributed to this view of the condition (Insel, 2014). Evidence from high-income countries (HICs) suggests that ADHD is a syndrome with complex genetic etiological factors, in which 80% of cases may be related to genetic inheritance (Flisher et al., 2010). Social determinants however, would also influence symptomatology. Some identifiable factors are low socioeconomic status, low education, parental mental disorder, family conflicts and severe early deprivation (Flisher et al., 2010). Other non-genetic factors associated with ADHD are those that affect early brain development, such as perinatal distress, smoking, and alcohol use during pregnancy, low birth weight, obstetric complications, epilepsy, and HIV (Flisher et al., 2010). Although these findings corroborate the hypothesis that ADHD is a heterogeneous disorder influenced by interactions between genes

and environment, there are comparatively fewer studies that delve into the interactions between genetics and environment in LMIC and as such, their findings do not always coincide with those observed in HICs (Flisher et al., 2010).

The global prevalence of ADHD is estimated to be between 5 and 7% (Polanczyk et al., 2007; Shaw et al., 2012; Raman et al., 2018), with ∼2.5% prevalence in adults. ADHD may persist in up to 65% of adults diagnosed during childhood (Fayyad et al., 2007; Shaw et al., 2012; Raman et al., 2018). Persistence of the condition would be related to the severity of ADHD symptoms, psychosocial adversity, presence of psychiatric comorbidities, and occurrence of ADHD in relatives. It is common for adults with ADHD to go undiagnosed and therefore untreated (Shaw et al., 2012).

ADHD symptoms can often lead to functional impairment in many spheres, with repercussions on quality of life and increased risk of lifelong psychiatric comorbidities (Flisher et al., 2010; Shaw et al., 2012). These findings have led to a shift in the intervention focus. It is understood that childhood and adolescence constitute an opportune moment for health promotion, the improvement of social and emotional skills and cognitive development (Kieling et al., 2011; Kieling and Belfer, 2012; Barry et al., 2013; Insel, 2014; Ordóñez and Collins, 2015). Thus, in addition to improving the immediate symptoms of ADHD, long-term functionality has been sought (Flisher et al., 2010; Shaw et al., 2012).

Global Mental Health Interventions for ADHD

GMH's approaches to ADHD stress the significant burden of disease for children and adolescents and life-long consequences associated with the condition. They also evince diverse diagnosis and treatment practices due to the fragility of health systems, shortage of trained professionals and stigma especially in LMIC. The need to address these problems leads to different proposals including sensitization of the population to risk factors, increasing recognition, and early detection in community settings such as schools, social welfare and the legal system, and the introduction of collaborative care (task-shifting) in contexts with shortage of skilled mental health professionals (Flisher et al., 2010; Kieling and Belfer, 2012; Barry et al., 2013; Patel et al., 2018). Moreover, the development of advocacy groups including professionals and individuals living with ADHD are also encouraged, especially in contexts of insufficient mental health professionals and community services (Flisher et al., 2010).

In general, the intervention with the strongest evidence involves the use of medication (Flisher et al., 2010; Patel et al., 2013; Raman et al., 2018). The preferred medications are psychostimulants (methylphenidate and amphetamine), given the findings on its efficacy and safety of usage (Flisher et al., 2010). Other interventions–e.g., psychotherapy, social skills training, psychoeducational interventions with caregivers–may be implemented in conjunction with psychopharmacological interventions (multimodal treatment) or without medication (Flisher et al., 2010; Kieling et al., 2011; Shaw et al., 2012; Patel et al., 2013; Beau-Lejdstrom et al., 2016; World Health Organization, 2016; National Institute for Health and Care Excellence (NICE), 2019). Drug prescription should be avoided whenever symptoms are mild to moderate, if there is diagnostic uncertainty and/or minimal functional impairment, and if there is a shortage of professionals and adequate services to attend to patients and their families (Flisher et al., 2010; Patel et al., 2018; National Institute for Health and Care Excellence (NICE), 2019).

Flisher et al. (2010) argue that the insufficiency of mental health professionals in LMIC should not be taken as an impediment to the introduction of packages of care in those countries. Those interventions would involve the screening of high-risk groups, psychoeducational interventions with caregivers, medication prescription and behavioral interventions.

Scholars agree that further studies are needed to assess the efficacy of ADHD interventions in LMICs (Flisher et al., 2010; Kieling et al., 2011; Patel et al., 2013). Patel et al. (2013) draw attention to the fact that, in addition to the scarcity of investigations regarding the treatment of ADHD in LMIC, the greater number of the existing studies focus on pharmacological strategies. Although studies aimed at evaluating multimodal interventions are increasing and providing meaningful results, the lack of evidence in relation to the effectiveness of psychosocial or combined interventions ("care packages") is a key hurdle to scaling up care packages, as these demand significant contextual adaptation (Patel et al., 2013; Raman et al., 2018).

More recently, research has addressed issues on the combination of treatments, as well as the duration of effects of different treatments and their combinations (Galera et al., 2014; Arnold et al., 2015; Patel et al., 2018; Raman et al., 2018; Lam et al., 2019). The best results in multimodal treatments and their lasting effects may apparently be related to effects on neuroplasticity, as well as to coping strategies developed during the use of medication (Lam et al., 2019). Although there appear to be long-term benefits in multimodal approaches (Arnold et al., 2015; Lam et al., 2019), the use of different treatment response criteria and the preference for psychotherapeutic interventions based on cognitive behavioral therapy may not coincide with ongoing therapeutic experiences in LMICs. In Brazil, psychodynamic interventions (especially psychoanalysis) are largely used within community mental health services (Menezes et al., 2018).

Moreover, as noted by Galera et al. (2014), elements related to the sociocultural and economic contexts, such as parental educational level, parenting style, social integration (e.g., history of immigration or low socioeconomic status) are associated with iniquities in access to different therapeutic modalities, as well as to the continuity of their use. Individual characteristics are not the sole variables that influence drug exposure and those additional factors have to be considered in order to expand care alternatives and reduce the risk of stigmatization of users and their families.

A recent study by Raman et al. (2018) examined prevalence and tendencies in the use of medication for ADHD among children, adolescents and adults in the period from 2001 to 2015 in four regions: Asia and Australia (Hong Kong, Japan, Taiwan, and Australia); North America (Canada and USA); Northern Europe (Denmark, Finland, Iceland, Norway, and Sweden), and

Western Europe (France, Spain and Great Britain). The study observed an increase in the prevalence of drug use in children and adults since 2000 in all regions, varying across regions and countries studied. Assuming that the prevalence of ADHD is similar worldwide when consistent diagnostic criteria and methods are used, the authors suggest that the variation in the use of medication may be related to: the different ways in which the diagnostic criteria are applied in practice; the structure, functioning and financing of health systems (for example, direct access to specialists, availability and cost of medication and availability of non-pharmacological treatments); proportion of off-label drug use and cultural variations in perception and treatment of ADHD. Moreover, such variation may still be associated with the influence on doctors of the guidelines and studies validating the effectiveness and/or safety of medications, as well as the long-term consequences of inappropriate treatment. While recognizing that there is no clear evidence on optimal rates of prescription, the study results indicate that many patients are likely to be treated inappropriately (especially in areas of low drug use), whereas others may be overtreated (Raman et al., 2018).

Raman et al. (2018) do not display data from Latin America, which indicates a significant information gap and exposes an important challenge regarding the consolidation of useful data not only for decision making and policy strategies, but also for the production of knowledge about the condition in LMIC. Furthermore, as noted below, it does not reflect the intense debate in about etiology, diagnosis, treatments and organization of care for patients living with ADHD.

GMH interventions for ADHD are therefore important to overcome the diagnosis and treatment gaps. Still, one should be wary of Western psychiatric classification systems and care models with little scalability outside HIC. The privilege of biomedical models of diagnosis and treatments frequently disregards local historical and sociocultural contexts. Issues of overdiagnosis, false positives, inadequate therapy and adaptation to local contexts are seldom or insufficient addressed.

Many of the arguments already presented by advocates and critics of the GMH agenda for ADHD are taken up in a particular form in the debates around the condition in Brazil, which we will now expose, after presenting data on ADHD prevalence and on the production, prescription and consumption of methylphenidate in the country.

THE BIOSOCIAL FIELD OF ADHD IN BRAZIL

Epidemiology of ADHD in Brazil

As in other countries, the prevalence of ADHD in Brazil evinces a huge variation among different studies. The Brazilian sanitation regulatory agency (ANVISA) estimates that the prevalence of the condition ranges widely, from 0.9 to 26.8% (Boletim Brasileiro de Avaliação de Tecnologias em Saúde (BRATS), 2014).

Several epidemiological studies in the country found 3.6 to 5% prevalence among school-age children (Barbosa and Gouveia, 1993) and other study estimates the prevalence of 3–6% in children aged 10 to 14 (Oliveira et al., 2016). Rohde et al. (1999) found a prevalence of 5.8% in a sample of teenagers based on DSM-IV criteria. Among students at four public schools in the state of Rio de Janeiro, Fontana et al. (2007) found a prevalence of 13%; yet in the same region of the country, a different study showed a prevalence of 17.1% (Vasconcelos et al., 2003). It is important to highlight that higher prevalence has been found in socioeconomically disadvantaged populations, which usually attend public schools in Brazil (Oliveira et al., 2016). Freire and Pondé (2005) studied 763 children attending a public school in Salvador, in the state of Bahia in northeastern Brazil. They estimated that 12 children (8%) had a high probability of having ADHD. Another study conducted in a different public school in Salvador in 2016 with 265 children ages 10 to 17 showed prevalence of 16, 6% (Oliveira et al., 2016). Guardiola et al. (2000) found 18% prevalence based on DSM-IV criteria in a sample of 35,521 students ages 6–14 in elementary schools in the city of Porto Alegre, in South Brazil. Of those students, 64.7% were in state public schools, 11.9% in municipal schools, and 23.4% in private schools. It has been highlighted that studies which use DSM-IV criteria have shown a higher prevalence than those using previous versions of DSM (Baumgaertel et al., 1995).

Thus, there is a huge variation in prevalence of ADHD across the country. As in other national contexts these discrepancies have fueled arguments of those who argue for the "social construction" of the condition driven by the interest of the pharma industry. Against this backdrop a widely cited meta-analysis of the global prevalence of ADHD conducted by Brazilian researchers linked the differences in prevalence to the diversity of methodologies used in the different studies. Taking this factor into account they estimated a global prevalence of ADHD of 5% among school-age children (Polanczyk et al., 2007). Other Brazilian scholars associated the variations in prevalence to the type of sample examined, the different instruments and diagnostic criteria and then observed a significant difference according to the person providing the information, whether the parents, teachers, or the children themselves (Rohde et al., 1998; Vasconcelos et al., 2003). Debates and controversies around ADHD in the country draw on the variations in the prevalence either to argue for over–or underdiagnosis of the condition.

Production, Prescription and Consumption of Methylphenidate in Brazil

The global production of methylphenidate increased from 28.830 kg in 2001 to 70.669 kg in 2017 (International Narcotic Control Board (INCB), 2018). Around 268 kg of methylphenidate were sold in Brazil in 2005, reaching 875 kg in 2012 (Barros, 2014). More recent data is unavailable, since Brazil and other major producers did not report their data to the International Narcotics Control Board (International Narcotic Control Board (INCB), 2013). In 2017 the country ranked seventh among the major importers of the medication (International Narcotic Control Board (INCB), 2018).

Since the early 2000's, reports about the pharmaco-epidemiological distribution of controlled substances such as amphetamines and other appetite inhibitors and

methylphenidate have been one of ANVISA's priority targets. Regarding the consumption of methylphenidate, the country had no electronic system for regulating controlled medications before 2007 (Relatório 2009–Sistema Nacional de Gerenciamento de Produtos Controlados (SNGPC), 2010). Local inspectors had to check records of purchases and sales by drugstores. ANVISA did not have access to these local data (Noto et al., 2002). According to the regulatory agency, the consumption of methylphenidate in Brazil in 2009 ranged from 5 kg in January to 20 kg in October (the discrepancy is attributed to the consumption decrease during school holidays). Data from the new information system reported an annual consumption of 156.623 kg in 2009, 266.092 kg in 2010, and 413.383 kg in 2011 (Sistema Nacional de Gestão de Prescrição Controlada (SNGPC), 2012; Gomes et al., 2019). Data presented by the Ministry of Health in 2015 declared that Brazil has become the second world market in methylphenidate consumption, with about 2,000,000 boxes sold in 2010, and indicated a consumption increase of 775% in the last 10 years in the country (CONANDA, 2015).

Methylphenidate demands a specific prescription for narcotics and psychotropic medication. The physician has to register at the corresponding regional council of medicine (CRM) to get the prescription for those substances. This requirement has faced strong opposition from many Brazilian physicians, who disagree with the current methylphenidate regulations. They argue that the procedures are excessive and outweigh the potential risks. Moreover, the notification process may intimidate and embarrass patients and multiply unnecessary bureaucratic procedures (Carlini et al., 2003).

In Brazil, the Ministry of Health does not include methylphenidate in its standardized dispensing lists via the Unified Health System (SUS), such as the National List of Essential Medicines (RENAME). Nevertheless, States and Municipalities have relative autonomy to include specific medications according to their local particularities. Parent and professional associations have exerted pressure to include methylphenidate in the lists cited above. Hence, under certain criteria SUS patients in the state of Espirito Santo and the cities of Sao Paulo and Campinas, in South East Brazil, have access to the medication.

The state of Espirito Santo included methylphenidate in its List of Essential Medicines (RENAME) (Espírito Santo, 2007) and was the first state in the country to create an ordinance regulating the public dispensation of the medication in September 2010 (Caliman and Domitrovic, 2013). It was followed by the municipality of São Paulo, in June 2014 (São Paulo, 2014) and by the city of Campinas, in October 2014 (Campinas, 2014). However, the three regulations diverge regarding inclusion criteria, such as age and symptoms, the dispensation place and the professional who may prescribe the medication. In Rio de Janeiro, a municipal act was approved but it did not suffice to establish a program for public dispensation (Rio de Janeiro, 2012). In 2012, former mayor Eduardo Paes approved draft act n. 710/2010, which granted rights to students with ADHD in the city of Rio de Janeiro. It established guidelines for parents and teachers and also determined the availability of medicines in municipal public health facilities (Esher and Coutinho, 2017).

The relative autonomy of each state and municipality to define their own list of "essential medications" ensures that some medications, which until then could only be accessed by the population through lawsuits against the state, may be requested through administrative processes in SUS state pharmacies (Caliman and Domitrovic, 2013). Critics underline the lack of national policies for ADHD treatments and the complexity involved in granting access for procedures for low-income patients to obtain methylphenidate within SUS (by lawsuits or through an administrative process beset by red tape). Maia et al. (2015) estimate that only the direct consequences of not treating children with ADHD ages 5–19 would amount ∼R$ 1,841 billion/year (Brazilian real), and if the country increases its investment in treatments from the current R$ 28 million spent by families out of pocket to R$ 377 million, the amount saved would be 3.1 times higher than the expenses.

Debates and Controversies Around ADHD in Brazil

Background: The Brazilian Psychiatric Reform and the Organization of Mental Health Services

The Brazilian mental health system has ensued from the psychiatric reform, which ran parallel and partly overlapped with the Brazilian health care reform (Fleury, 2011). The latter resulted from the Constitution of 1988, enacted after the redemocratization of the country following the end of the dictatorship and which led to the creation of the Brazilian Unified Health System (Sistema Único de Saúde–SUS, Paim et al., 2011). The SUS system is organized regionally, with a decentralized network of health services formed by a complex set of public, private and philanthropic providers, under coordinated management at each level of government and with strong community participation (Lobato and Burlandy, 2000; Souza, 2002). The regionalized structure of SUS starts at the municipal level with relative autonomy to define its own health policies and structures of care. This will have important consequences for the field of ADHD in the country, as we will show.

Since the establishment of the SUS there have been continuous efforts toward universal health coverage. Regrettably, the Constitution also enabled the participation of private health insurance companies in a "complementary" way to the public system. Hence, on a constitutional and legal basis, Brazil has a universal public health system, though in practice, health financing is mostly private due to the underfinancing of the public system and the absence of clear limits to the participation of private health companies (Oliveira and Dallari, 2016).

The Brazilian psychiatric reform was inspired by the Italian reform and the Italian democratic-psychiatry movement led by Franco Basaglia in Trieste. An additional influence was the Lacanian-inspired institutional psychotherapy program of La Borde in France (Barros, 1994; Passos, 2009; Foot, 2015). In the early 1970's, Brazilian mental health workers initiated the so-called "anti-asylum struggle" (luta antimanicomial) and criticized the psychiatry establishment's collaboration with the dictatorship. This movement developed within the context of the country's democratization and the sociopolitical mobilization

of that time (Delgado, 1992; Amarante, 1995; Tenório, 2002). Guidelines proposed by the Pan American Health Organization (1990) were adopted resulting in the reorientation of mental health care from a hospital-centered system to community mental health care and primary health care models. Mental health policies in the country were consolidated in 2001, when the Psychiatric Reform Law (Federal Law 10.216) was approved, which grants the protection and rights of those with mental disorders and redirects the model of care in mental health (Csillag, 2001). It encourages the programmed reduction of long-term admissions in psychiatric wards, and whenever possible the replaced replacement by beds in general hospitals for short periods of time. It also promotes the deinstitutionalization of psychiatric inmates and their psychosocial insertion through work, culture and leisure (Ministério da Saúde, 2004).

The mental health law contemplated the development of Psychosocial Care Centers (Centros de Atenção Psicossocial–CAPS), which is considered the keystone of the Brazilian Psychiatric Reform. CAPS are community mental health services that provide outpatient care or partial hospitalization for patients with severe mental illness, and are articulated with primary care units to organize psychiatric care in a defined catchment area, defined as "territory" (Mateus et al., 2008). Based on the universal logic of public health care CAPS system opposes framing mental health policies and specialized services according to specific diagnoses. Hence, the notion of a "citizen burdened by mental suffering" should replace different psychiatric labels and diagnoses (Ministerio da Saúde, 2004; Biehl, 2005: p. 134). Diagnoses at CAPS and CAPSi (specific form of CAPS for children and adolescents) are always ongoing processes and not definitive, but re-assessed according to the corresponding "care strategy," which may involve psychotherapy, rehabilitation, group activities and medication. At the center of the process is the singularity of the child–i.e., the child's history, family and everyday life (Couto, 2004, 2012; Couto et al., 2008)–and the "primacy of the ethical" to promote the patient's unique experiences and his position as a moral subject (Goldberg, 1994; Biehl, 2005). Thus, the so-called projeto terapeutico singular (unique therapeutic project) is the main tool for the work conducted at CAPS and reflects the strong imprint of psychoanalysis and its emphasis of singularity (Cunha, 2007). These strategies embody the basic tenets of the so-called Psychosocial Care Paradigm, considered an epistemological turn in mental health (Yasui et al., 2016). Correspondingly, human suffering is addressed in its complexity, as part of a psychosocial dynamics that suspends the labels of normality and sanity and examines the social and biopolitical interests and mechanisms behind those labels. Care is no longer understood as therapeutic isolation or moral treatment, but as "creation of socialities and subjectivities" and the patient is "no longer an object of knowledge, but a subject expressing insanity" (Yasui et al., 2016: p. 401).

Several parent associations oppose CAPSi principle of not organizing services according to specific diagnoses, demand specialized services for their children along with the involvement of the associations as political actors and criticize the limited connection to other sectors, such as education and social assistance (Nunes, 2016). Moreover, they also strongly disagree with psychoanalytic treatments at CAPSi. Despite claims to multidisciplinarity, several CAPSi–particularly those in the State of Rio de Janeiro, have a psychoanalytic orientation and promote a discourse of self-sufficiency and exclusivity of psychoanalytic treatments (Lima et al., 2018).

Professionals working at CAPSi do not consider ADHD as a severe condition and many are harsh critics of the disorder. Additionally, they resisted the introduction of specialized services and advance, rather demedicalizing strategies for issues of hyperactivity and attention problems. Conversely, parent and psychiatric associations advanced a biomedical understanding of the condition and have criticized the lack of specialized services for children with ADHD. There are very few specialized services for ADHD within SUS or the private sector[1]. Controversies around ADHD in the country have gravitated around the issue of medicalization of social problems, involving other medical and non-medical actors. Such debates have strongly impacted policy orientations, mental health care setup, professional knowledge and care practices, as we will further examine.

ADHD Activism

Debates around ADHD in the country oppose groups that support biomedical descriptions and classifications based on the countless scientific studies published on the topic and those that challenge biomedical models and psychopharmacological treatments (Associação Brasileira de Saúde Mental (ABRASME), 2010; Fórum sobre Medicalização da Educação e Sociedade, 2011; Mattos et al., 2012; Associação Brasileira de Psiquiatria (ABP), 2014). While the former advances a biomedical discourse and incorporates arguments from the GMH agenda, which stresses the treatment gap for the condition in Brazil, the latter draws on the medicalization narrative.

Different from countries like the US, Canada, UK or Australia, Brazil does not have such a strong tradition of patient support groups. Still, there are a growing number of associations for patients with autism, ADHD, and obsessive-compulsive disorder and their family members. These associations play an important role in disseminating knowledge about these conditions and fighting for treatments, services and citizens' rights (Frossard, 2015; Rios and Andrada, 2015, 2016; Nunes and Ortega, 2016).

Parallel to the development of patient and parent associations for ADHD, autism and other conditions in Brazil, and in the context of the psychiatric reform along with the following deinstitutionalization process, there have also emerged a small number of users' and survivors' groups. They are very few, and not restricted to service users, encompassing family members (mostly from lower classes) and professionals from public mental health services. Their role has been rather marginal when compared to the influence of those groups in other countries due to the lack of structure to organize their activities as well as insufficient funding and meager political support (Vasconcelos, 2013; Almeida, 2019). Several factors account for this precarious situation, including, the strong hegemony of

[1]https://tdah.org.br/category/profissionais-para-tratamento/locais-publicos-de-tratamento

patrimonial and hierarchical culture within Brazilian society resulting in a vertical organization with professionals on top of the hierarchy, enormous social inequality and the limited presence of public initiatives for mental health within the neoliberal public health policies (Vasconcelos, 2013). These organizations gravitate around the CAPS system and therefore promote the universal logic of public health care and oppose specialized policies and services for separate conditions.

Likewise, many CAPSi do not keep relations with family associations, in disagreement with the ideal of collaboration implicit in the principles of the psychiatric reform (Lima et al., 2017, 2018). This lack of dialogue is one of the reasons for the dissatisfaction of parent associations with mental health policies and services in the country. In Brazil, the middle class does not traditionally frequent public mental health services and users from lower classes have greater difficulties and economic, social and cultural limitations to engage in political activism (Vasconcelos, 2013). Thus, potential users and family members with greater educational, social and economic resources who may expand and give visibility to psychosocial care related activism, are not involved in such forms of activism. These individuals have opted for associations promoting biomedical treatments and specialized services for specific conditions, such as ADHD or autism (Vasconcelos, 2013).

Most ADHD associations in Brazil include patients, relatives, professionals, and researchers. The most important group with the highest level of visibility, political articulation and regional influence is the *Associação Brasileira do Déficit de Atenção* (ABDA). It is a non-profit organization created in 1999 with the aim of disseminating knowledge about the condition. Located in Rio de Janeiro, ABDA does not have local chapters but it has local support groups involving professionals, family and patients in the main cities of the country. With circa 200,000 visits a month its website (www.tdah.org.br) is a powerful vehicle of information; and the mixed membership of ABDA enables the dialogue between professionals and lay public and the spreading of a biomedical discourse around ADHD in the country. ABDA has a unique connection with pharmaceutical companies. Novartis and Shire Pharmaceuticals are key sponsors of the association. The mission of ABDA is to convey a biological discourse on ADHD, its causes, diagnosis and treatments. ABDA does not provide clinical assistance, diagnostics or any type of treatment. ABDA is focused on advocacy, information about professionals and specialized services and the dissemination of knowledge (https://tdah.org.br/a-abda/quem-somos/). The ABDA website is likewise used by professionals and researchers to comment on articles on ADHD in the mainstream press, and to share their views on the validity or legitimacy of such articles (Ortega et al., 2018). There are also smaller associations, such as Inspirare (http://www.associacaoinspirare.com.br/), which focus on ADHD, autism and dyslexia. It is a non-profit organization based in Sao Paulo and its aim is disseminating knowledge about the conditions, providing support groups and information about health and educational policies, as well as advancing advocacy and the fight for social and educational inclusion. No connections with pharmaceutical companies are known for Inspirare.

The *Grupo de Estudos do Déficit de Atenção* (GEDA), a research group associated with the Institute of Psychiatry of the Federal University of Rio de Janeiro, and the *Programa de Transtornos de Déficit de Atenção/Hiperatividade* (ProDAH; www.ufrgs.br/prodah) belonging to the Faculty of Medicine of the Federal University of Rio Grande do Sul, in Southern Brazil, have important links with ABDA. Some of their members are also on the board of ABDA. These research groups respond for most of the research on methylphenidate and ADHD published in the country. They also receive substantial funding from drug companies. ABDA and the associated research groups are engaged in producing research on ADHD, promoting patient and family support groups, and are the main drivers of the official biomedical discourse about the disorder in the country (Ortega et al., 2018).

The main scientific journals in Brazil, such as the *Jornal Brasileiro de Psiquiatria* mostly publish research by those groups, frequently with advertising from Concerta. Authors frequently disclose their funders, which in several cases are not explicitly declared. As an illustration, a supplement of the *Jornal Brasileiro de Psiquiatria* on ADHD, which was published in 2007, was funded entirely—from the articles to the advertisements—by a manufacturer of methylphenidate (Jornal, 2007). A study that compares scientific publications and newspaper and magazine articles in Brazil found that while scientific publications stressed the use of methylphenidate for ADHD treatment, lay publications included other approaches and also mentioned social pressures and demands as factors that influence individual attention and concentration (Itaborahy and Ortega, 2013). Moreover, the study also found that scientific and lay articles diverge on the role attributed to psychotherapy in the treatment of the disorder. While the former that the combined use of the medication and psychological therapies yielded worse results than the use of the drug alone, the latter emphasized the benefits of psychotherapy in treating the condition (Itaborahy and Ortega, 2013). This is also significant in a country where psychoanalysis is an important theoretical and clinical perspective in public mental health services, and the issue of its "scientificity" and evidence-based standards has come to close scrutiny and to inflamed controversies. Together with critical and anti-psychiatric models, psychoanalysis contributes to challenge biomedical understandings of ADHD that consider behavioral problems as symptoms of underlying pathological conditions (Hinshaw et al., 2011; Conrad and Bergey, 2014).

Parent and professional associations have embraced the disability model and joined demands for specialized services and policies for ADHD. However, ADHD associations did not succeed in cementing a disability perspective. Pressure to understand ADHD as disability challenges the universal logic that structures the model of public health in the country as a vehicle for the rights of those individuals to treatments, specialized services through the Health Care to the Person with disability Network and social and educational inclusion.

This approach is in line with the initiatives of several professionals who have sought to reinvigorate their demands and political articulation, occupying relevant spaces within the media, parliament, judicial system and health managers (Vasconcelos, 2012). Those professionals have approached patients and family members through organizations such as ABDA, thereby not

only legitimating biomedical discourse and interventions for the condition but also reproducing the patronizing logic of the associations in which professionals occupy the most prominent role vis-a-vis patients and family members.

The alliance between families, health and education professionals, policy makers, and the pharma industry in the country has built a successful lobby to propose bills and municipal, state and federal laws associated with ADHD and dyslexia over the last 10–15 years. Most bills and laws concern the school system, including the "diagnosis and treatment in the public basic education system" (Senate Bill 3517/2019), even determining the location of classroom chairs for children with ADHD in public and private schools in the state of Rio de Janeiro (Law 8192/18), and promoting free supply of medication and awareness campaigns (Lima, 2019).

As we already mentioned in the first sections of the article, GMH is currently one of the most powerful narratives for advancing ADHD specific policies, services and treatments and, what is more important for patients and family associations, the sponsor of advocacy groups (Flisher et al., 2010) The GMH agenda is primarily intended for low-income countries and Brazil is a middle-income country with a well-organized National Health System (SUS). However, GMH discourse, methods and metrics, such as the emphasis on the global burden of disease of ADHD and the disability-adjusted life years—DALYs lost to the condition, as well as the development of evidence-based interventions and treatments, have been taken up by health professionals and family associations not only to advance biomedical and behavioral approaches to ADHD but also, as a basis to criticize public mental health policies, services and interventions in the country. Specifically, those actors strategically draw on the GMH rhetoric and methods to justify and legitimize a certain view on diagnosis, treatments and service organization and to criticize the hegemony of psychoanalysis in public mental health services because it lacks "scientificity."

Treatment Gap and Accessibility

Global Mental Health and WHO strongly promote the concept of "treatment gap" which refers to the difference that exists between the number of people who need care and do not receive it, or receive it inadequately and those who receive it (Jacob et al., 2007; Patel et al., 2007; Saxena et al., 2007). This view emphasizes not only personal suffering, but also disability and economic losses for individuals and countries due to non-treatment (Jacob et al., 2007; Patel et al., 2007; Saxena et al., 2007). The estimate of the treatment gap depends on the prevalence of the disorder, the period of analysis of service use and the representativeness of the sample in relation to the population under analysis (Kohn et al., 2004). Therefore, its calculation derives from the adoption of standardized diagnostic criteria and epidemiological estimates of prevalence and information about monitoring by health services (Kohn et al., 2004). In this sense, it reveals both the lack of treatment and the lack of information in countries with less resources (Jacob et al., 2007). On the other hand, the treatment gap logic hides the diverse arrangements that take place in different contexts involving actors, institutions, knowledge and therapeutic practices (Bartlett et al., 2014; Orr and Bindi, 2017). Furthermore, as it bases its findings on psychiatric categories and epidemiological data, it can foster reductionist biomedical approaches (Jansen et al., 2015).

The diverse Brazilian groups promoting biomedical models, specialized services and specific health and education policies for ADHD share the global mental health discourse emphasizing a treatment gap for the condition. Thus, in an effort to support the hypothesis that ADHD is undertreated and underdiagnosed in Brazil, the researchers Paulo Mattos et al. (2012) published a letter to the editors of the official journal of the *Associação Brasileira de Psiquiatria* (www.abp.org.br) in which they argue that even if lower prevalence estimates were used instead of the expected prevalence, it could still be concluded that more than 80% of individuals with the disorder were not receiving medication-based-treatment (Mattos et al., 2012).

The Global Mental Health agenda combines discussions around treatment gap with a human rights discourse. Thus, to deny access to medication constitutes a human rights violation (Fernando, 2014). However, as we have seen, this is a very complicated issue. In a country like Brazil where there are strong controversies around issues of etiology, diagnosis, treatment, services and policies for a condition, whose very existence is being challenged, to advance biomedical discourses and treatments using an ethical and human rights alibi to coerce into its enforcement can further inflame an already polarized situation. Furthermore, it can hamper serious discussions and possible cooperation between mental health professionals and ADHD associations. Hence, we agree with Fernando (2014: p. 161), who claims that in the field of Global Mental Health the call on "human rights" should be restricted to "arguments for the rights of people to freedom, liberty and the exercise of personal choice," and any pressure to "argue for alleged 'rights' to 'treatment' or even 'care,' referring to models of what these mean in the West" should be met with extreme caution.

Human rights of individuals living with mental disorders are also a central concern for Brazilian public mental health, and are thematized in a broader perspective when compared with the limited understanding frequently associated with global mental health. Since the emergence of the psychiatric reform movement during the military dictatorship serious violations of human rights of imamates of psychiatric hospitals have been systematically denounced. The issue of guaranteeing human rights for people with mental disorders have expanded in the following decades for it was not a simple matter to humanize psychiatric hospitals, but rather to positively affirm the patients' right to fully exercise citizenship and to build community-based, intersectoral care strategies that advance social inclusion (Delgado, 2011; Amarante and Nunes, 2018; Almeida, 2019). The issue of access and right to treatment is part of the human rights agenda, as well as the approval of legislation to regulate interventions and services, the encouragement of social participation, and the awareness of society to the challenges posed by mental illness. There is a prolific debate around access to healthcare in the country and it is not limited to the evaluation of metrics related to diagnosis and treatment according to biomedical standards (Menezes et al., 2018; Almeida, 2019).

Hence, Brazilian discussions of access and accessibility are more nuanced and broader than discussions around treatment gap within GMH (Travassos and Martins, 2004; Andrade and Minayo, 2012). Brazilian studies acknowledge the polysemic and multidimensional character of the issue of accessibility and its associated political, socioeconomic, organizational and symbolic aspects. Therefore, accessibility transcends the mere availability of health services (Andrade and Minayo, 2012; Assis and de Jesus, 2012). Moreover, the evaluation of the different determinants of accessibility involve a diversity of approaches (Assis and de Jesus, 2012). Several studies examine the issue of access to mental health care and are characterized by the multiplicity of methodologies and conceptual articulations. Subjects such as community care, social determinants of health, equity and human rights modulate the debate. Although Brazilian literature on mental health evinces a variety of studies and local perspectives on the issue of access, this body of knowledge is fragmented, making it difficult to systematize their findings (Menezes et al., 2018).

Critiques to Medicalization of ADHD

The biosocial field of ADHD in Brazil is highly polarized. On the one hand, parent associations and biomedical oriented professionals promote biomedical views, specialized services and special policies for ADHD, as well as claim that there is a treatment gap in the country and the condition is underdiagnosed. On the other hand, and as reaction to those groups several public directives, recommendations and protocols have regulated prescriptions of methylphenidate and challenged biomedical diagnosis and treatments of ADHD in Brazil. The medicalization discourse is advanced by CAPSi professionals and other groups made up by education and health professionals who articulate with state councils of psychology and other political actors to promote those recommendations and protocols, as we will now examine.

A directive issued by the Secretaria Municipal de Saúde of São Paulo, the city's department of health, in 2014 regulates the prescription of methylphenidate and ADHD treatments and determines the referral of ADHD patients to CAPSi. This determination echoes the national mental health policy and states that "from a clinical perspective, it is a complex task to distinguish cases of ADHD from parts of educational problems which derive from inadequate educational models for the children's social context, increasingly complex family issues, and a sociocultural context in which there is competition, production of stigmas, and exclusion" (Portaria, 2014).

The *Associação Brasileira de Saúde Mental* (ABRASME) (www.abrasme.org.br), an association aligned with the psychiatric reform and the mental health policy in the country, supported the regulation because it assesses the complexity of the condition and its management (Associação Brasileira de Saúde Mental (ABRASME), 2010, 2014). On the opposite front, the directive of the *Associação Brasileira de Psiquiatria* (ABP), traditionally critical of the deinstitutionalization process and the mental health policy in the country, published an open letter [entitled "Carta Aberta a População" ("Letter to the People")] challenging the São Paulo directive, arguing that the regulation "is restrictive, bureaucratizes respectful access to treatment, mainly by people at a social disadvantage, and positions itself against scientific systematization in a mystifying, disrespectful way." In addition, it constitutes an "abusive barrier to access to pharmacological treatment by people with low income, and places restrictions on the full exercise and autonomy of Brazilian medicine and science" (Associação Brasileira de Psiquiatria (ABP), 2014; Ortega et al., 2018).

In the same year of the publication of the Sao Paulo directive, the Brazilian Bulletin on Health Technology Assessment (BRATS) issued a study that evinces the "high potential for abuse and dependence" of the medication and demanded "thorough assessment of the effect of methylphenidate on ADHD" (Boletim Brasileiro de Avaliação de Tecnologias em Saúde (BRATS), 2014). The authors highlighted methodological flows, short-term follow-up and low generalizability of the studies that addressed the efficacy and safety of methylphenidate among children and adolescents. They also stressed the number of false positives and unnecessarily treated children, given that several symptoms are also found in individuals without ADHD (Boletim Brasileiro de Avaliação de Tecnologias em Saúde (BRATS), 2014; Esher and Coutinho, 2017). Machado et al. (2015) strongly opposed the study arguing that such conclusions could not be inferred from the studies cited in the BRATS document.

Further directives and recommendations have been issued in recent years. Inspired in the Sao Paulo directive and a similar protocol in Campinas, the National Health Council released a public document entitled "Recommendations of the Ministry of Health for the adoption of non-medicalizing practices and for the publication of municipal and state methylphenidate dispensing protocols to prevent excessive medicalization of children and adolescents," and following the publication of data asserting that Brazil has become the second world market in methylphenidate consumption, the National Council for the Rights of Children and Adolescents (CONANDA) issued the Resolution 177/2015 which "provides for the right of children and adolescents not to be subjected to excessive medicalization, especially regarding learning, behavior and discipline issues" (CONANDA, 2015). The Ministry of Health also issued a recommendation for states and municipalities to publish methylphenidate dispensing protocols "to prevent excessive medicalization of children and adolescents[2]".

These documents and the professionals and organizations that support them share the concern with the "excessive medicalization" and promote the adoption of "non-medicalizing practices." They challenge limited understanding of access and accessibility to treatments and health services associated with treatment gap arguments and advocate for a broader and more complex understanding of the issue of accessibility. Hence the medicalization narrative shares some of the arguments prevailing in discussions around broader understandings of accessibility. While the former tends to adopt a more radical and polarizing perspective opposing ADHD policies and treatments the latter is more nuanced and favors an attentiveness to the specific contexts and their differences regarding access to treatments and services.

[2]http://www.saude.gov.br/images/pdf/2015/outubro/01/Recomenda----es-para-Prevenir-excessiva-Medicaliza----o-de-Crian--a-e-Adolescentes.pdf

The medicalization discourse is championed not only by many mental health professionals working at CAPSi and other public facilities, but also by groups such as *Fórum sobre Medicalização da Educação e da Sociedade*, whose founder the pediatrician Maria Aparecida Moyses participated to the São Paulo directive regulating the prescription of methylphenidate in the city. The forum was created in 2010 as a reaction to programs for dyslexia and ADHD in the city of Sao Paulo. The forum argued that the programs addressed social and educational problems from a biomedical perspective. From the beginning, the forum that gathers professionals from diverse areas, especially health and education, and involves state councils for psychology has established collaborations with different groups in Brazil and other countries (Fórum sobre Medicalização da Educação e Sociedade, 2013). As a result, after a meeting with an Argentinian movement, Forumadd (www.forumadd.com.ar), which also opposed the pathologization and medicalization of childhood, a document was issued establishing the collaboration and principles of the movement with the goal of spreading awareness among diverse groups and associations through Latin America. Their strong stance against medicalization involves opposing the increasing consumption of methylphenidate and other psychotropics among children and adolescents arguing that learning difficulties and ADHD are not pathologies, or simply "do not exist," and challenging policies to address those conditions (Fórum sobre Medicalização da Educação e Sociedade, 2011; Ortega et al., 2018).

In 2014 the Movement *Despatologiza—Movimento pela despatologização da vida* (https://www.despatologiza.com.br) was found by professionals across different fields, such as medicine, education, psychology, speech therapy as well as researchers from those fields and service users with the goal of collectively start "facing pathologization processes that transfigure differences in diseases to hide the inequalities that plague our society." The processes of pathologization of life, they argue, are displayed in "exaggerated or even mistaken diagnoses and interventions," by which the pathologization of children and adults expands both in scientific and lay discourses across practices and services in all areas, from education to mental health. The movement is really active and gathers professionals, researchers and users from different regions of the country. The "suggestions of depathologizing practices" encompass actions like continuous training for managers and coordinators of the Public Education Network to encourage depathologizing actions involving educators; the continuously monitoring of Legislative Bills to avoid the approval of laws of dyslexia and ADHD and, more broadly, to stimulate more depathologizing practices in health, education and social assistance areas.

Medical and non-medical actors (family associations) have relied on Global Mental Health discourses and its metrics to substantiate the scientificity and evidence-based of biomedical and behavioral approaches to ADHD and to claim for bridging the treatment gap. The existence of ADHD as a discrete entity is still disputed. Its ontological status and boundaries are hotly debated. For those who opposed biomedical approaches ADHD constitutes an illustration of medicalization of attention, understood as a process by which non-medical problems come to be defined and treated as medical problems, either as diseases or disorders (Conrad and Bergey, 2014; Zorzanelli et al., 2014).

On the other hand, as recent studies have shown, there has also been an expressive increase in the use of methylphenidate in Brazil unrelated to the diagnosis of ADHD. Such studies have observed that the growth is associated with the fact that prescriptions are largely done in the private sector (for middle- and upper classes) and to the off-label use for cognitive, physical, sexual and emotional enhancement also related to those classes (Coutinho et al., 2017; Esher and Coutinho, 2017; Lima et al., 2019; Castro, 2020).

The use of medication unrelated to medical diagnoses has been described as "pharmaceuticalization" and aims to enhance performance. There is still not enough data to understand the extent and impact of methylphenidate pharmaceuticalization in the country, but several scholars insist that it is a social and ethical problem that requires further investigation and action by the regulatory agencies of drug dispensation (Coutinho et al., 2017; Esher and Coutinho, 2017; Lima et al., 2019; Castro, 2020). Both phenomena, medicalization of ADHD and off-label use of methylphenidate, highlight the challenges imposed by the globalization of ADHD and the importance of ethically informed and ecologically sensitive clinical practices (Singh et al., 2013).

The increase of prescriptions in the private sector and the off-label use of methylphenidate for cognitive enhancement explains why despite methylphenidate is not included in the standardized dispensing lists of SUS, Brazil became, as already mentioned, the second world market in methylphenidate consumption. It also explains why there are still heated debates about lack of access to health care or even a "treatment gap. This offers a more nuanced view of the Brazilian situation which helps to move beyond polarized debates around treatment gap vs. medicalization. The difficulties in accessing methylphenidate in public health services heavily contrast with the huge dispensation in the private sector, leading to an uneven distribution of the medication according to social class and financing resources. As a result, part of the Brazilian population may be overmedicated, and critiques of medicalization of ADHD are well-placed and are relevant, while on the other hand, there is a problem of access not only to medication but also to social and educational inclusion for the poorer and vulnerable parts of the population. Therefore, those who claim that the condition is underdiagnosed and undertreated in the country are also right (beyond discussions of whether interventions and treatments should be restricted to psychopharmaceuticals or should also include psychosocial and educational interventions).

In contexts of extreme poverty and social vulnerability, pharmaceutical treatments are not foregrounded. As an illustration, an ethnography conducted in Nova Iguaçu, one of the poorest municipalities of the Rio de Janeiro Metropolitan Region, evinces that the lack of centrality of pharmacological treatments is associated to the fact that methylphenidate is not in the list of the essential medicines of the municipality (and therefore of free dispensation), and families with scarce

resources cannot afford to buy it. The second reason is that, in those contexts, professionals emphasized social aspects of ADHD, such as violence, poverty, lack of parental authority, and of leisure activities (Chagas, 2017). Those families accepted the existence of the condition but they were fully aware of the impact of family and community relationships in the severity of the symptoms. The child's improvement was equally associated with contextual factors. Medication was not only regarded as a "luxury" item but as one that would not target the genesis of the problem (Chagas, 2017: p. 123).

DISCUSSION

In this article we have argued that the Brazilian case brings interesting elements to Global Mental Health discussions around ADHD. The local context is permeated by tensions that go beyond GMH research and interventions (Clark, 2014; Smith, 2017).

Brazilian scholars aligned with the notion of treatment gap have produced quantitative studies in which the contextual aspects that modulate the condition and search for treatments are not included. They seem to assume that ADHD is a natural entity engaging in a close dispute with professionals affiliated with the tradition of the Brazilian psychiatric reform, critical to the biomedical model (Ortega et al., 2018). Both actors have invested in academic production and political activism to advance their goals. Moreover, they have grounded their proposals on the notion of treatment gap. This notion is advanced to justify the need for ADHD research, interventions and funding. Moreover, it allows Brazilian data to be included in global studies. Nevertheless, Brazil has not yet produced enough prevalence studies of ADHD that reflect the national and regional situation and their differences. Such research requires funding and coordination that are not easily available in the national territory (Menezes et al., 2018). Besides, the notion of treatment gap, unlike that of access (Assis and de Jesus, 2012), does not have enough scope to explain the social conditions that produce the gap, in addition to the risk of overestimating the data because they are based on estimates produced from biomedical standards, such as instruments for detection and diagnosis and classification systems (Jansen et al., 2015).

Furthermore, there is an important question raised by Orr and Bindi (2017) of whether the treatment gap emphasized by GMH actually refers to an absence of treatment, or whether it is due to the lack of recognition of other modes of care because they are not evidence-based. In this sense, it is important to remember that contemporary societies, whether high-income or low- and middle-income countries, are characterized by the provision of multiple care practices, institutionalized or not, and it is therefore essential that research, interventions and public health policies consider local contexts and their medical traditions (Orr and Bindi, 2017).

Regarding the association of these research groups with family members and activists, what is observed is the induction of a demand for a specific type of treatment based on evidence produced in developed countries and focused on medication. This demand does not provide elements for patients and family members to think about diagnostic and therapeutic alternatives or structural mechanisms that may help in the provision of care (Ortega et al., 2018).

On the other pole of the debate, groups concerned with the medicalization of childhood are mainly associated with the field of public mental health (traditionally opposed to the Brazilian psychiatric association and family associations). In general, their academic production is related to the field of Collective Health (Vieira-da-Silva and Pinell, 2014), characterized by a wide variety of studies concerned with the different dimensions of the issue of access and with local populations and their concrete situations. Unlike other LMICs, Brazil has a health system that seeks to reconcile services and network assistance with scientific production. However, such studies are still poorly articulated with each other and do not allow for a perspective of the broader national context (Menezes et al., 2018).

Activism within public mental health services, although important for the Brazilian psychiatric reform, is not as strong as in several countries in the Global North. Furthermore, as we have already mentioned, it evolved with tensions and the distancing of professionals from users and their families. The fragility of the movements and the detachment from health professionals restrict their critical capacity and ability of promoting public policies and care for ADHD (Vasconcelos, 2013). While middle class associations of patients and family members have gradually been able to advance their agendas and extend their influence through national forums (Coutinho et al., 2017; Castro, 2020), associations gravitating around public mental health services struggle with advancing a broader perspective related to the logic of psychosocial care. Such imbalance in the imposition of the agendas of these different styles of activism reinforces the inequality in relation to access to treatments and health and educational services for children and their families. Moreover, it hampers the necessary discussion of comprehensive patient care and careful reflection about ADHD beyond the biology vs. biology/culture binary.

Another important aspect to understand the Brazilian context concerns the organization of the health system. Since the founding of SUS, it was understood that municipalization would be a strategy to strengthen local authorities' views in the decisions adopted by managers and, especially, municipal councils with the objective of increasing social participation and recognizing the particularities of each city. Such strategy would enable the adaptation of the necessary interventions for health promotion and assistance (Lobato and Burlandy, 2000; Souza, 2002). One of the consequences of this approach is that municipal authorities effectively configure access to treatments and follow-ups and, consequently, to medication directly, giving the debate a political character. City halls have relative autonomy to make decisions regarding the allocation of resources for health services (which includes dispensing medication), but health secretaries and mayors are under pressure from municipal health councils, a body made up of several representatives of a city's social movements that express their opinions and supervise the proposed measures.

The associations described in the previous section, such as ABDA and Inspirare are directly and indirectly related to this configuration, either when they are invited to participate in the development of consensus and guidelines with the SUS

(municipal, state and federal) management spheres or when they associate with users and family members in initiatives such as those we described throughout this article. In this second case, what is observed is that such an alliance ends up generating greater demand for medication and even judicialization of the health system (Caliman and Domitrovic, 2013).

In this sense, the strategy of strengthening patient and family activism, also promoted by GMH, may induce the medicalization of ADHD. This is what Conrad and Bergey (2014) discuss regarding the factors that may be inducing the globalization of medicalization when they include the role of activism and the preference for DSM-based diagnostic criteria.

The Brazilian case is interesting for GMH because it enables the dialogue with experiences of health care, public policies and scientific production in mental health in a country characterized by diversity of mental health care services and strategies (Kieling and Belfer, 2012; Conrad and Bergey, 2014). The conflicting perspectives at stake update old controversies in psychiatry (such as the biological or cultural/social nature of mental conditions) and the challenges to improving research and intervention in mental health. Therefore, it is essential that GMH proposals are attentive to the production of research and interventions that articulate local and global knowledge, qualitative and quantitative methodologies, and, finally, but not least, biomedicine and social sciences. Otherwise, it puts itself at risk of becoming an agent that induces medicalization and the expansion of the Pharma industry (Clark, 2014; Mills, 2014).

CONCLUSIONS

Historian Charles Rosenberg (2006) describes psychiatric categories such as ADHD as "problematic categories" with disputed boundaries and ontological status. ADHD, therefore, constitutes a "contested illness" (Brown et al., 2011), a condition exposed to public negotiations by medical and lay actors. We have seen in this article how the controversies around ADHD go beyond the medical system and encompass the public sphere and even popular culture, and involve professionals, parents, self-advocates, and social networks. Despite uncertainty about the etiology and the lack of convincing and well-replicated biomarkers with diagnostic or clinical utility (Visser and Jehan, 2009; Freedman and Honkasilta, 2017), ADHD is depicted by biomedical discourses as a neurobiological disorder, a brain disease. Furthermore, and in spite of the existence of GMH strategies for ADHD, there is no consensus regarding treatments and best forms of care. The call to bridge the treatment gap and to strengthen access to (primarily) pharmacological interventions is seen with suspicion by those who argue that in the absence of clear boundaries for the pathology, the lack of reliable biomarkers and the variation of prevalence across countries, regions and even cities, such a condition does not exist. Moreover, its main symptoms (attention deficit, hyperactivity, and impulsivity) fall within the range of behaviors expected in any given population (Ortega et al., 2018).

ADHD is at the center of controversies regarding its legitimacy and medical, social, epistemic, and ontological status. The category mobilizes legal arguments, administrative classification, and legislative maneuvers. Individuals diagnosed with ADHD, their families and professionals frequently become activists, mobilizing "scientific" or "moral" facts in favor of the condition's legitimacy and forming groups to share their experiences and fight for rights (Ortega et al., 2018). However, there is no "one" universal history of ADHD that depicts it as a universal disorder with clear boundaries and with similar prevalence across populations. What there are instead are local histories of ADHD in individual nations, and they reveal the condition as a "much more flexible, mutable phenomenon," a notion that has been rejected as often as it has been accepted and that behavioral and educational problems "remain very much a product of local historical, cultural and political factors" (Smith, 2017: p. 786, 767).

In this article, we have told the national history of ADHD in Brazil against the backdrop of the global mental health agenda for the condition. Most of the arguments advanced by advocates and critics of GMH are taken up in a particular form specific to the history of ADHD in Brazil by those who claim that ADHD is underdiagnosed and undertreated, and that therefore there is an important treatment gap for the condition, and those who argue that the disorder is overdiagnosed and overtreated and speak of medicalization of childhood.

We have examined how global issues and controversies in mental health take local forms, illustrated in the issue of ADHD in Brazil. The national history of ADHD in the country is permeated by social, political, economic and cultural factors involved in the framing of diagnosis and treatments. Those factors are also present in other national histories of the condition. But they take up different configurations across nations. Examining the local and historical specificities alongside the practices of professionals make the abstract, globally circulating ideas meaningful in particular forms.

It is important that GMH research and interventions around ADHD are able to transcend and negotiate local and global knowledge production and practices and to integrate those binaries in the everyday life of subjects affected by the disorder (professionals, parents and individuals living with the condition). By considering such approach, global mental health may contribute to designing "better diagnoses" and reducing the threat of structural violence (Singh et al., 2013: p. 4, 5) in which the individualization of interventions can assume the restricted facet of increased access to drug interventions.

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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Antiparasitic Drugs in the United States—Two Roads to High Prices

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High prescription drug prices contribute significantly to healthcare spending in the United States and compromise patients' access to quality medical care. A number of factors allow drug manufacturers to set much higher prices in the US than in other comparable high-income nations. Price-control depends primarily on the entry and persistence of generic products following the expiration of the market exclusivity period granted to the manufacturer of the brand name drug. Unfortunately, barriers to generic entry are common, allowing off-patent drugs like albendazole to remain relatively expensive despite having been marketed in the US for decades. By contrast, miltefosine became FDA approved more recently and has maintained a high price tag by way of a novel incentive program—the neglected tropical disease (NTD) priority review voucher (PRV) program. The voucher has a high market value and can be sold or transferred well before the drug for which it was awarded becomes available on the market. While both drugs are used to treat parasitic infections that are uncommon in the US, they differ by market and regulatory conditions—each telling an interesting pricing story.

Keywords: antiparasitic, drug pricing, drug costs, price hike, albendazole, miltefosine

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The United States spends nearly twice as much on healthcare as other comparable high-income countries in the Organization for Economic Cooperation and Development (OECD), while performing worse by several key public health outcomes. An important driver of this difference in spending are the high prices of prescription drugs (Emanuel, 2018; Papanicolas et al., 2018). Brand-name drugs account for the majority (74%) of US prescription drug spending despite constituting only 10% of total prescriptions (Association for Accessible Medications, 2017). This is primarily due to the combination of government-granted market exclusivities ("monopoly rights") and the limited ability of public US payers—namely Medicare and Medicaid—to limit coverage and negotiate drug prices with manufacturers. By contrast, in countries with national health insurance systems, such as Canada or the UK, a central body negotiates drug prices or rejects coverage of products if the price demanded by the manufacturer outweighs the benefit of the product (Kesselheim et al., 2016). At the level of the patient, a recent nationally representative survey found that one in four Americans have difficulty paying for prescription medications (Kaiser Family Foundation, 2019).

Once the exclusivity period for a brand-name drug ends, the entry and persistence of generic manufacturers often leads to decreased prices (Kesselheim et al., 2016). After about 2–3 years, generic drug prices generally decrease by 60–70% compared to their branded equivalents, and the degree of price decrease is strongly associated with the number of manufacturers (IMS, 2016).

This "free-market" system is the primary mechanism of cost-control for drugs that no longer have market exclusivity in the US (Shrank et al., 2006; Gupya et al., 2019).

Sufficient market competition among generic manufacturers is generally a predecessor to low-cost generic drug products. However, barriers to generic entry are common and can lead to monopoly-like conditions that result in high prices. A recent analysis of over 1,000 generic drugs found a clear association between price hikes and lack of competition. On average, drugs with the lowest levels of market competition experienced a 47% price increase over the 5-year study period (Dave et al., 2017). By comparison, generic drugs with relatively high levels of competition decreased in price by an average of 32% in the same time period (Dave et al., 2017).

One reason why manufacturers may not bring a generic drug to the US market is a low financial incentive, stemming from low clinical demand for that particular drug in the US. From the standpoint of the manufacturer, the incentive to enter such a market may be outweighed by the risk: that subsequent generic entry causes a downward pressure on the price of a drug with already-low sales volumes, jeopardizing profit. Paradoxically, these low-volume generic US markets appear to have become incubators for opportunistic manufacturer behavior: a recent study of generic drug price changes between 2008 and 2016 identified a much higher prevalence of price-hikes among infrequently prescribed (low-demand) generic drugs as compared with their more-frequently prescribed counterparts (Dave et al., 2019).

The nationally-publicized case of Daraprim (pyrimethamine), the first-line drug to treat toxoplasmosis, is an example of this opportunistic behavior. In 2015, Turing Pharmaceuticals (now Vyera Pharmaceuticals) acquired the rights to Daraprim and increased the price by 5,433% in 1 day (Alpern et al., 2016). This tactic was heavily scrutinized by the public (Pollack, 2015, September 20), professional infectious disease organizations (Calderwood and Adaora, 2015), and bipartisan presidential candidates (Eunjung Cha, 2015; LoGiurato, 2015). Yet, the negative press appeared to have no impact on the price of the drug, which remains cost-prohibitive. Turing's strategy was legal and demonstrates the vulnerability of certain drug markets to exploitation by the pharmaceutical industry.

Daraprim is not unique among antiparasitic drugs approved for use in the US—a market that has become the embodiment of price hikes on off-patent essential medicines (Alpern et al., 2019). Many of these drugs are widely available and low-cost in the developing world where tropical parasitic infections are endemic, but have become more expensive in the United States where these infections have relatively low incidence and prevalence. In this article, we describe the pricing and market conditions of two anti-parasitic drugs: albendazole and miltefosine.

Whereas albendazole has become the poster child of price hikes on essential off-patent drugs (Alpern et al., 2016), miltefosine was only recently approved by the FDA and has ongoing regulatory market exclusivity. Although very different drugs with respect to their market and regulatory conditions, both drugs are used to treat neglected tropical diseases that are relatively uncommon in the US: hydatid disease, neurocysticercosis, and soil-transmitted helminth (STH) infections (albendazole) and leishmaniasis (miltefosine).

ALBENZA (ALBENDAZOLE)

In October 2019, a 12-year old girl, who recently arrived in Minnesota from Ecuador, presented to a free clinic with diffuse abdominal pain and fatigue. She was diagnosed with hookworm infection—a soil-transmitted helminth (STH) that affects over 500 million people worldwide (Hotez et al., 2004). Like other STH infections, hookworm has a much higher prevalence in areas of extreme poverty—predominantly in the developing world—where a common mode of transmission is walking barefoot on soil (Hotez et al., 2004; CDC, 2013). Hookworm infection can cause chronic blood loss and may reduce school attendance in children, with subsequent effects on productivity and wage-earning potential in adulthood (Hotez et al., 2004). The clinic is usually able to provide free prescription medicines to the patients it serves, many of whom are uninsured or underinsured. In this case, however, the average wholesale price (AWP) of the first-line treatment—a single dose of 400 mg albendazole—was over $400 (Dynamed Plus, 2020; Micromedex 2.0, 2020). At the time, the lowest price available with a coupon discount on GoodRx was still prohibitive for both the clinic and the patients' family. Instead, she was prescribed a trial of pyrantel pamoate, a less-effective over-the-counter alternative which failed to resolve the infection. Out of options, the free clinic referred the patient to a nearby federally-qualified health center, hoping she would be able to access albendazole or mebendazole through a public program.

The antiparasitic medication, albendazole, has been marketed outside the US since 1982 and was approved by the FDA in 1996. In addition to the treatment of hookworm (*ancylostoma duodenale* and *necator americanus*) it is first-line for the treatment of neurocysticercosis and echinococcosis and is a preferred treatment option for *ascaris lumbricoides* and pinworm (*enterobius vermicularis*)—the most common parasitic infection in the US (CDC, 2013).

In 2010, CorePharma acquired the marketing license for Albenza (albendazole) from GlaxoSmithKline (GSK) and then sold the drug to Amedra Pharmaceuticals, a private equity firm. Amedra then purchased the primary competitor in the US market, mebendazole. Between 2010–2015, the AWP of Albenza increased by 3,299%, from $5.92 per 200 mg tablet in 2010 to $201.27 in 2015 (Alpern et al., 2016). In 2015, Impax Labs (now Amneal Pharmaceuticals Inc.) acquired Amedra. This led to subsequent increases in the price of Albenza, eventually landing on its current average wholesale price of $291.21 per tablet, and bringing the total increase in AWP since 2010 to 4,819% (Micromedex 2.0, 2020). It took until September of 2018 for the first generic manufacturer to begin to market albendazole in the US, and since then five other companies have entered (FDA, 2020). According to a recent FDA report, drug prices decline to ∼47% of brand-name drug prices with 2 generic manufacturers, 32% with 3 manufacturers, and 14.4% with 5 manufacturers (Food and Drug Administration, 2019a).

While historical data are limited, between January 2018 and August 2020, the lowest out-of-pocket price of a single 200 mg tablet of albendazole (half of the first-line 400 mg treatment dose for hookworm) after the use of GoodRx coupons decreased from $191 to $49 (GoodRx, 2020; Wayback Machine, 2020). Interestingly, despite the presence of multiple generic manufacturers and the decline of the GoodRx post-coupon price for patients, the average wholesale price (AWP) of generic albendazole remains high. As of August 2020, the mean AWP of a single 200 mg tablet, among the five available generic products, is $248 or 85.2% of the brand-name (Micromedex 2.0, 2020). Although the AWP is not a good measure of the price actually paid for a drug, it can translate to high out-of-pocket costs for patients—particularly the uninsured. One possible explanation for this observation is that insufficient time has passed to realize the effect of competition on price. However, some evidence suggests that a more significant AWP reduction for generic albendazole tablets should have been observed by now (IMS, 2016; Food and Drug Administration, 2019c). Although prices do not appreciably decline after the entry of one generic manufacturer, prices typically decrease rapidly with the entry of subsequent generic manufacturers (Food and Drug Administration, 2019c; Gupya et al., 2019).

The delayed entry of manufacturers for generic albendazole could reflect FDA policy in the last few years to incentivize generic entry in non-competitive markets. Since 2017, the FDA has maintained a list of off-patent off-exclusivity (OPOE) drugs with one manufacturer in the US in order to encourage generic entry for candidate drugs (Food and Drug Administration, 2019a). Under the FDA Reauthorization Act of 2017 (FDARA) Congress also created a competitive generic therapy (CGT) designation for Abbreviated New Drug Applications (ANDAs) in drug markets with only one manufacturer (Food and Drug Administration, 2019b). The CGT designation allows for an expedited and prioritized review process, as well as eligibility for a 180-day period of market exclusivity (Food Drug Administration, 2018). As of March 2019, the FDA had received more than 245 CGT requests and granted over 70% of them (Food and Drug Administration, 2019b).

IMPAVIDO (MILTEFOSINE)

Miltefosine is the only oral drug FDA-approved to treat leishmaniasis, a parasitic disease that can present in a cutaneous, mucocutaneous, or visceral form. Untreated, the visceral form has a high mortality (Sunyoto et al., 2018) and causes 20,000–30,000 deaths annually (WHO, 2019). Stigma and disability due to cutaneous and mucocutaneous lesions can be devastating (Hofstraat and van Brakel, 2016). Miltefosine costs ∼$57,600 for a 28-day regimen in the US, resulting in barriers to access due to high out of pocket costs (WHO, 2019). In contrast to albendazole, which has generic manufacturer competition, the sole manufacturer of miltefosine has orphan drug market exclusivity through March 2021.

The effort to bring miltefosine to the US market for the treatment of leishmaniasis began in 2008 when Paladin Labs acquired the rights to the drug from Zentaris for $8.5M. Between 2008 and 2014, Paladin acted as the drugs' sponsor and spent roughly $10M working toward FDA approval (Doshi, 2014). In late 2013, Paladin Labs was acquired by Endo Pharmaceuticals for $1.6B (WHO, 2019). By this point, Paladin's new drug application for miltefosine was nearing approval and Paladin placed a $100M+ price tag on miltefosine, a price Endo was unwilling to pay (Doshi, 2014). Thus, as Endo absorbed Paladin, Knight Therapeutics—led by the CEO of Paladin—was spun off in February 2014 with worldwide rights to miltefosine. Less than a month later, miltefosine was approved by the FDA for the treatment of leishmaniasis, granting Knight a tropical disease priority review voucher (PRV). The tropical disease PRV is a reward meant to incentivize research and development (R&D) for neglected tropical disease (NTD) drugs. Since the conception of the PRV program in 2007, if a sponsor achieves approval for a new chemical entity that constitutes a significant improvement for one of the listed tropical diseases, the sponsor can be granted a PRV (Kesselheim et al., 2015). The voucher is redeemable at the FDA for the priority review (as opposed to standard review) of a different drug or biologic product, and may also be transferred or sold—with market value estimates as high as $350M at the time (2017) (WHO, 2019).

Only 5 months after being granted the PRV, Knight Therapeutics sold the voucher in November, 2014 to Gilead for US $125M in cash, well before the drug was made available in the US market (DNDi, 2014; Garde, 2014; Knight Therapeutics Inc, 2014). The drug did not enter the US market until April 2016, priced at an average wholesale price of US$685.70 per capsule, or roughly US$57,600 for a 28-day regimen (84 capsules).

The case of miltefosine provided some of the earliest evidence that the PRV may not be driving research and development of tropical drugs it had originally intended. Manufacturers are able to bring an existing drug to the US market while avoiding some or all of the research and development costs and receive a tropical disease PRV—which can be sold for a profit (Kesselheim et al., 2015), arguably over-compensating the manufacturer. In addition to the profits enjoyed from the sale of the PRV, companies who commercialize orphan drugs are also granted market exclusivity of up to 7 years, giving them the ability to demand high prices. Global experts have suggested that preconditions on PRVs should stipulate that applicants seek regulatory approval of the drug in endemic countries and demonstrate appropriate access strategies (WHO, 2019).

LOOKING AHEAD

Some segments of the US antiparasitic drug market have been targeted by a pharmaceutical industry increasingly focused on financialization and short-term returns. This business model is troubling to healthcare providers because it seems that vulnerable patients have been disproportionately affected (Hotez, 2014; Alpern et al., 2016). The examples of albendazole and miltefosine highlight different but equally important ways in which the US drug development mechanism has failed patients.

The neglected tropical disease PRV program has been in effect for over a decade. The story of Miltefosine provides

some evidence that the program may be functioning sub-optimally. An analysis of NTD drug development in the 7-year period preceding and succeeding the PRV program's conception demonstrated no association between the NTD PRV program and an increase in innovative, early-stage NTD product development (Jain et al., 2017). This finding stands in contrast to other markets, such as drugs used to treat rare pediatric diseases, where a similar PRV program has demonstrated some effect on early-stage drug development (Hwang et al., 2019). If the PRV program is to persist in the NTD space, requirements specific to the NTD market conditions may be warranted. For example, the FDA could hold manufacturers accountable for certain access benchmarks and consider withholding the voucher until the drug has been become available at what is deemed to be a fair price.

In the case of albendazole, generic entry alone may not be sufficient to lower prices significantly. If similar trends are identified in other drug markets, additional policies may be needed. While this piece was being written, one of the authors was traveling in Ecuador for the holiday and visited a licensed local pharmacy. There, a 400 mg dose of albendazole (FAGOL 400), the first-line treatment for hookworm (Dynamed Plus, 2020), sold for $0.33 USD—less than a pack of gum. In Minnesota, as of August 2020, the lowest out-of-pocket price (after coupons) of the same 400 mg dose is still $98.46 (GoodRx, 2020). It is indeed a paradox that a patient from Ecuador seeking healthcare at a free clinic in Minnesota would be better served receiving this care in Ecuador, where the retail out-of-pocket cost of first-line treatment is <0.5% of what it is here.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

AS: research and preparation of the manuscript. JA: critical review and preparation of the manuscript. Both authors contributed to the article and approved the submitted version.

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Deconstructing and Historicizing Access to Medicines: The Changing Priority of Pharmaceutical Governance in China

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Securing access to medicines (ATM) is critical for improving public health outcomes. Existing research has long identified and analyzed various barriers that may impede ATM at the global, national, or local levels. However, it tends to adopt a normative perspective to prescribe what infrastructures, resources, and measures *should* be put in place to improve ATM. Little scholarship has explored how and why countries may prioritize certain dimensions of ATM over others in pharmaceutical governance within specific historical contexts. This article fills that gap by deconstructing and historicizing the concept of ATM. The author aims to make two arguments. First, tensions easily arise between different dimensions of ATM, and prioritizing certain dimensions in pharmaceutical policy may impede improvements in others (e.g., availability vs. affordability). Second, which dimension(s) of ATM might be prioritized in the state's pharmaceutical policy hinges upon social, economic, and political forces. To substantiate these arguments, the author draws on interview and archival evidence from China. Specifically, the author provides a historical account of how and why the priorities of pharmaceutical governance in China changed over time: 1) 1949—late 1970s: pursuing both drug availability and affordability through socialist planning; 2) early 1980s—2015: priority shifting from availability (before the mid-1990s) to affordability (after the mid-1990s); 3) 2015—present: striving for a rebalance between drug availability and affordability.

Keywords: access to medicines, pharmaceutical governance, drug availability, drug affordability, China

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INTRODUCTION

The entire world has been waiting for the birth of effective covid-19 drug treatments. But normally, a new drug cannot be successfully developed until after years of experimentation, from preclinical molecule screening and animal testing to phase I, II, and III clinical trials. Let us assume one of the current covid-19 drug candidates turns out to be the perfect cure. Will this scientific breakthrough help improve access to medicines (ATM) for people all over the world? It largely depends on which country one resides in. First, the drug must obtain marketing approval from a certain country's regulatory agency. The application must provide substantial and convincing clinical data in compliance with specific registration guidelines. Second, the drug must be manufactured on a large scale and distributed widely across the country; otherwise, it would be inaccessible to people in remote and/or underdeveloped areas. Third, adequate protocols and regulations must be enforced to guarantee appropriate levels of drug safety, quality, efficacy, and rational use. Last, the price of the

drug and out-of-pocket payments must be set within a reasonable range so that even households living in poverty can afford it.

Ideally, only after satisfying all of these requirements can a country claim to have achieved a significant improvement in ATM—in this case, access to covid-19 drug treatment—for the majority of its citizens. These requirements, in my view, correspond to the four dimensions of ATM: 1) availability: the extent to which an innovative drug can be developed and produced in a timely manner; 2) accessibility: the extent to which a drug can be widely distributed and delivered within a territory; 3) appropriateness: the extent to which a drug is safe, efficacious, qualified, and rationally used; and 4) affordability: the extent to which a drug is reasonably priced and reimbursed. Scholarship and international organizations, such as the World Health Organization (WHO), have carefully deconstructed ATM from multiple angles. Horizontally, ATM is disentangled along slightly different dimensions. For instance, the WHO-MSH (2000, Center for Pharmaceutical Management 2003) uses a framework of availability, affordability, accessibility, and acceptability. Chaudhuri (2007) draws on the Indian case and proposes availability, affordability, and appropriateness as the three dimensions of ATM. Frost and Reich's (2010) framework includes availability, affordability, and adoption. Vertically, as summarized by Bigdeli et al. (2013), constraints over ATM can be analyzed at five levels: 1) individuals, households, and community; 2) health service delivery; 3) health sector level; 4) public policies cutting across sectors; and 5) international and regional level. Hence, they advocate for a health system perspective to analyze complex and interconnected ATM barriers that span across different levels of a health system.

Despite these efforts, however, relevant studies on ATM usually adopt a normative, rather than historical, perspective. That is, ATM research mostly draws on public health theories and data to prescribe what infrastructures, resources, and measures *should* be put in place to improve ATM (e.g., Leach et al., 2005; Bigdeli et al., 2014). Little scholarship has addressed the fact that, depending on historical contexts, countries almost always prioritize certain dimensions of ATM over others in pharmaceutical governance. Even less attention is paid to exploring how and why this is the case. This article fills such gaps by not only deconstructing but also historicizing the concept of ATM. To do so, it focuses on drug availability and affordability, which are the two major dimensions of ATM that can pose trade-off problems for any state regulatory agenda. In particular, the author aims to make two arguments.

First, tensions easily arise between different dimensions of ATM, and prioritizing certain dimensions in pharmaceutical policy may impede improvements in others. For instance, there could be significant trade-offs between the goals of enhancing drug availability and improving drug affordability. Stressing affordability may result in aggressive price control mandates, which could discourage investment in new drug development or provision of low-priced essential medicines, thus potentially undermining drug availability in the long run. Second, which dimension(s) of ATM might be prioritized in the state's pharmaceutical policy hinges upon social, economic, and political forces. The priority order changes along with shifts in these three historical conditions. For example, when a country is suffering from a serious drug cost inflation, it may prioritize affordability improvement over all else in pharmaceutical governance.

To substantiate these arguments, the author draws on interview and archival evidence from China. Specifically, the author gives a historical account of how and why pharmaceutical governance in China shifted its priorities regarding drug availability and affordability in the past decades. First, from 1949 to late 1970s, the Chinese government under Mao pursued both drug availability and affordability in its state-led reorganization of the pharmaceutical sector on the basis of a socialist planned economy. Second, from the early 1980s to 2015, China's pharmaceutical policy first stressed drug availability by liberalizing the domestic industry in the early reform years but shifted toward prioritizing drug affordability over all else in the face of serious drug cost inflation after the mid-1990s. Third, from 2015 to the present has been the era of balancing innovation promotion and cost containment. Both availability and affordability have been stressed as the major priority by the central state, though coordination among different state agencies must be further improved.

By deconstructing and historizing the concept of ATM, the study not only highlights the tension between different facets of pharmaceutical access, but also reveals how such tension plays out in specific political, economic, and social contours. Although the Chinese case is more or less unique in that the state plays a heavy hand in almost all areas of social life, the pharmaceutical sector is also unique in that it is one of the most highly regulated sectors, to the extent that, even in the most laissez-faire countries such as the United States, the state's role in pharmaceutical governance is indisputably strong. Hence, while the trade-offs between drug availability and affordability (and perhaps other dimensions of ATM) surely exist beyond China, they may take varied forms, stem from different historical roots, and provoke divergent state responses in other countries. Further research is needed to explore such variations. In any case, this paper takes a valuable first step toward unpacking how such trade-offs may play out in history.

THEORETICAL FRAMEWORK

A holistic and systematic view is certainly necessary for understanding ATM barriers synchronically. However, as social scientists, we need a framework that can set the research context for deconstructing ATM diachronically. In this paper, the author proposes a framework that helps divide ATM research into two research traditions with varying levels of analysis, different perspectives, and diverse methods. The first is the macroanalysis of the political economy of healthcare/pharmaceutical sectors, which conditions the two

TABLE 1 | Framework of ATM for social scientific research.

Social systems	Dimensions	Major relevant stages of drug life cycle	Levels of analysis	Analytical lenses	Methods
Social system of drug production Social system of drug distribution	Availability Affordability	Drug development and manufacturing Drug pricing and reimbursement	Macro (global, national, regional)	Political economy of healthcare/ pharmaceutical sectors	Historical & comparative analysis, interview, survey, and statistics
	Accessibility Appropriateness	Drug procurement and delivery Drug prescription and reception	Meso and micro (community, household, individual)	Cultural, community, organizational dynamics of healthcare /pharmaceutical delivery	Interview, ethnography, survey, field experiment

most commonly recognized pillars of ATM: drug availability and affordability. This research focuses on transnational or national laws, regulations, policies, and programs concerning drug development and manufacturing. In this line of work, scholars commonly used methods include historical and comparative analysis, interviews, and surveys. Researchers in this tradition have analyzed the political contests over the strength of drug patent regime (Parthasarathy, 2017; Shadlen, 2017), the challenges and opportunities faced by the development of neglected disease drugs (Moon et al., 2012; Craddock, 2017), the problematic knowledge production regime of drug discovery that disadvantaged populations in less developed countries (Pollock, 2019), the developmental foreign aid that helped low-income countries build drug production capabilities (Chorev, 2019), and the public insurance system's battle against monopolistic drug prices set by Big Pharma (Scherer, 2004), just to name a few.

The second research tradition includes the meso- and microanalysis of the organizational, cultural, or community dynamics of healthcare/pharmaceutical delivery. Such dynamics shape the social constraints over drug accessibility and appropriateness (or other terms with similar connotations, such as acceptability, adaptability, and adoption). They include the rules and infrastructures for the distribution and reception of qualified drugs. Relevant research is usually conducted through methods such as interviews, surveys, ethnographic observation, and field experiment. Scholarship in this tradition has investigated the professional and civil movements for the expansion of access to medicines (Flynn, 2014; Harris, 2017), the suppressed local protest groups that could have joined transnational advocacy networks (Long, 2018), the racialized community health movements that advocated for alternative therapies (Decoteau, 2017), the incompetent procurement programs that failed to guarantee drug delivery for public hospitals (Chaudhuri, 2007), the health institutions and professionals that affected the prospect of drug rational use (Wirtz et al., 2013; Xiao et al., 2013), and so on. The framework proposed in this paper summarizes these two research traditions, as shown by **Table 1** .

Building upon this framework, which has deconstructed ATM, the author takes one step further to historicize the concept. To do so, the author focuses on the tension between availability and affordability, the two primary goals of pharmaceutical governance at the macrolevel. In countries capable of drug production, governments often strive to develop an indigenous pharmaceutical industry. In particular, for Southern states whose firms mostly produce generic drugs, the aspiration for enhanced ATM is twofold. A booming local industry would significantly increase 1) the availability of drugs that have yet to be imported to the country and 2) the affordability of drugs that have been available but marketed at excessively high prices (often by Big Pharma). Here, this twofold ideal promises both availability and affordability. Yet, in practice, tensions easily arise between the two goals. For instance, aggressive price regulations may discourage investment in drug development or imports (Thomas, 2001). The author argues that, depending on the historical context, the state may prioritize one over another when designing and enforcing the rules of pharmaceutical governance. Several crucial questions are thus left unanswered: When and why would the state prioritize one dimension of ATM over others in its national pharmaceutical policy? Could the order of priority change over time? What are the driving forces of such change? To provide exploratory answers to these important questions, this paper examines ATM priority shifts between availability and affordability in China's pharmaceutical governance from a macropoint of view. In the mid-20th century, China was one of the poorest countries in the world, but it has since grown into the world's second largest pharmaceutical market with a huge, vibrant, local industry. It thus provides a convenient site for observing and analyzing historical changes in pharmaceutical governance priorities.

MATERIALS AND METHODS

The archival and interview data used in this paper were collected from a larger project exploring the political economy of the Chinese pharmaceutical sector between 2016 and 2018. First, archival data include law and policy documents, historical biographies, and media reports that reflect changes in pharmaceutical regulatory priorities. During the data collection for the larger research project, the author used a database called PKULaw[1] and compiled 6,254 drug-related law and policy documents published by different Chinese state agencies and relevant media reports in the past four decades. For the purpose of this paper, the author selected all the 169 major documents concerning critical reforms issued by leading agencies in the sector for detailed analysis, such as those by the Ministry of Health (MOH), the drug administration, and the State Development Planning Commission (SDPC). The author also reviewed some historical biographies gathered from the author's fieldwork in Beijing, such as the Report on the Development of the Pharmaceutical Industry in China: 1949–2009 published by the China Pharmaceutical Enterprise Management Association.

Second, the author drew the interview testimonies from 45 of the 156 interviews conducted for the larger project, which covered questions regarding the broader transformations in the political economy of the Chinese pharmaceutical sectors. The informants were recruited through purposive and snowball sampling, with a high response rate of 88.1% (156 out of 177 interview requests). The interviews were around 1.5 h long on average, and most of the interviews were recorded and transcribed. The author used the software Atlas.ti to store and analyze the transcripts and selected 45 interviews for this paper because they were the ones in which there were specifically asked questions about the priority shifts of drug regulation over time. These 45 interviews were collected in two groups of regions:

(1) 31 interviews from Beijing and Shanghai. In these regions, which are the political and economic centers of the country, the author interviewed former or current government officials, as well as policy consultants, who had witnessed crucial regulatory reforms in the past decades, and asked them to recall the primary goals of pharmaceutical reforms in certain periods and explain the reform dynamics.
(2) 14 interviews from selected cities and towns of Hebei, Jiangxi, Hubei, and Jiangsu Provinces. In these regions, which represented different levels of health institutions at the city, town, and rural levels, the author interviewed local health practitioners whose daily work had been impacted and asked them to describe their experiences with critical pharmaceutical reforms and shifting priorities with regard to ATM.

[1]PKULaw is a bilingual database for searching China's laws and regulations, cases, journal articles, and gazettes. It has been widely used as a credible database for socio-legal research in the Chinese context. The author accessed this database through the Peking University Library. See http://www.pkulaw.cn/

ANALYSIS

China: Pharmaceutical Governance Changes in ATM Priorities

1949—Late 1970s: Pursuing Drug Availability and Affordability Through Socialist Planning

The Chinese government under Mao pursued both drug availability and affordability in its state-led reorganization of the pharmaceutical sector on the basis of a socialist planned economy. Facing a serious drug shortage, the state tried to promote the local pharmaceutical development and production with full force to reduce import dependence. Meanwhile, like many other goods, local drugs were priced very low under central planning to satisfy the socialist ideal, and the medical reimbursement scheme achieved extensive coverage through state or collective insurance systems. Despite the persistent drug shortage, therefore, drugs were generally affordable at the time.

In 1949, when the Communist Party took power in China, the country was so devastated by long-lasting wars[2] that it barely had an industrial base capable of producing Western medicines. For routine treatment, many people relied on traditional Chinese medicines. However, as poor public health and hygiene facilities exposed the world's largest population to constant threats from deadly infectious diseases like *tuberculosis* and malaria, Chinese society desperately needed mass-produced antibiotics and other chemical drugs (Lee et al., 2009). One review of the terrible drug shortage described it as follows:

> There were only 370 pharmaceutical factories nationwide, with merely 13,000 employees and pathetically meagre medical products except traditional medicines and simple gentian violet, merbromin (red potion), absorbent cotton, and gauze. Chemical drugs were in extreme shortage, which was exacerbated due to economic embargo by Western countries. The broad mass who just got emancipated faced a dire situation of "shortage of doctors and medicines" (queyi shaoyao). (China Pharmaceutical Enterprise Management Association, hereafter CPEMA, 2009, pp. 2, pp. 2)

Meanwhile, anticipating geopolitical conflicts and potential warfare in the near future, Mao's government saw antibiotics as wartime strategic goods in an isolated economy. Hence, starting in the 1950s, the Mao government prioritized the development and production of active pharmaceutical ingredients (APIs) of chemical drugs, especially those of "antibiotics, sulfanilamide, febrifuge, vitamins, endemic medicines, and antituberculosis drugs" (CPEMA, 2009, pp. 3). Hence, the government incorporated antibiotics

[2]The most recent ones included the Japanese invasion from 1937 to 1945 during World War II and the civil war between the Nationalist Party and the Communist Party of China from 1945 to 1949.

production into its centralized industrial plans. With Soviet assistance, it established Huabei Pharma (founded in Shijiazhuang, Hebei Province) as one of the 156 national industrial projects (Dong and Wu, 2004). Huabei Pharma was the largest state-owned pharmaceutical enterprise at the time. It was famed as one of the "Four Sons of the People's Republic" along with Dongbei Pharma (Shenyang, Liaoning Province), Taiyuan Pharma (Taiyuan, Shanxi Province), and Xinhua Pharma (Jinan, Shandong Province).

In 1956, the central state reorganized the State Administration of Medicines (SAM) from the Ministry of Health (MOH) into the Ministry of Chemicals and Industry (MOCI), and the SAM began to take charge of pharmaceutical development, production, and distribution through central planning. Many of these efforts in new drug research and development were part of state-led military and diplomatic missions. Youyou Tu, China's first Nobel prize winner in science, exemplified the scientific breakthrough of collective and socialist style. Tu and her team successfully synthesized artemisinin from traditional Chinese medicines, which was developed into the world's most effective antimalaria drug and saved 200 million lives in the following decades (Tu, 2016). Additionally, there were other collective achievements, such as the creation of synthetic crystalline bovine insulin (Sun, 2015). Despite these occasional breakthroughs, however, "shortage of doctors and medicines" (*queyi shaoyao*) persisted as a salient problem due to a scarcity of capital, technology, and personnel in the Mao era. Research and production were practically paralyzed by the 10-year Cultural Revolution from 1966 to 1976, with intellectuals and professionals despised as antirevolutionary underdogs. Few factory leaders were educated enough to know anything about pharmaceutical development or manufacturing (Beijing, Interview 43).

On the distribution side, the socialist state played a heavy hand as well. Drugs were delivered to public health institutions through a three-tiered distribution system (regional, provincial, city) in fixed volumes, frequencies, and prices (Wei 2009). The Ministry of Health (MOH) was in charge of all of the publicly run health institutions (either nationalized or collectivized), which were responsible for prescribing and dispensing low-priced drugs to patients. During this period, with minimal professional and financial autonomy, public hospitals and doctors received fixed subsidies and salaries as civil servants working for the socialist government in the *danwei* system (Liu 2011). In principle, public hospitals could add a 15% markup to final drug prices to earn some profits (Sun et al., 2008), but since drug supplies were subject to strict central planning, this portion of revenue was also fixed.

In addition to the low and fixed prices, drug affordability was further guaranteed by the state or collective insurance schemes. Not long after the CCP took power, China established two urban schemes and one rural scheme to take responsibility for citizens' medical expenses (Yu 2015): Government Insurance System (GIS, 1952) covering government employees, their dependents, and college students; Labor Insurance Scheme (LIS, 1951) for urban employers with 100 or more employees; Cooperative Medical Scheme (CMS, late 1950s) covering the majority of rural population on the basis of village communes. In the urban areas, people got their prescription drugs at hospital pharmacies with reimbursements from their employers (*danwei*). Hospitals would send the bills to their public employers, which covered the employees' welfare costs from the womb to the tomb. The employees only need to pay for the registration fees ranging from 5 to 10 cents, although benefits can vary hugely across different types of enterprises (Beijing, Interview 34).

As for the CMS in the rural area, although it got praised as an unprecedented public health achievement by the WHO and other international observers, it was still far from adequate to address the unequal access to medicines between the urban and rural areas. With the serious drug shortage, most villagers could only access traditional medicines in the Mao era. A retired researcher affiliated with the MOH, who had rich experiences studying the CMS, explained that the collective commune leaders had the absolute authority to allocate the very limited medicine resources, "taking the good medicines (Western drugs), and leaving the mass herbal medicines" (Beijing, Interview 34).

Despite the widespread inequalities between different urban *danwei* communities and between urban and rural areas, however, it was almost never costly to seek medical service or drug prescriptions thanks to the very low, fixed prices and the extensive reimbursement system. Although the country was still suffering from serious drug shortage by the end of the 1970s, the state had been trying to improve both drug availability and affordability by exerting heavy intervention in each stage of drug supply, from development and production to distribution and reimbursement. It was true that the state only succeeded in achieving the latter aim due to the failure of isolated, planned economy, but its policies have stressed both goals. Such a balanced (though inefficient) policy regime would not change until the economic reform and opening began in the early 1980s.

Early 1980s to 2015: Priority Shifting From Drug Availability to Affordability

In the early reform years until the mid-1990, the priority of China's pharmaceutical policy shifted toward enhancing drug availability following the trend of economic liberalization. Both central and local governments were motivated to not only privatize state-owned pharmaceutical enterprises gradually, but also establish joint-venture firms to attract foreign investment. The domestic industry quickly flourished as a result. However, the marketization of the healthcare and pharmaceutical sectors was rather uneven: while drug production became more and more privatized, drug distribution was still monopolized by public hospitals that remained under tight government command and control. As the state reduced subsidies for public hospitals and urged them to generate revenues from pharmacy business, such uneven reform led to dramatic drug cost inflation beginning around the mid-1990s. Worse still, the collapse of the old socialist insurance schemes took medical safety

nets away from the majority of the population. Facing the rapidly growing medical costs, a large part of which was spent on pharmaceuticals, the discontented public pressured the state to step in. The government responded by pursuing new healthcare reforms in the following decades, which prioritized aggressive drug price control measures over all else in pharmaceutical policy design. As such, from the late 1990s to the early 2010s, enhancing drug affordability became the first and foremost political goal of China's pharmaceutical governance, while availability was gradually sidelined in drug-related reforms.

To accommodate the reform and opening agenda, the Chinese state began to liberalize pharmaceutical production in the early 1980s. In this regard, the industry was no different than many other Chinese manufacturing sectors that embraced gradual, state-led liberalization. On the one hand, the State Administration of Medicines, the Drug Administration Department (DAD) under the Ministry of Health (MOH), and local governments all enforced developmental drug regulations to stimulate the extensive growth of local firms (Liu, 2011). For instance, the author's interview data show that local drug approvals accelerated under loose quality standards. The agencies saw this as a strategy to kill two birds with one stone: boost the economy while increasing the drug supply. It did not take long for the local industry to significantly increase its productivity in manufacturing commonly used drugs, from vitamins to antibiotics, from APIs to generic formulations.

On the other hand, the government encouraged many Northern-based Big Pharma companies, such as Tianjin Otsuka, Shanghai Bristol-Myers-Squibb (BMS), Wuxi Huarui, Sino-US Tianjian Shike, Xi'an-Janssen, and Dalian Pfizer, to found joint ventures in China (China Pharmaceutical News, 2004). The central state also established China National Pharmaceutical Foreign Trade Corporation to facilitate foreign technology transfer and international cooperation. For example, with the assistance of the United Nations Development Program, Sichuan Antibiotics Institute and Beijing Institute of Pharmaceutical Preparations established research centers to nurture and screen antibiotics and other microbial drugs in 1986 (CPEMA, 2009). To better engage with the global market, China even yielded to United States pressure and installed a pro-MNC drug patent regime in 1992.

While the pharmaceutical reform in this period prioritized industrial prosperity, which contributed most to the improvement of drug availability among all the ATM dimensions, demand-side liberalization seriously lagged behind. The Chinese state began to retreat from the public healthcare sector at the beginning of the 1990s, reducing hospital subsidies to as low as 10% of their operating costs while maintaining strict price control over public medical services (Eggleston et al., 2008). Recognizing their financial pressure, the health ministry thus encouraged underfunded public hospitals and doctors to "generate revenues" from selling certain "advanced" drugs, medical examinations, and specialist services that could be priced high at discretion. Such partial price liberalization forced underfunded public hospitals to exploit their monopoly over pharmacies, seeking drug profits and commercial rebates from pharmaceutical firms as a major revenue source.

In addition to this new medical financing model "feeding the hospitals with drug sales" (*yiyao yangyi*), another factor also pushed up drug expenses: following import liberalization in the 1980s, Big Pharma often marketed their monopolistic import drugs at a very high price. For instance, Roche's famous brand-name drug Rocephine (ceftriaxone) could be several dozen or even a hundred times more expensive than its local generics (Jiangxi, Interview 9; Beijing, Interview 38). Not surprisingly, total health expenditures grew fast after the mid-1990s, with an average of 45.7% spent on pharmaceuticals between 1990 and 2009 (Shi et al., 2014).

To make matters worse, the old socialist welfare regime collapsed around the same time. The LIS that used to cover medical costs of urban employees working in the *danwei* system began to fall apart as many debt-ridden SOEs underwent market reform and reorganization in the 1990s. Hundreds of millions of SOE workers lost their "iron bowls" and the accompanying benefits in just a few years, finding no way to get their medical bills reimbursed. As for the rural area, the old CMS collapsed even earlier in the 1980s, when people's commune and collective farming came to the end. Indeed, thanks to the economic reform, township and village pharmaceutical enterprises, drugstores, and rural clinics boomed and greatly enhanced the availability of basic Western medicines in villages. However, farmers also began to feel the burden of rapidly increasing out-of-pocket drug costs after the mid-1990s, whether they remained in the village or migrated to the city for new jobs. Their financial burden was only stronger than urban counterparts due to the depreciation of their agricultural products and the decline of township and village enterprises (Beijing, Interview 34).

Starting around the mid-1990s, therefore, the biggest headache for pharmaceutical governance became fast-growing drug costs. Public outrage pressured the state to react. While open protests were rare, media reports about rising expenses and public complaints attracted the attention of the central state (Beijing, Interview 38). To appease the public, a few state ministries moved to address the problem. There were three major price control measures in this period. One was the drug retail price regulations, enforced by the State Development Planning Commission (SDPC, reorganized into National Development and Reform Commission—hereafter NDRC—in 2003). The other two were centralized drug bidding platforms and National Essential Medicine System (NEMS), both launched by the Ministry of Health (MOH). As the two agencies leading healthcare reforms, the SDPC and the MOH were able to set aggressive price control as the major goal of pharmaceutical governance.

The SDPC's move began in 1996. To tackle the "market price disorder" in the pharmaceutical sector and appease a discontented public, the central state resumed its price-setting power and assigned this power to the Pharmaceutical Office of the Price Department at the SDPC. The Office issued a catalog covering drugs "of large amount and wide application," which included some newly imported and commonly used drugs in the market (Dong and Wu, 2011, pp. 31). Drug prices at different

stages of circulation, including factory price, procurement price, and retail price, were all set by the catalog. Although the SDPC relinquished this price-setting power in 2000, it mandated that retail prices for over 2000 drugs be reduced by 15–20% more than 20 times between 1996 and 2007 (Dong and Wu, 2011). Even if these measures turned out to have had a very limited impact on inflated drug expenditures, they represented the most prominent pricing regulations enforced by the SDPC.

Additionally, the SDPC (reorganized into NDRC in 2003) retained its power to cap drug retail prices after 2000. It stipulated that drugs with specific therapeutic or economic values could apply for the status of "separate pricing," which would allow for a higher retail price ceiling.[3] However, such rules could be rather arbitrary, with the NDRC officials enjoying huge pricing discretion. Despite being justified as a cost-saving measure, this practice only nurtured a hotbed for rent seeking. By 2015, all of the five major officials in the Office had been arrested and accused of corruption.[4] Only then did the NDRC forfeit its price-setting power, which was criticized by my interviewees as unnecessary, corruptive, and cost-inducing:

> For example, there was a "differential pricing" principle. What was a differential pricing principle? Let's say, tablets, capsules, granules, and sustained release agents were all different dosage forms of an active ingredient. How to price them? It sets price for one piece, for example, one ordinary piece (e.g., tablet) and then sets other forms' prices based on a coefficient. Very complicated. People couldn't understand what he had done. Even the Prime Minister did not understand! . . . Too complicated, too much detail! Very technical. In the end, only he (the rule maker) can understand. Many dirty tricks in it! (Beijing, Interview 45)

Although such policies consistently proved to be ineffective and even counterproductive as the cost of corruption ultimately reflected in the final price, aggressive price control remained an orthodoxy for central state agencies. Among them was the most powerful MOH. Instead of loosening price control over medical services to grant more financial autonomy to public hospitals so that they might reduce dependence on drug revenues, the MOH chose to reinforce its command and control over hospital pharmacy business. It adopted two aggressive drug price control measures.

First, it experimented with centralized drug bidding and procurement platforms (referred to as centralized bidding platforms hereafter) to crack down on inflated drug prices and commercial rebates. Throughout the 2000s, the MOH kept promulgating documents[5] in the hope of perfecting rules for such platforms. Moreover, after the central government launched the new healthcare reform plan in 2009,[6] the MOH further centralized the bidding platforms at the provincial level.[7] The procurement principle of "low prices trump all" (*wei dijia shiqu*), which originated with the Anhui Province's "two-envelope" system, gained wide popularity in many provinces. This principle allowed government bidding platforms to put an excessive emphasis on price over quality, thus often leading to a race to the bottom among local firms (Mossialos et al., 2016).

Second, the MOH established a National Essential Medicine System (NEMS), which was one of the top five priorities in the 2009 healthcare reform plan. In this new system, the logic of prioritizing price cuts over all else became even more salient. The MOH created a national essential medicines list that covered 307 drugs, and it required all of China's primary care institutions to implement the NEMS and sell drugs at zero markup within three years (Guan et al., 2011). Although many of the essential drugs were already very cheap before the reform, the producers had to engage in cut-throat price wars on the bidding platforms. As such, while these medicines' procurement and retail prices decreased, problems such as substandard quality and drug shortage became very common at the grassroots level (Liu et al., 2017; Beijing, Interview 16; Hebei, Interview 25). Echoing some quantitative findings (Fang et al., 2013; Liu et al., 2017), the author's fieldwork revealed that drug availability plummeted in township and rural clinics. In the past, the majority of these primary care institutions' revenues came from drug sales, with the drug markup averaging 40.5% (Guan et al., 2011). With few advanced technologies or specialists, they mainly treated common diseases by prescribing drugs. Under the NEMS mandates and zero markup policy, however, many of these institutions fell into significant financial trouble, since their major revenue source was cut off without sufficient and timely government subsidies to make up the loss. As a township clinic head complained:

> Patients would come and ask for certain drugs, those with chronic diseases like high blood pressure or diabetes. Or just cold and stomachache. But you can see us here. Look, this is our drug shelf. All drugs (are) here. We don't even have enough drugs for stomachache! Even their rural clinics have four kinds of stomach drugs! How many do we have? One! Only one! Nonsense! ... My salary is so low here. I would not let my son be a doctor. Never! Our operation is very difficult here. Just some basic public health service, but how are we gonna feed ourselves? Before, we can cut the

[3]Notification of the SDPC on Questions about Separate Drug Pricing (No. 13), on January 4, 2001.

[4]See http://m.y-lp.com/pages/Article.aspx?id=5118500835304745641

[5]A few milestone documents include the following: Notification of Working Norms on Pharmaceutical Bidding and Procurement Process in Medical Institutions (Interim Procedure) (No. 308) on November 12, 2001 and Notification of Some Regulation on Further Standardization of Pharmaceutical Bidding System and Procurement Process (No. 320) on September 23, 2004.

[6]Opinions of the CPC Central Committee and the State Council on Deepening the Health Care System Reform (No. 6) on March 17, 2009.

[7]Working Norms on Pharmaceutical Bidding and Procurement Process in Medical Institutions (No. 64) on July 7, 2010. Guiding Opinions on Establishing and Standardizing Essential Drug Procurement Process in Public Primary Healthcare Institutions (No. 56) on November 19, 2010.

> procurement price and save the markups for ourselves. The price was not high at all! We all know the market price. (Hebei, Interview 25)

In sum, even though other dimensions of ATM were mentioned in formal policies, the priority of actual pharmaceutical governance shifted from availability to affordability after the mid-1990s. While the three price control measures—price caps, centralized drug bidding platforms, and NEMS—seem to have reduced the nominal prices of many generic drugs, they failed to contain the inflation of either drug costs or overall health expenditures (Liu et al., 2017). More importantly, they often unexpectedly undermined drug availability at the grassroots level. Notably, few price control measures were targeted against Big Pharma's brand-name drugs, which enjoyed "supranational treatment" by claiming superior technology/quality over generic products (Mossialos et al., 2016; Beijing, Interview 40).

2015—Present: Rebalancing Availability and Affordability

Beginning in 2015, however, China's pharmaceutical governance entered the era of balancing innovation promotion and cost containment. A series of drug regulatory reforms set drug availability as a top priority along with drug affordability. This time, the availability of cutting-edge medicines to treat deadly diseases such as cancer, rather than that of commonly used drugs like antibiotics, was at stake. It is the first time since the economic reform that the Chinese government began to strive for a balance between drug availability and affordability. What social, economic, and political forces account for this progress? On one hand, as cancer became a leading cause of death in China, the public demand for cutting-edge medicines grew dramatically. On the other hand, the national industrial policy aimed at transforming the economy from a manufacturing giant to an innovative powerhouse, and in the pharmaceutical sector, it encouraged local firms to shift investment from generic production to new drug development. In response, the state assigned two agencies to accommodate these socioeconomic demands: it empowered the central drug administration to improve new drug availability through registration reforms, and it established a new State Medical Insurance Administration (SMIA) as the most powerful agency in drug pricing regulations in replace of the MOH. One of SMIA's major goals was to increase drug affordability without discouraging new drugs from entering the market.

First, the increasing demand for cutting-edge cancer drugs gained public prominence in late 2014 during a national sensation: the criminal charge against Lu Yong, the "first broker of Indian cancer drugs" (Hong, 2015). As a leukemia patient, Lu has survived on the Indian generic Gleevec since 2004 (for more details, see Yang, 2014). Out of altruism, he also helped thousands of fellow patients obtain Indian Gleevec (unlicensed in China, labeled as fake) via informal brokerage. After getting caught, he was accused of the crime of selling fake drugs. The media exposure of this criminal charge turned his case into a national sensation overnight, and the procuratorate eventually dropped the charge under great public pressure (Hong, 2015). For the first time, the Chinese public came to realize that there had been a huge gray market of transnational cancer drug brokerage and that it was the only life-saving channel for many desperate patients. Lu's case not only revealed the striking price discrepancy between Chinese and Indian cancer drugs, but also exposed the lengthy drug lags that had inhibited the availability of innovative medicines for years.

Before 2015, it took a new drug 5 years on average to gain drug approvals from the day the application was submitted.[8] Cutting-edge drugs developed by Big Pharma, which had gained approval in Northern markets, were forced to redo clinical trials in China to be eligible for market entry. Chinese people suddenly learned that foreign drug providers like those in India not only sold drugs of much cheaper prices, but also offered the latest therapies, which had not been available in the Chinese market (Beijing, Interview 2; Jiangsu, Interview 29). Since the exposure of Lu's case, the inadequate availability and affordability of life-saving drugs have gained increasing media and public attention. In summer 2018, the release of the top-rated blockbuster movie *Dying to Survive* (*wo bushi yaoshen*) further amplified the call for reform. Adapted from Lu's case, the movie dramatized the struggles of informal drug brokers and dying cancer patients. Becoming one of the best-selling movies in Chinese history, it provoked widespread public discussion over the role of the state in satisfying unmet local medical needs. One of the major debates became about what government action is required to achieve a balance between drug availability (innovation promotion) and affordability (generic drug provision).[9]

Besides changing disease burden and societal demand, macroeconomic policy was another driving force of the priority shift. Around 2015, President Xi pushed forward economic plans such as "Supply side Reform" (*gongji ce gaige*) and "Made in China 2025." For higher value-added products, such as electronic chips and medical devices, China had been heavily reliant on foreign imports. The core ideal of these reforms was to reduce such reliance and steer Chinese industries toward innovation-oriented transformation. Local firms would be further propelled to compete with international giants on advanced products. The pharmaceutical industry was listed as one of the strategic sectors for this ambition. To accommodate the reform agenda, the government increased funding for innovation promotion programs such as the National Science and Technology Special Project for "New Drug Development,"[10]

[8]For more detail, see the report by Insight, http://yao.dxy.cn/article/92630?trace=related

[9]For instance, a law firm cited the movie in the beginning of its blueprint for the reform of China's pharmaceutical sector. See https://www.cliffordchance.com/content/dam/cliffordchance/briefings/2019/11/chinas-blueprint-for-its-pharmaceutical-sector-chinese-version.pdf

[10]http://www.nmp.gov.cn/zxjs/zdxy/201012/t20101208_2128.htm

launched by the Ministry of Science and Technology (MOST) as part of the 12th five-year plan.

In pursuit of the new policy goals, the State Council assigned Bi Jingquan as the leader of the China Food and Drug Administration (CFDA) in 2015. Bi has served as the deputy secretary of the State Council and the deputy director of the National Development and Reform Commission (NDRC). Thanks to his political clout, Bi soon moved to echo the macroeconomic policy in the arena of drug regulation, as well as addressing the public's growing medicine demand (Beijing, Interview 37). After Bi took office, the empowered CFDA identified the lengthy drug lag as a major obstacle to improving new drug availability in China. As explained by a CFDA official:

> At that time, the focus was on how to allow common people to use innovative and good medicines as soon as possible. This was a consistent idea. Like our center's research work (aiming) to protect and promote public health. Our mission was to make good medicines and drugs available in the global market enter the Chinese market more quickly. Why was it proposed as such? Because before, indeed, some provisions in the Registration Measures and the Drug Administration Law were not conducive to the accelerated market entry of foreign drugs in China. Some of the procedural settings were not in line with the international standards. (Beijing, Interview 37)

To improve drug availability, the agency launched aggressive reforms to streamline the registration procedures, encourage pharmaceutical innovation, and accelerate review speed.[11] For instance, it joined the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) in 2017. In doing so, it made the Chinese drug registration regime much more compliant with international conventions (e.g., recognizing clinical data collected overseas as evidence for drug safety and efficacy). The agency also simplified the registration procedures by removing the requirement of administrative approvals for conducting clinical trials.[12] In a word, the CFDA prioritized improving the availability of innovative drugs in their groundbreaking reforms.

Yet the updated priority did not come at the expense of loosening drug cost control. Another crucial regulatory change took place on the demand side. The new SMIA, established in 2018, took over all authority on drug procurement from the MOH and the Ministry of Human Resources and Social Security (MOHRSS). Tasked with containing the inflation of drug costs while encouraging the market entry of cutting-edge therapies, the SMIA became the most powerful agency in the sector. In 2018, while commenting on the movie *Dying to Survive*, Prime Minister Li Keqiang promised to do more in addition to removing tariffs over import cancer drugs.[13] Soon, the SMIA, which was endowed with strong institutional purchasing power, seized the political opportunity to push forward negotiations with pharmaceutical firms (Beijing, Interview 40). It added 17 cutting-edge cancer drugs to the national reimbursement list, with an average price cut of 56.4%.[14] Moreover, the SMIA began to experiment with national drug bulk-buy schemes (*dailiang caigou*) in major localities around the same time, which aimed to negotiate unprecedented price cuts with both MNCs and domestic drug producers upon the promise of extensive insurance coverage. Along with the CFDA's reform, such moves exemplified the Chinese state's radical efforts to strike for a rebalance between availability and affordability in the rules of pharmaceutical governance. Both foreign and local firms were incentivized to speed up the development and registration of innovative drugs, which would earn large market shares once covered by the SMIA's insurance reimbursement list.

DISCUSSION

The author has shown how Chinese pharmaceutical governance priorities shifted between drug availability and affordability over time and finds that, in the Mao era, the socialist regime prioritized both drug availability and affordability in the central planning of the pharmaceutical sector. With the launch of the reform and opening in the 1980s, the Chinese state began to put more emphasis on availability through the liberalization of pharmaceutical production. However, the state gradually shifted the priority to affordability after the mid-1990s, when drug price and cost inflations became a major financial burden on patients. Only after 2015 did the state launch another round of pharmaceutical reforms to strive for a rebalance between drug availability and affordability.

This case substantiates the importance of deconstructing and historicizing the ATM: enhancing ATM can be a task that poses very different expectations for different governments across historical periods. By analyzing the Chinese case, the author shows that shifts in social, economic, and political forces collectively contribute to changes in the state's perception of what is the most urgent priority. A major limitation of this study is that it only involves two dimensions of ATM, whereas the incorporation of the other two dimensions (drug accessibility and appropriateness) may further enrich and complicate the analysis. Also, looking forward, the author calls for additional research on whether and to what extent this framework can apply to other contexts. We need more inquiries into how and why states may change the priority of pharmaceutical governance with regard to ATM over time. Only through such historical analysis can we have a better understanding of the opportunities and challenges presented for people aspiring for better ATM in the present and future era.

[11]See the landmark Opinions of the State Council on Reform of the System of Evaluation, Review and Approval of Drugs and Medical Devices (No. 44), on August 9, 2015.

[12]The reform formally came into effect on July 27, 2018. See http://www.nmpa.gov.cn/WS04/CL2111/329716.html

[13]See http://www.gov.cn/guowuyuan/2018-04/13/content_5282287.htm

[14]See http://society.people.com.cn/n1/2018/1011/c1008-30333639.html

DATA AVAILABILITY STATEMENT

The datasets generated for this study will not be made publicly available. The interview data are protected for confidentiality.

AUTHOR CONTRIBUTIONS

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

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Prevalence and Predictors of Self-Medication Practice Among Teachers' Education Training College Students in Amhara Region, Ethiopia: A Cross-Sectional Study

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Background: Self-medication practice is the use of medications without healthcare professional requests. It can lead to inappropriate medication usage, wastage of resources, increased chance of microbial resistance, and adverse drug reactions. Therefore, this study aimed at assessing the prevalence and associated factors of self-medication practice among teachers' education training college students in the Amhara region, Ethiopia.

Methods: A multicentre cross-sectional study was conducted on 344 teachers' education training college students in the Amhara region, Ethiopia, from January 1 to February 28, 2020. Data on sociodemography, the practice of self-medication, and factors associated with self-medication practice were collected through a self-administered structured questionnaire. Systematic random sampling was used to select participants. Descriptive statistics and univariate and multivariate logistic regression analyses were done to determine various variables and factors associated with self-medication practice.

Results: Out of the 344 respondents, 234 (68.0%) practiced self-medication. The most commonly cited indication for self-medication practice was headache (75, 32.05%), followed by abdominal discomfort (53, 22.6%). The respondents who were older than 26 years of age (AOR: 2.47, 95% CI: 1.18–3.94), were in the third year of study (AOR: 3.14, 95% CI: 1.94–5.79), lived in urban residence (AOR: 2.97, 95% CI: 1.06–3.64), had accessibility to a nearby pharmacy (AOR: 2.12, 95% CI: 1.43–4.46), and had peer/family pressure (AOR: 2.34, 95% CI: 1.53–3.56) were significantly associated with self-medication practice.

Abbreviations: AOR, Adjusted odds ratio; COR, Crude odds ratio; ETB, Ethiopian birr; OTC, Over the counter; SPSS, Statistical package for social sciences

Conclusion: More than two-thirds of the study participants practiced self-medication. Being from an urban area, having access to a private pharmacy, and higher year of study positively affect self-medication practice.

Keywords: practice, self-medication, Gondar, student, Ethiopia

INTRODUCTION

According to the World Health Organization (WHO) definition, self-medication is the selection and use of medicines to treat self-recognized illnesses or symptoms (Organization, 2010). Inappropriate self-medication practice results in wastage of resources, increases the chance of drug resistance, and causes serious health problems such as adverse drug reactions, treatment failure, misuse of medications, and drug dependence (Bekele et al., 2016). Despite this, self-medication may reduce health costs and save the time spent waiting to see doctors for minor health problems (Leiet al. 2018; Karimy et al., 2019).

Currently, self-medication is becoming a worldwide public health problem. The study report showed that up to 80% of drugs in developing countries were purchased without a prescription (Gore and Madhavan 1994; Shokrzadeh et al., 2019). Similarly, the study conducted in Iran showed that more than two-thirds of individuals had a history of self-medication practice (Karimy et al., 2019; Shokrzadeh et al., 2019). Studies showed that most of the university and college students were practicing self-medication, for example, in Serbia (Lukovic et al., 2014), Nagara (Johnson et al., 2016), and South India (Xiao et al., 2011), 79.9%, 92.4%, and 78.6% of the students, respectively, practiced self-medication. Despite the increased practice of self-medication among students all over the world, the majority are unaware of the harmfulness of self-medication (Gore and Madhavan 1994; Johnson et al., 2016; Karimy et al., 2019).

Many studies reported the factors associated with self-medication practice such as young age (Garofalo et al., 2015), low level of education, previous experience of self-medication, lack of time to visit physicians, low income (Arrais et al., 2016; Helal and Abou-ElWafa 2017), urban residence, greater availability of the medical product, media exposure, the urgency of the problem, trivial health problems, unavailability of means of transport, ability to self-manage the symptoms, and increase of pharmaceuticals advertisements (Lei et al., 2018; Shokrzadeh et al., 2019). Accordingly, individuals practiced self-medication for different purposes. Studies reported that headache, fever, cough (Parakh et al., 2013), gastrointestinal diseases, respiratory tract infections, maternal/menstrual, eye diseases, skin diseases, injury, and sexually transmitted diseases were common indications of self-medication practice (Garofalo et al., 2015; Johnson et al., 2016; Kassie et al., 2018). In Ethiopia, some studies were conducted regarding self-medication practice among university students. However, no study was conducted among teachers' education training college (TETC) students in Ethiopia (Ayalew and adherence 2017). Therefore, the current study aimed to explore the prevalence and associated factors of self-medication practice among TETC students in the Amhara region, Ethiopia.

METHODS AND MATERIALS

Study Design and Area

A multicentre cross-sectional study was conducted in TETC of the Amhara region from January 1 to February 28, 2020. Amhara region is the second biggest administrative region in Ethiopia. This region has ten universities and seven TETCs. Currently, 12,206 students are taking their training in TETC in the Amhara region. This study was approved by the ethical committee of the School of Pharmacy, University of Gondar, with an approval number of SoP-318/2012. Informed verbal and written consent was obtained from study participants before data collection. The collected information from respondents was kept confidential.

Sample Size Determination and Procedure

The source population of the study was all students at the Amhara region TETC, while the study population was those students who are studying at TETC during the data collection period. Regular undergraduate students who were available during the study period were included in the study, while students who were seriously ill and incapable of hearing and speaking during data collection were excluded. Single population proportion formula ($n = [(Z\alpha/2)\ 2 \times P\ (1-P)]/(D/2)$) was applied with the assumption of 95% confidence interval, 5% margin of error, the prevalence (p) of self-medication practice in Ethiopia (50%) (Ayalew and adherence, 2017), and 5% for possible nonresponse to determine a final adjusted sample size of 372. The number of students to be interviewed in each college was calculated based on proportion of the total number of students found in each college. Since the sample is homogeneous, a systematic random sampling method was used to recruit the final interviewed students. The interval was determined using the systematic sampling formula: interval (i) = total number of students in each college/total number of students to be interviewed in each college. Then, the first interviewed student (r) was selected randomly. The next interviewed student was selected by adding interval on the first sample (r) and we kept adding members in the sample (r, r + i, r+2i . . .) to recruit the interviewed students in each college.

Data Collection Tools and Techniques

Data collection was performed by three final year pharmacy students through a self-administered questionnaire. The questionnaire was developed after a careful literature review of the published studies (Garofalo et al., 2015; Bekele et al., 2016; Johnson et al., 2016; Helal and Abou-ElWafa 2017; Kassie et al., 2018). First, it was prepared in English, translated into the local language (Amharic), and then back-translated to the English language to ensure consistency. The tool was further pretested on 18 students who were not included in the final analysis and relevant

TABLE 1 | Sociodemographic characteristics of respondents.

Variable	Frequency (%)	SM practice (n = 234)		AOR (95% CI)
		Yes (n)	No (n)	
Age group in years				
16–20	232 (67.4)	143	89	1
21–25	94 (27.3)	80	14	**2.47 (1.18–3.94)***
≥26	18 (5.3)	11	7	**1.55 (1.19–2.88)***
Sex				
Male	169 (49.1)	117	52	1
Female	175 (50.9)	117	58	1.11 (0.67–2.83)
Year of study		(n = 184)		
1st year	98 (28.5)	40	58	1
2nd year	119 (34.6)	66	53	**1.20 (1.04–3.17)***
3rd year	127 (36.9)	78	49	**3.14 (1.94–5.79)***
Residence				
Rural	80 (23.3)	61	19	1
Urban	264 (76.7)	193	91	**2.97 (1.06–3.64)***
Parents' educational level				
Cannot read and write	138 (40.1)	94	44	1
NF education	87 (25.3)	61	26	1.16 (0.93–3.43)
Grades 1–8	85 (24.7)	56	27	1.41 (0.46–3.75)
Grades 9–12	18 (5.2)	11	7	**1.47(1.46–3.21) ***
≥diploma	16 (4.7)	10	8	**2.27(1.32–3.71) ***
Department				
Amharic language	16 (4.7)	9	7	1
English language	44 (12.8)	26	18	1.14 (0.65–2.42)
Mathematics	46 (13.4	20	26	1.97 (0.56–2.79)
Natural Science**	78 (22.7)	36	42	1.21 (0.47–2.24)
Art***	85 (24.7)	43	42	1.29 (0.34–2.75)
Social Science ****	75 (21.8)	52	23	1.85 (0.67–2.92)
Monthly income				
<200 ETB	111 (32.3)	62	49	1
200–500 ETB	134 (56.4)	74	60	1.22 (0.47–2.45)
>500 ETB	39 (11.3)	21	18	1.65 (0.66–3.45)
The distance of HI				
<30 min	39 (11.3)	18	21	1
30 min–1 h	126 (36.6)	72	54	**1.12(1.01-2.43)***
>1 h	179 (52.1)	110	69	**2.67(1.44-3.34)***
Access to pharmacy				
No	193 (56.1)	77	74	1
Yes	151 (43.9)	125	68	**2.12(1.43-4.46)***
HP in their family				
Yes	72 (20.9)	27	45	1
No	272 (79.1)	187	85	1.45 (0.21-3.14)
Peer/family pressure				
Yes	212 (61.6)	134	78	**2.34(1.53-3.56)***
No	132 (38.4)	60	72	1

*SM: self-medication; NF: nonformal; HI: health institution; HP: health professional; ≥ diploma = parents' education diploma or above diploma; *significant at* p *value < 0.05; Natural Science**: biology, physics, and chemistry; Art***: art generalist, music generalist, special needs, and physical education; Social Science ****: civics and ethics generalist, geography, amd history. ETB: Ethiopian birr (1 USD = 32 Ethiopian Birr).*

modifications were performed before the commencement of the actual data collection. Completeness and fulfillment of all questions were checked by the principal investigator and data collectors. The final questionnaire consisted of 17 items that were divided into three main sections. The first section was focused on the sociodemographic characteristics, including age, gender, department, years of study, monthly income, residence, and parents' education level. The second section aimed to assess the prevalence of self-medication practice, reasons for self-medication practice, factors that promote self-medication, sources of supply, and information source for self-medication. The final section focused on the environmental characteristics of participants, including the distance of health institution, accessibility to pharmacy, presence of health professionals into the family, presence of medication at home, and peer/family pressure.

Statistical Analysis

The final collected data were checked for completeness, and responses were entered into and analyzed using the Statistical Package for the Social Sciences software version 24.0 (SPSS v24.0) for Windows. Frequencies and percentages were used to express different variables; bivariant and multivariate logistic regression analyses were used to determine factors associated with self-

TABLE 2 | Prevalence and source of the drug for self-medication practice among TETC students, Amhara region, Ethiopia, 2020 (N = 344).

Statement	Answer	Frequency	%
Do you have ever practice self-medication in your lifetime?	Yes	234	68.0
	No	110	32.0
When you started to practice self-medication practices? (n = 234)	Before joining college	50	21.4
	After joining college	184	78.6
If your answer is yes for the above question, how many times practiced in your lifetime? (n = 234)	Once	33	14.1
	Twice	54	23.1
	Three times	69	29.5
	≥4 times	78	33.3
Duration of self-medication (n = 234)	For1 day	57	24.4
	For 2 days	52	22.2
	For 3 days	45	19.2
	Four days	33	14.1
	≥5 days	45	20.1
Do you always read the instruction? (n = 234)	Yes	99	42.3
	No	135	57.7
Do you have ever faced any adverse drug reaction? (n = 234)	Yes	72	30.8
	No	162	69.2
Where did you get that medication? (n = 234)*	Pharmacy	171	73.1
	Friends	89	38.0
	Family	72	30.8
	Others (specify	27	11.5

**Respondents have more than one choice.*

medication practice. Univariate analysis was done and variables with a p value less than 0.2 were further taken to the multivariate logistic regression analysis for proper adjustment with the possible confounders. In this study, adjusted odds ratio (AOR) at 95% confidence interval (95% CI) with p value < 0.05 was considered statistically significant.

RESULTS

Sociodemographic Characteristics

Out of the 372 respondents invited to participate, 344 responded to the questions giving a response rate of 92.5%. The mean age [standard deviation (SD)] of respondents was 20.96 (2.40) years, and half (175, 50.9%) of the respondents were female. Among the respondents, 127 (36.9%) were in the third year of study. More than half of the respondents (134, 56.4%) had 200–500 ETB monthly income. Regarding the study department, the most cited department was Art (85, 24.7%), followed by Natural Science (78, 22.7%). The majority of the participants (179, 52.1%) traveled more than 1 h to reach health institutions, whereas 193 (56.1%) had access to pharmacies. The detailed sociodemographic and self-medication related characteristics of the respondents are summarized in **Table 1**.

Prevalence, Source of Drug, and Indication of Self-Medication Practice

Of the total respondents, 234 (68.0%) practiced self-medication. The majority (184, 78.6%) of students started self-medication practice after they joined college. Among students who practice self-medication, 78 (33.3%) practiced more than four times and 72 (30.8%) faced adverse drug events. More than half of the students (135, 57.7%) did not read the instruction. From the total self-medication users, 171 (73.1%) got medication from the pharmacy and 89 (38.0%) from friends (**Table 2**).

In this study, the most commonly cited indication of self-medication was headache (75, 32.1%), followed by abdominal pain (53, 22.6%) and common cold (46, 19.7%). The indication of self-medication practice among respondents is summarized in **Figure 1**.

Reasons for Self-Medication Practice

The most common reasons for choosing self-medication reported by the respondents were similarity of illness with previous illness (90, 38.9%), followed by nonserious disease (57, 24.4%) and ease of accessibility to drugs (40, 17.1%) (**Table 3**).

Factors Associated With Self-Medication Practice Among Students

Variables that were significantly associated with self-medication practices in the bivariate analysis were further examined in multivariate logistic regression. The result showed that respondents aged 21–25 years were 2.47 times more likely to practice self-medication (AOR: 2.47, 95% CI: 1.18–3.94) than those aged16–20 years. Based on years of study, third-year students were 3.14 times more likely to practice self-medication (AOR: 3.14, 95% CI: 1.94–5.79) than first-year students. The odds of self-medication practice were 2.97 times higher among urban residents than among rural residents (AOR: 2.97, 95% CI: 1.06–3.64). Those who had accessibility to pharmacies were nearly two times (AOR: 2.12, 95% CI: 1.43–4.46) more likely to experience self-medication practice compared to those who had no accessibility to pharmacy. The odds of self-medication practice among respondents who had

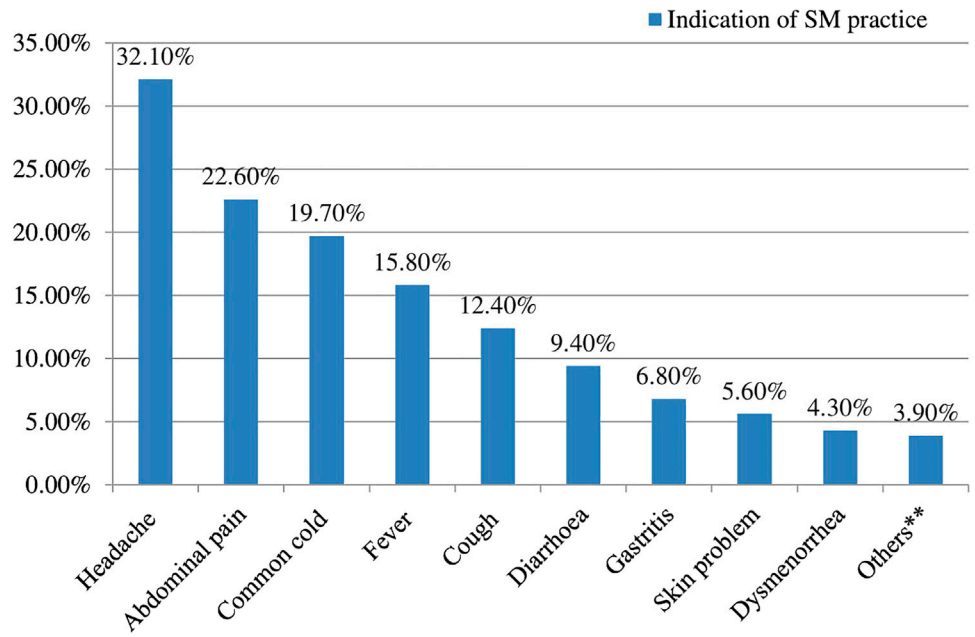

FIGURE 1 | Indication of drugs for the self-mediation practice among students, Amhara region, Ethiopia, 2020 (n = 234)*.

TABLE 3 | Reasons for self-medication practice among TETC students, Amhara region, Ethiopia, 2020 (n = 234)*.

Variable	Frequency	Percent
The similarity of illness with previous illness	90	38.9
Disease not serious	57	24.4
Easily obtaining drugs	40	17.1
Friends' suggestion	30	12.8
Self-medication being cheaper	29	12.4
Long waiting time in health service	23	9.8
Long distance to the health facility	22	9.4
Being embarrassed to talk about the disease	19	8.1
Affordability of the cost of drugs	14	6.0
Not trusting health professionals	10	4.3
Others	8	3.4

**Respondents have a chance to select more than one.*

peer/family pressure was 2.34 times (AOR: 2.34, 95% CI: 1.53–3.56) more likely to practice self-medication compared to those who had not peer pressure (**Table 1**).

DISCUSSION

Self-medication is a common practice in both developed and developing countries (Ayalew and adherence 2017). This may lead to incorrect selection of medication, harmful drug interactions, incorrect dosage, risk of drug dependence, and abuse (Mamo et al., 2018). Several studies revealed that self-medication practice is common practice throughout the world (Araia et al., 2019).The current study is designed to assess the prevalence and association factors of self-medication practice among TETC students in the Amhara region, Ethiopia. Furthermore, this study can provide baseline information for healthcare policymakers and education curriculum designers.

According to this study, 68.0% of students have practiced self-medication. This finding is nearly comparable with a study done at Addis Ababa, Ethiopia (75.5%) (Shafie et al., 2018), and Egypt (62.9%) (Helal and Abou-ElWafa 2017). However, it was lower than the findings from Nigeria (92.39%) (Johnson et al., 2016), Nepal (81.9%) (Badiger et al., 2012), Southwestern Nigeria (91.4%) (Osemene and Lamikanra 2012), and South India (84.6%) (Kumar et al., 2013). This might be due to the presence of advanced telemedicine services and awareness about medications. Another possible explanation may also due to the differences in sociodemographic factors and sample sizes. On the other hand, the finding is higher than those of the studies done in Jiangsu University (47.9%) (Zhu et al., 2016), West Bengal (43.24%) (Banerjee and Bhadury 2012), Mekelle University (43.24%) (Gutema et al., 2011), and Jimma University (45.9%) (Ararsa and Bekele 2015), Nekemte (36.7%) (Sado and Gedif 2014), Dire Dawa (41%) (Abrha et al., 2014), South India (35.9%) (Divya et al., 2016), Bahir Dar (23,3%) (Mihretie 2014), Sire town (27.16%) (Jaleta, Tesema et al., 2016), Silt'e zone (24.40%) (Mossa et al., 2012), and Brazil (16%) (Arrais et al., 2016). The reason for the wide variation in the prevalence of self-medication practice might be due to the variation of social determinants of health, beliefs, and the culture of the population.

In this study, 30.8% were faced with adverse drug events. This was in line with a study done in North India (29.77%) (Parakh et al., 2013). However, the finding was higher than that in a study reported from South India (5.4%) (Badiger et al., 2012) and Eretria (9.2%) (Araia et al., 2019). Several previous studies

revealed that pharmacy was the main source of medication and friends, relatives, and leftover medications from previous prescriptions were denoted as some of the frequently reported sources (Abay and Amelo 2010; Osemene and Lamikanra 2012; Ahmadi et al., 2016; Helal and Abou-ElWafa 2017). The present finding also showed similar results that pharmacy accounts for 73.1% as the main source for self-medication practice. Easy accessibility to drugs from pharmacies might be linked to the absence of clear legislation concerning access to medicine in Ethiopia. This legislation gap may attribute to the increment of the number of persons who might practice self-medication. Therefore, such practice may lead to irrational drug use and the development of drug resistance, possibly endangering human life.

The present study revealed that the commonest indication of self-medication practice was a headache (32.1%), followed by abdominal pain (22.6%). Some studies reported comparable findings in which headache was the leading indication of self-medication (Kumar et al., 2013; Shehnaz et al., 2014; Gyawali et al., 2015). Unlike the finding of this study, the common indications for self-medication were urinary tract infection (UTI), sore throat, and diarrhea in Nigeria (Osemene and Lamikanra 2012). A study conducted in Egypt revealed that cold, headache, sore throat, intestinal colic, and cramps were among the main diseases related to self-medication practice (Helal and Abou-ElWafa 2017), whereas a study conducted in Southwestern Nigeria reported that UTI, sore throat, and diarrhea were among the core diseases linked to self-medication practices (Osemene and Lamikanra 2012). This may be due to the difference in the prevalence of these diseases across the study area. In this study, the most commonly cited sources of drugs were pharmacy (73.1%), followed by family (38.2%). This finding is similar to the study done in India (Johnson et al., 2016).

In the current study, the topmost three reasons that led participants to practice self-medication were similarity of illness with previous illness (38.9%), feeling the disease is not serious (24.4%), and friends' suggestion (12.8%). This finding was similar to studies done in Jimma town (Ararsa and Bekele 2015), Iran (Jaleta et al., 2016), and Asella, Ethiopia (Bekele et al., 2016). In contrast, other studies reported previous experience as the first main reason for self-medication (Abay and Amelo 2010; Gutema et al., 2011; Abdi et al., 2018; Araia et al., 2019).

The multivariate analysis revealed that third-year students were 3.14 times more likely to practice self-medication (AOR: 3.14, CI: 1.94–5.79, $p < 0.05$) than first-year students. This finding is similar to the study done in Southwest Nigeria, Egypt, and Ethiopia that stated a significant association between years of study and self-medication (Osemene and Lamikanra 2012; Karthik et al., 2014; Helal and Abou-ElWafa 2017). However, a previous study conducted in Peru and Ethiopia did not show a significant association between the years of the study (Núñez et al., 2016; Gelayee, 2017). This may be associated with students' awareness and knowledge about drugs and disease. In most Ethiopian TETC, students come from a rural area and live in town using a rent house. Through time and years of study, student's awareness and knowledge about drugs and diseases might increase because of the Internet and social media access. The result showed that respondents aged 21–25 years were 2.47 times more likely to practice self-medication (AOR: 2.47, CI: 1.18–3.94, $p < 0.05$) than those aged 16–20 years. The current finding is in agreement with previous similar studies (Osemene and Lamikanra 2012; Gelayee 2017; Helal and Abou-ElWafa 2017). In contrast, some studies reported that no significant association between self-medication practice and the age of the participants was found (Bekele et al., 2016; Kassie et al., 2018).

In the present study, participants whose permanent residence was in urban areas tended to practice self-medication more often (AOR: 2.97, CI: 1.06–3.64, $p < 0.05$) than those who live in rural areas. This finding was in line with the study conducted in Egypt (Helal and Abou-ElWafa 2017). The possible explanation could be that those who lived in urban areas may have some awareness about the treatment and may have seen drug promotions, which may encourage them to practice self-medication rather than consulting the health professionals and visiting health institutions. Another reason for such a difference in practice related to residence might be related to the variance of accessibility to healthcare service. The logistic regression also showed that students whose parents had more than diploma certificate education level was 2.27 times more likely to practice self-medication (AOR: 2.27, CI: 1.32–3.71, $p < 0.05$) than those whose parents were unable to read and write. This finding is in agreement with a similar study conducted in Eretria (Araia et al., 2019). The possible explanation could be that those who had a diploma may have some awareness about drugs and diseases, and as a result, may encourage their children to practice self-medication rather than seeking healthcare institutions. However, a previous study was done in Serbia reported that the high level of parents' education was independently associated with self-medication practice (Karthik et al., 2014).

Respondents who had access to the pharmacy were nearly two times more likely to practice self-medication (AOR: 2.12, CI: 1.43–4.46, $p < 0.05$) as compared to those who had not. This result is consistent with those of students in China (Wen et al., 2011), India (Divya et al., 2016), and Nigeria (Abdulraheem et al., 2016). This might be because most of the private pharmacies sold medication without a prescription and due to the lack of income and time to consult healthcare professionals. The current finding is supported by the inability to afford healthcare fees noted as the means for self-medication practice. The odds of self-medication practice among respondents who had peer/family pressure were 2.34 times more likely to practice self-medication (AOR: 2.34, CI: 1.53–3.56, $p < 0.05$) as compared to those who had not. The current result is consistent with those of studies carried out in China (Wen et al., 2011) and Uganda (Ocan et al., 2014). The possible explanation may be that friends/families were common sources of information about medication in developing countries like Ethiopia.

Strengths and Limitations

This study had some limitations that should be taken into account when interpreting the results. As the study is cross-sectional and depends on self-reported assessment, underreporting is more

likely to occur. This study did not include attitudes, awareness of the participants towards self-medication practice, social desirability, and types of medication. Even with the above limitations, the survey has a positive impact on the implications of health service in Ethiopia. Moreover, the study was multicentre and considered nonresponse participants. Finally, we recommended that future researches should consider participants' attitudes, awareness, beliefs, and culture, which may be affected by self-medication practice.

CONCLUSION

The result of the study revealed that two-thirds of the study participants practiced self-medication. Being from an urban area, having access to a private pharmacy, higher year of study, parents' education level, and having peer/family pressure are significant factors for self-medication.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University of Gondar, Ethiopia. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AM contributed to designing the study, writing the final research, data interpretation, data analysis, final manuscript preparation, and supervision of the study. MT and MG participated in data analysis and data interpretation. TA contributed to writing the final research, data interpretation, and manuscript preparation. All authors read and approved the final manuscript.

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A Stalled Revolution? Misoprostol and the Pharmaceuticalization of Reproductive Health in Francophone Africa

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Misoprostol entered the global market under the name Cytotec in the mid-1980s for the treatment of gastric ulcers. Decades of research have since demonstrated the safety and effectiveness of off-label use of misoprostol as a uterotonic in pregnant women to prevent and treat post-partum hemorrhage, treat incomplete abortion, or terminate first-trimester pregnancy. Global health experts emphasize misoprostol's potential to revolutionize access to reproductive health care in developing countries. Misoprostol does not require refrigeration, can be self-administered or with the aid of a non-physician, and is relatively inexpensive. It holds particular promise for improving reproductive health in sub-Saharan Africa, where most global maternal mortality related to post-partum hemorrhage and unsafe abortion occurs. Although misoprostol has been widely recognized as an essential obstetric medication, its application remains highly contested precisely because it disrupts medical and legal authority over pregnancy, delivery, and abortion. I draw on fieldwork in Francophone Africa to explore how global health organizations have negotiated misoprostol's abortifacient qualities in their reproductive health work. I focus on this region not only because it has some of the world's highest rates of maternal mortality, but also fertility, thereby situating misoprostol in a longer history of family planning programs in a region designated as a zone of overpopulation since the 1980s. Findings suggest that stakeholders adopt strategies that directly address safe abortion on the one hand, and integrate misoprostol into existing clinical protocols and pharmaceutical supply systems for legal obstetric indications on the other. Although misoprostol has generated important partnerships among regional stakeholders invested in reducing fertility and maternal mortality, the stigma of abortion stalls its integration into routine obstetric care and availability to the public. I demonstrate the promises and pitfalls of pharmaceuticalizing reproductive health: despite the availability of misoprostol in some health facilities and pharmacies, low-income and rural women continue to lack access not only to the drug, but to quality reproductive health care more generally.

Keywords: misoprostol, reproductive health, abortion, Francophone Africa, pharmaceuticalization, population control

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INTRODUCTION

Misoprostol offers a particularly vivid example of how pharmaceuticals inhabit multiple "social lives" or "biographies" throughout various stages of their production, marketing, distribution, prescription, and consumption (Geest et al., 1996; Whyte et al., 2002). In the late 1980s, medical professionals in Brazil began reporting that women who used misoprostol to terminate pregnancy experienced less severe complications of incomplete abortion (Coêlho et al., 1994; Löwy and Dias Villela Corrêa, 2020). Produced under the brand name Cytotec by pharmaceutical giant Pfizer, this drug had been available on the global market since 1985 for the treatment of gastric ulcers. In pregnant women, misoprostol acts as a uterotonic, causing the cervix to soften and the uterus to contract. In addition to terminating pregnancy, misoprostol may also be used to induce labor, prevent and treat post-partum hemorrhage (PPH), and treat complications of incomplete abortion (also known as post-abortion care or PAC). While off-label utilization of misoprostol is challenging to measure, in 2007 an estimated total of 129,300 mcg of misoprostol were sold in pharmacies and hospitals worldwide. Off-label use of misoprostol is thought to be highest in Asia, where the drug has been approved for managing PPH and medication abortion (MA) where legal, and where the cost of the drug is the lowest (Fernandez et al., 2009). While misoprostol is sold in brick and mortar health facilities and pharmacies, it may also be purchased from informal drug vendors, and where available, the Internet. For example, since launching in 2018, the online organization Aid Access has distributed at least 600 medication abortion kits including misoprostol to women in the United States (Lussenhop, 2018).

Although World Health Organization (WHO) listed mifepristone and misoprostol used together as a safe form of early MA in 2005, clinical research has shown that misoprostol alone can effectively terminate first-trimester pregnancy (von Hertzen et al., 2007). WHO placed misoprostol on its List of Essential Medications (LEM) for labor induction in 2005, for PAC in 2010, for preventing PPH in 2011, and for treating PPH in 2015 (WHO, 2019a). More recently, in 2018, WHO listed misoprostol alone as an alternative to the recommended combination regimen for MA (WHO, 2019b). In response to increasing access to MA worldwide, WHO shifted its abortion classification system. While epidemiologists had previously differentiated between safe and unsafe abortion in terms of the legality of the procedure (safe abortions are legal, unsafe abortions are illegal), abortions are now classified along a spectrum from safe, less safe, to least safe (Ganatra et al., 2017).

In both popular media and public health literature, misoprostol has been described as a "revolution" in reproductive health care because of its potential to reduce mortality and morbidity related to unsafe abortion and PPH in countries with restrictive abortion laws or with under-resourced health systems (Kristof, 2010; WLP, 2010; Henderson et al., 2012; Harvey, 2015). Misoprostol is an effective alternative to oxytocin for both the prevention and treatment of PPH (Raghavan, Abbas, and Winikoff, 2012; Sheldon et al., 2012). Furthermore, studies have shown that community-based health workers such as traditional birth attendants (TBAs) can safely administer misoprostol to prevent PPH (Prata et al., 2012; Smith et al., 2013; Bell et al., 2014). The drug is equally as effective as the manual vacuum aspiration (MVA) syringe in administering PAC (Dao et al., 2007; Ibiyemi et al., 2019). Generic brands of misoprostol are sold in smaller quantities and thus available with or without prescription at a lower price than the brand name Cytotec (sold in quantities of at least 14 tablets), in brick and mortar pharmacies and in informal drug markets. Additionally, misoprostol does not require refrigeration and can be used safely in low-resource settings.

Misoprostol holds particular promise for pharmaceutically revolutionizing women's access to quality reproductive care in sub-Saharan Africa (SSA), where the burden of abortion-related mortality is the highest in the world (nearly 62% of global abortion deaths occurred in Africa in 2008 [WHO, 2011a]), where hemorrhage accounts for 25% of maternal death (Say et al., 2014), and where there are only 2.2 health workers per 1,000 population (WHO, 2016). Indeed, the availability of misoprostol for safe abortion, PAC, and PPH could avert more maternal deaths than other large-scale interventions in developing countries (Prata et al., 2009).

Critical scholars of global health are more skeptical about the extent to which medication alone can lead to a revolution in access to health care. More specifically, they have cautioned against reducing solutions to complex public health problems like maternal mortality to "magic bullets": cost-effective drugs or interventions that promise to save the most lives at the lowest cost, but with inadequate attention to the social and economic context in which these technologies are applied (or not) (Farmer et al., 2013; Adams, 2016). Magic bullet approaches have been incentivized within a broader landscape of neoliberal health reform since the late 1970s, in which the competitive distribution of health goods and services through the market, rather than the government, purportedly leads to greater standardization, accountability, access, and quality (Erikson, 2012; Basilico et al., 2013; Chorev, 2013). In developing countries, structural economic reform, led by the International Monetary Fund (IMF) and the World Bank, has decreased government support for health care, leaving private organizations to fill in service delivery gaps (Pfeiffer and Chapman, 2010; Packard, 2016; Pfeiffer, 2019). Within a context of economic scarcity, aid donors and governments prioritized the implementation of practical, technologically driven approaches whose effectiveness can be statistically measured, ideally through randomized controlled trials (Adams, 2013; Adams, 2016). For example, starting in the 1980s, the World Bank supported a collection of primary health care interventions for children—growth monitoring, oral rehydration therapy, breast feeding, and immunizations—known as GOBI (Basilico et al., 2013; Packard, 2016).

The desire for technological solutions and measurable results has led to what critical scholars of global health have termed the "pharmaceuticalization" of public health, a process through which medication comes to stand in for health infrastructure

and human resources that constitute public health systems (Biehl, 2006; Biehl, 2007; Bell and Figert, 2012). For example, studies in Brazil and Mozambique have shown how HIV/AIDS programs that prioritize the availability of anti-retroviral therapy (ART) overlook, and in some cases reinforce, inequalities in basic health needs such as nutrition, housing, and clean water that increase people's vulnerability to HIV infection (Biehl, 2006; Biehl, 2007; Kalofonos, 2010). In Tanzania, mass administration of deworming medication took precedence over environmental interventions to reduce the burden of parasitically transmitted diseases such as onchocerciasis and trachoma (Samsky, 2015). Even in wealthy countries like the United States, stratified access to life-saving drugs and technologies reinforces racial and class inequalities in health outcomes (Clarke et al., 2003; Phelan et al., 2010). While medication may effectively treat disease, pharmaceutical approaches do not adequately address underlying inequalities that render some people at greater risk of disease and limit their access to preventive and curative care. From this perspective, misoprostol alone may not be enough to reduce maternal mortality in SSA.

Framing misoprostol as a revolution in reproductive health care further belies the complex geopolitical and professional processes—a transnational "regime of values" (Geest et al., 1996)"—involved in approving and registering drugs, determining who can administer them and how, and in making them available (and affordable) to relevant populations. Despite misoprostol's potential to reduce maternal death, its off-label obstetric indications, and in particular its capacity to terminate pregnancy, have rendered it a "pharmaceutical outlaw" (MacDonald, 2020) in a global arena of reproductive health that remains reluctant to accept abortion as a legitimate part of obstetric care (Suh, 2018). For example, US policies like the 1973 Helms Amendment and the 1984 Mexico City Policy (also known as the Global Gag Rule [GGR]) prohibit US development assistance from being used to procure abortifacient technologies or to support abortion-related activities in developing countries. As recently as May 2020, in a letter to the UN Secretary General, US Agency for International Development (USAID) threatened to withdraw funding from the UN Humanitarian Response to the global Covid-19 pandemic because of its alleged "promotion" of abortion through "the widespread distribution of abortion-inducing drugs and abortion supplies" (USAID, 2020). Additionally, faith-based, anti-abortion organizations such as Maternal Life International have expressed opposition to WHO's inclusion of misoprostol for preventing PPH on its LEM, arguing that it promotes a lower standard of obstetric care outside the hospital for pregnant women in developing countries (Adams, 2020).

Misoprostol's relatively recent "biography" as an abortifacient is connected to a longer history of (neo)colonial population governance in SSA. In this article, I explore politics and practices related to misoprostol in the Francophone region of SSA, which includes countries in West and Central Africa. I focus on this region not only because it has some of the world's highest rates of maternal mortality, but also the highest rates of fertility and lowest rates of modern contraceptive use. Since at least the 1980s, family planning has factored prominently into structural adjustment policies designed to increase economic growth throughout the region under the guidance of the IMF and the World Bank (Hartmann, 1995; Robinson, 2015). By the turn of the millennium, Francophone Africa was designated as a climate change "hot spot" (Mutunga et al., 2012) due to population growth. By focusing on this region, I locate the misoprostol revolution in a longer geopolitical history of magic bullet approaches to address population problems in this region.

In this article, I situate misoprostol, a highly flexible reproductive health drug with multiple obstetric indications, in a fractured landscape of reproductive governance (Morgan and Roberts, 2012) that includes population control, maternal mortality reduction, safe abortion, and PAC. I draw on in-depth interviews conducted in 2019 with individuals from national and international non-governmental organizations (NGOs) and philanthropic agencies currently engaged in reproductive health research, advocacy, and service delivery in the region, and a review of national, regional, and global literature on misoprostol. My findings show that these organizations pragmatically engage in approaches that, on the one hand, openly signal their support for safe abortion through training and advocacy, and quietly support the approval of misoprostol for legitimate obstetric indications by national pharmaceutical regulatory agencies and its integration into national LEM and private and public pharmaceutical supply systems, on the other. For advocates of safe abortion, both approaches are necessary in a region where abortion laws remain highly restrictive, USAID remains an influential donor of reproductive health aid, and health officials and medical workers face immense pressure to meet national and global demographic targets to reduce fertility and maternal mortality.

By exploring how these actors integrate misoprostol into health policy and practice, I offer insight into the benefits, challenges, and pitfalls of pharmaceuticalizing reproductive health. I argue that access to misoprostol cannot simply be boiled down to its availability in pharmacies, or its affordability on the market. The narrative of revolution, while hopeful about the drug's potential to reduce maternal mortality, insufficiently captures the complex transnational politics that shape how and where it is available and used (or not), and by whom. Attention to global, national, and regional practices, strategies, and discourses related to misoprostol reveals how access to pharmaceuticals falls short of reproductive justice in a region significantly influenced by gendered, racialized, and classed geopolitics of reproduction.

METHODS

This study was accomplished through ethnographic research conducted between July and August 2019 in Dakar, Senegal. My research on misoprostol stems from a longer professional and scholarly engagement with reproductive health, and in particular PAC, in Senegal. During the mid-2000s, I worked with Management Sciences for Health (an international health NGO) on PAC in five of USAID's regions of intervention in Senegal. Between 2009 and 2011, I conducted research on PAC in

Senegal, and since then have remained connected with colleagues in the Ministry of Health (MOH) and national and international NGOs involved in reproductive health research and programming.

First, I conducted in-depth, semi-structured interviews with 17 individuals involved in reproductive health care advocacy, research, and programming in Francophone Africa. Interviews with participants in Senegal occurred in person, while others took place over Skype with participants based throughout Francophone Africa, Europe, and the US. At the time of fieldwork, research participants worked with philanthropic agencies and NGOs. While some participants had worked in the past with national MOH or as health workers in government health facilities, I did not interview current MOH officials or government health workers as part of this study. Participants represented a variety of nationalities including Senegalese, Ivorian, Burkinabé, American, British, and Dutch. Although I purposefully selected some participants due to their organizational positions, others were referred to me through snowball sampling. This personalized approach, and my previous research experience in PAC in Senegal, facilitated sensitive conversations about misoprostol and abortion. The names of individuals and organizations have been anonymized to protect confidentiality. Permission for this project was obtained from Brandeis University and the Ministère de l'Enseignement Supérieure, de la Recherche, et de l'Innovation in Senegal.

Second, I conducted literature reviews on misoprostol and MA. Sources include clinical research on misoprostol's safety and efficacy in obstetric care; technical guidelines on abortion care issued by WHO; sociological and anthropological literature on women's and health workers' experiences with misoprostol in SSA; and public health literature on availability and use of misoprostol in public and private health care sectors. Also included in my analysis are data from reports on MA published by international NGOs and donor agencies. Some of these reports describe the proceedings of stakeholder meetings, while others outline national and regional strategies for expanding access to MA in Francophone Africa. In light of the sensitive nature of abortion in this context, I do not reveal the identities of individuals or organizations involved in the publication of these reports, unless the report is available to the public online.

Drawing on multiple sources of data, I identify various institutions, professions, industries, communities, and technologies that make up the complex and rapidly evolving "pharmaceutical regime" (Biehl, 2006: p. 207) of misoprostol in Francophone Africa. This approach offers insight into how misoprostol is simultaneously entangled with and isolated from global, regional, and national goals, discourses, and policies related to maternal and reproductive health. While tracing how misoprostol activities are unfolding on the ground, this methodological approach allows us to see how access remains limited for some populations. I draw on the mapping exercises and situational analyses of MA in NGO reports to supplement study participants' explanations of misoprostol marketing and registration. I compare participants' perceptions and descriptions of misoprostol strategies and practices with national and regional goals established for MA during global and regional stakeholder meetings. I juxtapose participants' perceptions of misoprostol practices among health workers and women with findings from ethnographic research on misoprostol in SSA. Where possible, I draw on national surveys to estimate the availability of misoprostol in public health facilities.

THEORETICAL SIGNIFICANCE

Science and technology studies and critical studies of global health offer useful theoretical tools to understand the production, marketization, distribution, prescription, and availability of pharmaceuticals across a variety of contexts. In this section, I draw on these tools to illuminate the gap between misoprostol's promise as an obstetric pharmaceutical in transnational arenas of maternal and reproductive health policy making and the practical realities of misoprostol on the ground. Pharmaceuticals are not inherently safe or effective, but acquire meaning through the social, economic, and political dimensions of their utilization (Timmermans and Berg, 2003; Casper and Morrison, 2010). As pharmaceuticals circulate through various "lives" or "biographies" related to experimentation, production, or consumption, they are embedded in shifting "regimes of values," or ideas about efficacy, disease, treatment, and patient populations (Geest et al., 1996; Whyte et al., 2002). Pharmaceuticals are never finished products, but are engaged in complex "human and non-human processes and practices (p. 119)" through which they are continually "made and remade (p. 118)" (Hardon and Sanabria, 2017).

Professional and lay debates about what makes a particular drug or technology "the right tool for the job" (Clarke and Fujimura, 1992), and for whom the drug is appropriate, reveal inequalities along the lines of gender, race, class, and nationality with respect to who can and should use pharmaceutical products and for what purpose. In the United States, for example, opposition to the Human Papillomavirus (HPV) vaccine on the grounds that it would encourage promiscuity, especially among young girls, delayed its integration into pediatric care (Mamo and Epstein, 2014). Some scholars have attributed the delay in expanding access to ART in SSA to racist perceptions of Africans' inability to follow drug regimens, and the drug resistance that would surely arise from non-compliance (Nauta, 2010; Crane, 2011).

The "job" that pharmaceuticals are designed to accomplish, or their "biography" at a particular moment in time, may shift in response to social, professional, economic or political factors. Pharmaceutical companies have encouraged off-label prescription of drugs, despite a lack of clinical evidence, to maximize profits through expanded patient populations. Examples include drugs for sexual disorders, social anxiety, Attention Deficit Hyperactivity Disorder (ADHD), depression, and other mental illnesses (Abraham, 2010). Off-label prescription of drugs is neither uncommon nor new: a 1998 study found that nearly 39% of drug prescriptions in pediatric wards of European hospitals were off-label (Conroy et al., 2000).

Some off-label "jobs" may be deemed too controversial by pharmaceutical companies to promote in clinical practice. Despite the integration of misoprostol into national and global guidelines for obstetric care, Pfizer has not applied for a license to cover the reproductive health indications of Cytotec, a drug that is registered for treatment of ulcers in at least 80 countries (Weeks et al., 2005). Nevertheless, Pfizer likely profits from off-label utilization of misoprostol for abortion (Morgan, 2019).

In the global South, pharmaceuticals are "reinscribed (p. 120)" with meaning related to safety, efficacy, and patient populations not only in clinical trials, consumer markets, and health care settings (Hardon and Sanabria, 2017), but also in health policy arenas according to "shifting global priorities and funding arrangements (p. 150)" (Hardon and Dilger, 2011). This terrain is composed not only of UN agencies, international NGOs, and bilateral donors, but increasingly "philanthrocapitalist" organizations like the Gates Foundation (Birn, 2014) and pharmaceutical companies. In Brazil, for example, anthropologist João Biehl describes the role of the World Bank and global pharmaceutical companies in a "pharmaceutical regime" that made ART universally available to the population in 1996 (Biehl, 2006).

Misoprostol's potential to improve reproductive health has been framed as revolutionary precisely because beyond its capacity as an abortifacient, it is the "right tool" for multiple obstetric "jobs," including labor induction, preventing and treating PPH, and PAC. In this sense, misoprostol is anchored in multiple "regimes of value" related to global efforts to reduce maternal mortality. Although the 1987 Safe Motherhood Initiative called on donors and governments to invest in maternal health care comprehensively as a matter of social justice (Smith and Shiffman, 2016), its twenty-first century iteration—Women Deliver—has demanded investment in specific interventions that have demonstrated, through statistical evidence, cost-effectiveness in reducing maternal death (Storeng and Behague, 2014; Storeng and Behague, 2017). Misoprostol is the ideal "silver bullet (p. 272)" for maternal health because its cost-effectiveness in preventing and treating PPH and administering PAC has been demonstrated statistically in randomized controlled trials (Storeng and Béhague, 2014).

At the same time, despite its proven safety record and integration into national and global LEM, misoprostol's capacity to terminate pregnancy continues to threaten its legitimacy as a reproductive health drug (Starrs and Winikoff, 2012; MacDonald, 2020) and renders it incompatible with US funding mechanisms for family planning aid. Despite USAID support for research and programming on misoprostol for PPH and PAC (Grenier et al., 2013; Barot, 2014), misoprostol cannot be procured with US development assistance under the 1973 Helms Amendment, which prohibits the "performance of abortion as a form of family planning (Barot, 2013: p. 9)." In addition to donations of misoprostol from NGOs and other agencies, national health authorities must purchase the drug from wholesale distributors, at times leading to gaps and inconsistencies in supply (Samnani et al., 2017). In this sense, the anti-abortion funding restrictions of the largest donor of global reproductive health aid (Grollman et al., 2018) may influence supplies of misoprostol in government health facilities.

Even for a legitimate obstetric indication like PPH, misoprostol's capacity to disrupt medical power over pregnancy, abortion, and delivery continues to generate professional debates over where it should be used, and by whom (MacDonald, 2020). Indeed, misoprostol disrupts conventional knowledge about where maternal health care itself should be administered. Since the 2000s, global maternal health authorities have stressed the importance of skilled birth attendance (births attended by doctors, nurses, or midwives), ideally in well-equipped health facilities, to reduce maternal death (Stanton 2008). The 2015 Sustainable Development Goals have maintained skilled birth attendance as a key indicator of progress toward reducing maternal death (Chou et al., 2015). Yet, even as WHO and other global maternal health stakeholders have promoted skilled birth attendance, other maternal health advocates have critiqued this approach, pointing to evidence that TBAs can use misoprostol in community-based settings to safely and effectively manage PPH (Potts et al., 2006; Potts and Hammerling, 2006).

Some maternal health scientists and organizations have been critical of WHO's recognition of misoprostol as an alternative medication for preventing and treating PPH in the absence of the gold standard, oxytocin. In 2011, Maternal Life International, a faith-based organization, wrote to WHO to question the evidence base for misoprostol's inclusion on the LEM for preventing PPH, arguing that it fostered sub-standard, unregulated care outside of health facilities for poor, rural women in SSA (WHO, 2011a; Adams, 2020). Similarly, in 2018, researchers from Newcastle University in the United Kingdom requested that WHO remove misoprostol for the prevention of PPH from its LEM in light of a lack of rigorous statistical evidence supporting community-based administration of the medication (WHO, 2019b). In counter-response, Médecins Sans Frontières (MSF) argued that misoprostol must remain on the LEM to ensure "an alternative for prevention of PPH in resource-poor community and rural settings where injectable oxytocics are not available, or cannot be safely administered" (WHO, 2019c). Additionally, some misoprostol advocates have argued that in some developing countries, it may be financially, ethically, and logistically "impossible" to conduct randomized, placebo-controlled trials that produce rigorous statistical evidence of the medication's efficacy in managing PPH, and that demands for additional statistical evidence unjustly delay women's access to safe and effective care (Potts et al., 2010).

Given the recent resurgence of attention to family planning as a global health matter, surprisingly little attention has been directed to misoprostol's capacity, as an abortifacient, to achieve global targets related to fertility reduction. Compared to modern contraception, abortion plays a limited role in fertility reduction. Yet, the "contraception-abortion paradox (p. 12)" exists in many developing countries, where limited access to or inconsistent use of contraception increases the risk of unwanted pregnancy, which in turn frequently leads to abortion (WHO, 2011b). There is precedent for the deployment of abortion technologies, along with long-acting

reversible contraceptives (LARCs), in the achievement of fertility reduction goals in the global South. Starting in the late 1960s, modern contraception was identified as a technical solution to the perceived problem of overpopulation in newly sovereign nations in the global South. Neo-Malthusian predictions of political and economic instability and environmental degradation due to overpopulation catalyzed an era widely known as "population control," during which developing countries were compelled to establish population policies that articulated fertility reduction goals in exchange for development assistance from bilateral and multilateral donors. Through family planning programs established by international NGOs, USAID "inundated" developing countries with low-cost contraceptives (Murphy, 2012; Takeshita, 2012). These programs have been widely critiqued for coercive practices and inadequate attention to women's needs, comfort, and safety (Hartmann, 1995; Kuumba, 1999).

Before the MVA syringe became a preferred technology for PAC in the early 1990s (Suh, 2015), it was promoted by USAID as a technology for "menstrual regulation" (a euphemism for abortion) in parts of Asia and Latin America during the early 1970s (Murphy, 2012). After the passage of the 1973 Helms Amendment, USAID delegated MVA research and distribution to NGOs such as International Planned Parenthood Federation (IPPF), Pathfinder International, and Ipas. Even with the Helms Amendment and the GGR in place, MVA had been distributed in over 100 countries by 1993 (Adams, 2018).

At the 1994 UN International Conference on Population and Development (ICPD), the global community rejected the target-oriented population control paradigm in favor of the concept of reproductive health, which called for comprehensive, rights-based approaches to ensuring women's reproductive well-being. By the early 2000s, however, fertility reduction through voluntary family planning emerged yet again as a key component of global approaches to address the environmental dangers of climate change (Sasser, 2018). Over the next decade, SSA was identified as a region particularly vulnerable to the impact of climate change on food security, water, and health. The Gates Foundation explicitly identified population growth as a cause of "disease burden, environmental degradation, poverty, and conflict" (Bill and Melinda Gates Foundation, 2012). Nearly all of the 26 countries designated as population and climate "hotspots"—areas characterized by "high rates of population growth, high projected declines in agricultural production and low resilience to climate change" (PAI, 2011, p. 2)—in 2011 were in SSA. As the "primary collectors" of food, water, and fuel in SSA, women were more vulnerable to climate change and therefore the ideal target population for contraception to help them "cope" (Mutunga et al., 2012, p. 12).

In SSA, family planning in the form of "birth spacing" has been tightly connected to maternal health through its capacity to avert undesired or unplanned pregnancies (Duclos et al., 2019; Brunson, 2020). In 2012, the global reproductive health community called for revitalized investment in fertility reduction. The Family Planning 2020 Initiative (FP 2020), with over one billion dollars in funding from the Gates Foundation, committed to providing 120 million women with modern contraception by 2020 in 69 of the world's poorest countries. Over half (58%) of FP 2020 countries are in Africa. In 2012, nine Francophone African countries formed the Ouagadougou Partnership (OP), a regional collective that aimed to add an additional 2.2 million contraceptive users by 2020. Donors and NGOs have worked with OP countries to establish targets for number of users and contraceptive prevalence (Bendix et al., 2019). With financial support from the Gates Foundation, global pharmaceutical companies and NGOs have redesigned and tested LARCs like Depo Provera and Norplant for widespread use in SSA (Hartmann, 2014; Bendix et al., 2019).

Feminist scholars have argued that population, development, and climate interventions like FP 2020 must be situated in a longer history of (neo)colonial strategies to control African fertility (Kuumba, 1999). Some colonial population policies were designed to increase fertility, ensuring a robust colonial labor supply (Knoppers et al., 1990; Hunt, 1999), while others aimed to curtail African fertility to shore up white supremacy (Brown, 1987; West, 1994; Klausen, 2016). More recently, at the 2017 G20 Summit, French President Emmanuel Macron was accused of racism when he framed high fertility rates in SSA as a "civilizational" problem (Wintour, 2018).

Although FP 2020 uses the language of reproductive rights and maternal mortality reduction to frame contraceptive use, it reanimates neo-Malthusian logics of population control that posit fertility in SSA as a threat to the economic, political, and environmental stability— "the abundant life" (Murphy, 2017)—of wealthy countries in the global North (Hartmann, 2014; Bhatia et al., 2019). Such initiatives prioritize a technical solution—contraception—to complex social, political, and economic problems such as food insecurity, land dispossession, and disinvestment in subsistence agriculture (much of which is performed by women in SSA [Rodgers and Akram-Lodhi, 2019]). They disproportionately burden women in SSA for solving the problem of climate change, despite the fact that at 3%, this region has the lowest greenhouse gas emissions in the world (Sy, 2016). They reduce women to mere instruments through which governments can manipulate problematic demographic characteristics—such as SSA's "youth bulge"—to maximize economic growth (Nyambura, 2018). Put differently, the nexus between population, development, and climate change exemplified by global interventions like FP 2020 reinforce race, gender, and class hierarchies that devalue the reproduction of women of color in the global South.

Through its multiple "lives," misoprostol is anchored in multiple global regimes of maternal and reproductive health governance. And yet, the qualities that render it a potentially revolutionary medication for achieving maternal mortality reduction simultaneously raise the specter of unregulated abortion and increased participation of TBAs in obstetric care. As an abortifacient, misoprostol's ties to a neo-Malthusian past and present threaten to destabilize precarious global agreements on achieving fertility reduction targets in a post-ICPD landscape. In the following sections, I explore how reproductive health advocates have negotiated these qualities in their efforts to increase the availability of misoprostol in Francophone Africa.

"RIGHT AT THE PRECIPICE": REGIONAL PRIORITIZATION OF SAFE ABORTION

Some study participants are explicitly engaged in advancing access to MA, and safe abortion more generally, in Francophone Africa as part of a broader maternal and reproductive health agenda. Abortion-specific meetings have been held, either as stand-alone events or tied to other global or regional maternal and reproductive health conferences starting in 2016. Some of these events have been organized and held in secrecy because of the politically sensitive nature of abortion. These meetings have been attended by representatives from national and international NGOs, research organizations, bilateral donor agencies, UN agencies, and philanthropic agencies. During these meetings (none of which I attended), safe abortion advocates have discussed trends, progress, and challenges related to MA in the areas of research, legal environment, advocacy, commodities, community engagement, funding priorities, and services. For example, during a January 2019 meeting on safe abortion, almost 40% of participants indicated that their funds were allocated to MA services, and 88% identified Francophone West Africa as a priority region (SAD, 2019a). Safe abortion advocates use these meetings to rethink priorities, conduct situational analyses, coordinate and synergize activities, and articulate next steps.

Catherine, Maxine, and Roberta, who worked for two philanthropic foundations, identified reproductive health more generally as a long-standing goal within their funding portfolios related to "population." Although these foundations have supported safe abortion advocacy and research among national and international NGOs for several decades, they explained that the 2012 OP served as a catalyst for increased regional interest in safe abortion, with a particular focus on MA. They identified new actors, including NGOs and bilateral donor agencies, that had become involved in family planning, and eventually began to dedicate attention and resources to safe abortion. Catherine believed that despite the OP's focus on family planning, this initiative had catalyzed a regional approach to MA that was poised to transform the landscape of abortion:

> There's a lot more interest as a region, the conceptualization of the region as a space, thinking of it regionally, like these are lots of small-ish countries so when we think regionally, a lot can be done. Donors think regionally. I think it's been great and catalytic for safe abortion work. And of course, there's the MA revolution happening all this time and that has really changed safe abortion work globally, of course. But I think it's right at the precipice of being extremely fundamentally shifting, especially in Francophone Africa.

Maxine agreed that there had been a "general shift towards West Africa," but did not attribute it solely to safe abortion. Instead, she located it in a broader recognition within the global reproductive health community that Francophone Africa was underserved compared to other regions in SSA. Some stakeholders have identified the region's official language as a deterrent among Anglophone donors (SAD, 2019b). Prior to working with her foundation, Maxine had been engaged in reproductive health work with another organization in the region and felt as if "we were begging for support for our programs in West Africa." While there was some support from a few European bilateral agencies, "it was hard to get other donor support because it looked like there were more opportunities and movement and government support in East Africa, and to some extent, some of the Central African countries." She linked these geographic foci to a "huge surge" of interests and resources related to HIV/AIDS. She believed that stakeholders had recently turned their attention to Francophone Africa as a place that was "still in need." For her, "there has been a general growing interest in West Africa around reproductive health, and then, maybe safe abortion is a part of that."

Study participants who worked with international NGOs throughout the region identified an extensive array of abortion-related research, service provision, commodity distribution, training, and professional and legal advocacy. According to Eva, these activities were less about "promoting abortion" than they were about "reducing unsafe and less safe abortions." NGOs conducted situational analyses on reproductive health and Knowledge, Attitudes, and Practices (KAP) surveys on abortion and contraception with women and girls. Others have evaluated the availability of MA products in public and private health care facilities. In one country, health workers were trained to monitor maternal deaths, paying special attention to the contribution of unsafe abortion to maternal mortality in their facilities.

In some countries, NGOs have deployed these data in advocacy regarding the harmonization of national laws with the 2003 Maputo Protocol of the African Union, which calls for safe abortion in the case of rape, incest, or when pregnancy threatens a woman's mental or physical health (African Commission on People and Human Rights, 2003). Some countries have established action plans, with stakeholders in medicine, law enforcement, religion, and other sectors, that endeavor to move toward the integration of the Maputo Protocol. This approach has materialized into legal change in some countries, but not others. Several study participants pointed to the Democratic Republic of Congo (DRC) as an example of an advocacy success story: in March 2018, the government acknowledged that the Maputo Protocol superseded national law (PRB, 2018), and reminded health authorities that safe abortion should be available in public facilities under the conditions specified by the Protocol (SAD, 2019b). In contrast, in Senegal, the abortion law remains unchanged despite advocacy related to the Maputo Protocol (Archer et al., 2018).

Even in countries with legal indications for abortion, study participants explained that provision of and training for MA in the public sector remained limited. PAC remained an important part of their work as women often waited until after they had terminated pregnancy (often unsafely) before seeking care. Some international NGOs were directly involved in "comprehensive" abortion training—safe abortion and PAC—for public sector health workers. Others provided abortion and PAC services in their own clinics (SAD, 2019b). In countries where MA products were registered with national

pharmaceutical regulatory agencies, they trained public and private health workers to use them. Additionally, they worked with national partners to include MA in national conversations about reproductive health commodities and supported national health authorities' efforts to integrate misoprostol into national LEM and protocols for reproductive health care. In several countries, NGOs have conducted "values clarification" workshops to raise awareness of the clinical and legal environment of abortion with a wide variety of stakeholders, including health workers, parliamentarians, journalists, law enforcement officials, youth groups, and professional associations.

While some study participants were directly involved in programming these events, others took more of a behind the scenes approach. For example, Eva differentiated her organization's "advocacy work" from its "hands-on work." She understood "hands-on work" as technical in nature: health worker training and registration of commodities. In contrast, she understood her organization's participation in advocacy as less direct: "We aren't necessarily the front line to the Parliament or anything like that. I know there are partners who are much more active at that level of Parliamentarians. I would say that we're not playing that role." Her organization "supported the movement" by participating in working groups, and providing financial support for national organizations such as the national association of women lawyers, to meet and discuss strategies for legal advocacy.

"A PRODUCT LIKE ANY OTHER": MISOPROSTOL RESEARCH, REGISTRATION, AND MARKETING

While the previous section describes advocacy, programming, and services that are directly related to abortion, and at times publicly-facing, here I describe how study participants are engaged in strategies with less direct ties to safe abortion, and more oriented toward professions and institutions in private and public sectors of the health system. These strategies entailed conducting research on misoprostol's safety and efficacy for legal obstetric indications such as PAC and PPH, registering generic brands of misoprostol with national pharmaceutical regulatory agencies, supporting misoprostol's integration into national LEM and clinical protocols for maternal and reproductive health, and marketing misoprostol directly to health workers and health facilities. In other words, this approach aimed to increase the availability of misoprostol for legal obstetric indications in public and private sectors of the health system, with the knowledge that it would likely be used off-label for abortion.

Some of the earliest activities related to misoprostol in Francophone Africa have involved investigating its feasibility for managing PAC and PPH. A 2004 study in Burkina Faso confirmed that misoprostol was just as effective in treating incomplete abortion as MVA (Dao et al., 2007). In 2012, *BMC Pregnancy and Childbirth* published results from a multi-country (Senegal, Niger, Nigeria, Mauritania, Burkina Faso, and Mauritania) study showing that misoprostol could be used safely for PAC (Shochet et al., 2012). In Senegal, a study showed that midwives in primary health care facilities were able to effectively administer misoprostol for PAC (Gaye et al., 2014). Another study showed that misoprostol could be used by TBAs to prevent PPH (Diadhiou et al., 2011). More recently, a study found that misoprostol was just as effective as oxytocin delivered via Uniject in preventing PPH at the community level (Diop et al., 2016).

In response to this research, MOH in several countries in the region have placed misoprostol on national LEM for the purposes of PAC and preventing and treating PPH. Senegal, for example, placed misoprostol on the national LEM in 2013. In 2014, the Senegalese National Pharmacy of the Ministry of Health integrated misoprostol into its procurement system (Ndao et al., 2014). Following these developments, at least one generic brand of misoprostol has been registered in each country in the Francophone region (SAD, 2019b). A 2019 report on MA commodities in Africa stated that in Senegal, misoprostol was available in packets of three under the brand name Misoclear for $1.75 (approximately 1000 CFA francs) (Mann Global Health, 2019). Study participants in Senegal reported a slightly higher price of between 2,000 and 3,000 CFA francs. In some countries, there are multiple brands of misoprostol: three in Mali and Benin, and two in Niger (IPPF, 2020). As part of their regional strategy, safe abortion advocates encouraged the presence of multiple brands of misoprostol to keep prices low, thereby increasing access to the drug (SAD, 2019b).

With the exception of Senegal, where abortion is not permitted under any circumstance, there is at least one legal indication for abortion in all of the Francophone countries. In Côte d'Ivoire and Chad, there are five and six indications, respectively. In countries with legal indications for abortion, combination MA packs of mifepristone and misoprostol have been registered (SAD, 2019b). Similarly, the "combi-pack" is registered and available in other African countries with legal indications for abortion, such as Ethiopia, Mozambique, Uganda, and Zambia (Mann Global Health, 2019). John, who worked with an international reproductive health NGO with operations in Senegal and other countries in the region, expressed doubts that combi-packs would be registered in Senegal given its highly restrictive abortion law.

Safe abortion advocates described the pharmaceutical system in Francophone Africa as highly "centralized," with close ties to French wholesalers (SAD, 2019b). Local commercial distributors may be reluctant to take on "the extremely slow and delicate process of registration" with national pharmaceutical registration authorities, which in some places has taken up to three years (Mann Global Health, 2019). In Senegal, organizations that register drugs with national pharmaceutical regulatory agencies are prohibited from directly engaging in social marketing. Consequently, international NGOs that have registered misoprostol have outsourced social marketing to pharmaceutical wholesalers in the private sector. These commercial distributors procure the drug from a French company, and in turn promote and sell the drug to pharmacies and health facilities (Mann Global Health, 2019).

According to Zeinab, who worked with an international reproductive health NGO in Senegal, these companies "created demand" on the part of pharmacists and health workers by providing them with information about how to dispense, prescribe, and use misoprostol for authorized purposes such as PPH and PAC. When confronted with health professionals' concerns about misoprostol's abortifacient qualities, she explained that the social marketing agents emphasized the fact that the drug "saves lives," and that it's a "product like any other" that "should be accessible." In other words, misoprostol distributors framed the drug in public health terms to highlight its legitimacy in obstetric care in a restrictive legal context.

For some study participants, it was precisely the privatized nature of misoprostol procurement and distribution, along with national recognition of misoprostol's legal obstetric indications, that had the potential to revolutionize access to safe abortion. Despite legal indications for abortion in all Francophone countries (except Senegal), MA provision in the public sector remains low (SAD, 2019b). Adja, who worked for an international reproductive health NGO in Senegal, pointed out that in the public system, "there are always stock outs" of medication, meaning that health workers may have difficulty procuring misoprostol even for legal indications of PAC and PPH. Working through the private health sector, where pharmaceutical wholesalers procured supplies and sold them to pharmacies and health facilities, offered a more reliable approach to ensuring access to misoprostol.

Catherine, who worked for a philanthropic organization, described misoprostol as a "game changer" for abortion access in Francophone Africa: "Misoprostol is such a subversive and exciting thing because if we can get this stuff on shelves and get pharmacists who know how to get it out. . .I mean, work within the provisions. . .it feels like it could be big." Catherine discussed how MA had been "revolutionary" in countries like India and in parts of Anglophone West Africa. "We've seen some places in Anglophone West Africa where MA has already exploded. Ghana is just off the shelves. A pretty amazing amount of product is sold." For her, medication abortion was a "story waiting to be told" in Francophone Africa. It was just a matter of "figuring out what—following that story and pushing it where it can be pushed."

John, who worked for an international reproductive health NGO, echoed Catherine's vision of MA when he said that revising abortion laws should no longer be the "holy grail" of abortion advocacy. Instead, getting misoprostol directly "into women's hands" through pharmacies should be the focus. Similarly, Julia, who had worked with an international reproductive health NGO for many years, expressed that working "outside" the government health system, through private pharmacies, was the best way to reduce unsafe abortion in places with under-resourced health systems.

For Jacques, who supervised the regional MA strategy for an international NGO, the privatized approach to registering and distributing misoprostol was a double-edged sword. On the one hand, getting the drug into private pharmacies ensured access to the drug for women who could reach these facilities and purchase the medication. On the other hand, procuring an abortifacient drug within the public health system remained a serious challenge. He characterized the act of registering the drug for PPH as a "big battle" because "everyone knows that it's a product that is used to make abortions safer." He joked that even the MOH "hid" behind obstetric indications like PPH and PAC to place misoprostol on the national LEM. For Jacques, this approach made people reluctant to order misoprostol "publicly" in government health facilities, even for legal indications. "Everyone knows that they need the product," he said, "but no one will say, 'listen, we need to order miso.' Jacques described a situation in one Francophone country where a multilateral agency donated a quantity of misoprostol to the MOH, which was "only buying contraceptives." The MOH then sent the drug to "university hospital centers," but not secondary health facilities. In other words, in the public sector, misoprostol was not always, as Zeinab had suggested, a "product like any other," precisely because the medication is negatively associated with clandestine abortion.

THE "STIGMA" OF ABORTION

Although several participants pointed to the 2012 OP as an important catalyst to the MA revolution in the region, abortion has factored into the landscape of global reproductive governance since at least the introduction of PAC across the region starting in the late 1990s. While PAC was recognized in the 1994 ICPD as a harm reduction approach to the public health problem of unsafe abortion, health workers and health authorities in countries with restrictive abortion laws have had to frame PAC, and the MVA syringe in particular, in ways that distinguish the intervention from pregnancy termination to remain in compliance with national prohibitions on abortion and the US GGR (Suh, 2021).

Study participants who worked for philanthropic agencies recognized that safe abortion had long been part of the reproductive health, or more broadly, "population" portfolios of their employers. Roberta alluded to "interest" in intersections between "climate change and environmental issues" and "reproductive health access in the Northwest and along the Sahel." Maxine described hearing from former colleagues in West Africa "about European concerns about migration and feel that this is playing into—in negative ways—the increased attention to West Africa's population." Within her agency, however, Maxine believed that work on environment and reproductive health had traditionally been kept "separate." Roberta agreed, saying "I think there's been concern about how you talk about it together and the potential negative incentives of linking them together." She went on to describe, however, how her agency intended to "test the waters" in supporting a project that brought together reproductive health, agriculture, and conservation in an East African country.

Regardless of where one draws the start line for the MA revolution in Francophone Africa, it is clear that global abortion politics significantly complicate stakeholders' activities related to misoprostol. The GGR prevents national organizations

that receive USAID funding for family planning from using money from other sources to do abortion-related work. Consequently, international NGOs and donor agencies exercise caution in distributing abortion-related work and funding to national organizations. Eva described how her NGO ensured that, in the Francophone countries where they worked, their contracted social marketing agencies did not "touch" anything related to abortion. Her NGO had to "separate out" misoprostol and combi-packs from their national partners' portfolios.

Maxine described her philanthropic agency as one that "places a lot of emphasis on funding local organizations and not international NGOs." The GGR affected her organization "in small and large ways." Sometimes, she had to scrap plans for collaborating with an organization when it was discovered that they'd signed the GGR. In some situations, her organization had to increase funding for grantees that refused to sign the GGR and therefore lost USAID funding. When presented with opportunities for collaborating directly with USAID, her organization had to consider whether USAID's "bigger dollars and influence" were worth "compromising on the abortion piece." Sometimes, they decided "to go it alone without their support." She described the reinstatement of the GGR in 2017 as having "a chilling effect" in terms of planning meetings and conferences at higher levels related to reproductive health:

> I was at a meeting the other day that was three quarters contraception, one quarter abortion, and no one from AID could come to the meeting. . .It's definitely a problem. There's plenty of other examples of meetings and conferences where all the abortion talk has to be pushed to one end of the meeting so the USAID folks could leave the room before any discussion of abortion begins.

The 2012 OP has simultaneously served as a catalyst to organizing regionally around safe abortion and heightened political anxieties about abortion. Two of the OP's donors, USAID and the Gates Foundation, do not fund abortion-related work. Due to the "stigma" of abortion, according to Catherine, "the OP, which is family planning specific, has been very resistant to allowing anything related to abortion to enter the Partnership." Discussions related to abortion have been "limited" to PAC. Even the Gates Foundation had to be reassured of the programming connections between PAC and family planning (Curtis et al., 2019). While Catherine recognized the challenges presented to abortion stakeholders, she did not believe the OP was fundamentally resistant to abortion. "The OP is a commitment of nine governments to do better with family planning," she explained. "The needs are immense, and the gains are fragile. They're not the opposition. The OP is not opposing abortion work: they're protecting very important political gains they've made." Instead, she believed that MA advocates had to pragmatically "harness" the research, programming, and advocacy synergies generated by the OP in ways that moved the MA agenda forward.

Mariam, who worked for an international NGO, seemed less convinced of this approach. She explained how her organization struggled to participate in OP meetings and to integrate abortion into discussions of reproductive health commodities. "We've never been invited to these OP meetings which only discuss contraception." Her organization's solution was to continue "pushing" the issue and speaking "openly" about abortion.

National abortion politics further complicated the integration of misoprostol into health systems. Laila, a midwife in Senegal who had previously worked with the MOH and now worked with an international NGO, described how "when they started giving misoprostol to *matrons* (TBAs) for PPH, they made them record the serial number and link to each patient used." This was a way to "safeguard" an abortifacient drug that "shouldn't be used like aspirin." Mariam and Eva, each representing a different international NGO, described a situation in one Francophone country where, shortly after training a group of health workers to use misoprostol, the MOH released an official statement warning health workers to limit misoprostol use and prescription to legal obstetric indications. Mariam described how, in another country, health workers reported that MOH officials had removed misoprostol from their facility because of suspicions that it was being used illegally to provide abortions. "They completely stopped supplying misoprostol," Mariam explained, "so the health workers had to hide and use their own money to buy misoprostol and sell it to women in the facilities." She went on to describe how in such a political context, "sometimes you have the impression that you take one step, and then there's something that pushes you back." Eva echoed her concerns when she said "it just shows that in the region while things are advancing, there is still a lot of possibility for things to go quickly backwards."

Other study participants suggested that Francophone Africa was a particularly difficult place to work on MA because of institutionalized abortion stigma, even in countries with legal indications for abortion. Maxine contrasted the region to Ethiopia, "where we talk much more openly, freely with the government and the Ministry about abortion services." When I asked John what it was like to promote misoprostol in Senegal or other African countries with restrictive abortion laws, he explained that his organization takes a "step back" when it comes to abortion by focusing on the legal obstetric indications such as PPH and PAC. From a sales perspective, he said, his organization's hands were "clean" even if others were purchasing and using the drug for abortion. Zeinab, who worked for an international NGO in Senegal, described her activities related to misoprostol as "commercialization." She distinguished these activities from off-label utilization for abortion, which she acknowledged was happening among some health workers. Her job, was to market the drug, and to "keep a low profile" with respect to the country's abortion debate.

ACCESS: "THERE ARE MANY THINGS THAT STILL BLOCK WOMEN"

Despite global and national recognition of misoprostol as an essential medication for maternal and reproductive health, study participants who worked for NGOs identified significant barriers to accessing the drug in both public and private health sectors. Mariam, who worked for an NGO with activities in multiple Francophone African countries, explained: "It's still difficult for women to get misoprostol because of legal restrictions. There are many things that still block women." Jacques, who worked for the same NGO as Mariam, pointed out that "just because the product is in the country does not mean that it is accessible." This observation is relevant not only for women seeking the drug in the private sector, but also health workers in government health facilities. Ayo, who worked in Côte d'Ivoire, estimated that beyond large hospitals, less than 10% of public health facilities stocked the medication. In Senegal, a survey of obstetric care conducted between 2015 and 2016 showed that only 3.4% of referral facilities carried misoprostol (MSAS, CEFOREP, and UNFPA, 2017). Laila explained that despite misoprostol's integration into national norms and protocols, Senegalese midwives were more likely to have received MVA training for PAC, and that misoprostol training for PPH was still lacking.

One of the main barriers to obtaining misoprostol, despite its availability in pharmacies under various brand names, was the need for a prescription for a legal obstetric indication. Even with a prescription, Jacques pointed out that women may experience difficulty procuring the amount needed to terminate pregnancy. Misoclear, for example, is sold in packets with three 200 mcg tablets. To meet the recommended dose for up to 12 weeks of gestation, a woman would have to buccally, sublingually, or vaginally take 800 mcg (four pills) every three hours until expulsion (Ipas, 2020). This would require four packs of Misoclear. Requests for multiple packets of Misoclear at a pharmacy might raise suspicion, and prompt pharmacy workers to question clients about why they were purchasing this quantity (Mann Global Health, 2019). Alternatively, Jacques explained, the woman might visit several pharmacies to purchase one or two packs of Misoclear at each, an equally challenging process requiring additional time, transportation costs, and possibly multiple prescriptions.

Adja, who worked for an NGO in Senegal, believed that women's access to misoprostol depended less on prescriptions for legal obstetric indications than on health workers' willingness "to take the product and give it to women." Women relied on health workers for misoprostol because "it's health workers who have the power to get the product." Jacques agreed, saying, "there are nurses and midwives who are known for providing this kind of help. Often, it's a business. You do it off the records, and that's that." Laila, a midwife in Senegal, believed that misoprostol was mostly "controlled by doctors." Mariam explained that while obtaining misoprostol directly from health workers might increase some women's access to the drug, dependence on health workers also left women vulnerable to exploitation. Health workers may purchase a supply of misoprostol and "resell" it to women at a higher price. "This is the kind of dysfunction that comes out of all these restrictions," she said. "They'll buy it with their own money and then sell it clandestinely in the system."

Study participants' perceptions of the informal routes through which women obtain misoprostol resonate with ethnographic literature on abortion practices in SSA. In countries like Burkina Faso, Kenya, and Tanzania, women obtain misoprostol from multiple sources, including friends, relatives, health workers, pharmacists, and informal pharmaceutical vendors. While some health workers administer misoprostol directly, others dispense it to women and instruct them on how to use it at home. Women may obtain misoprostol from brick and mortar pharmacies with or without a prescription. Although many women seek misoprostol from health workers in the private sector, some health workers in government facilities may provide the service themselves, or refer women to a colleague. Women obtain misoprostol not only from skilled health workers, but also TBAs and other paramedical providers (Izugbara et al., 2015; Drabo 2019; Solheim et al., 2020; Ouedraogo and Juma, 2020).

Jacques believed that compared to urban women, rural women had less access to misoprostol and relied on "street" medication (also colloquially described as "Chinese" medicine because such pharmaceuticals may be produced in Asian countries like China or India). Ayo explained that for many women, street medication was much more affordable than misoprostol purchased at a pharmacy or through a health worker. "Instead of paying 5000 CFA francs for misoprostol, she can buy Chinese medicine for between 200 and 500 francs." Both Jacques and Ayo asserted that while such purchases might be more affordable, women faced the risk of encountering inauthentic drugs or receiving inadequate information related to dosage or gestational age, all of which could lead to complications. "In all of the Francophone African countries, we have these people who make these abortifacients available," Jacques said. "But what is the quality of that medication? What is the quality of the prescribed dosage? That's the problem. In these circuits you can often find good miso or bad miso, or drugs that are supposed to be miso but are not."

Jacques disagreed with people who pointed to the risk of complications as a reason to restrict misoprostol because women were "not ready" for self-medicated abortion. "It's not true," he argued. For him, the problem was the gap between pharmaceutical distribution systems and clients:

> Our pharmaceutical distribution system has completely missed its target. The environment has evolved, but our pharmacies and our distribution policies have not evolved. We wait for the client to come, thinking it's the client who has to come to us even if they are 100 or 120 km away.

According to Jacques, this gap between distribution policies and clients' needs essentially "abandoned" those populations who lived far from pharmacies to street medication.

DISCUSSION

Although SSA's maternal mortality ratio has reduced by 38% since 2000 (WHO, 2019d), the pharmaceutical revolution in

reproductive health envisioned by advocates of misoprostol has yet to materialize in Francophone Africa. Attention to how misoprostol's pharmaceutical regime is unfolding in this region reveals a great deal about the opportunities and limitations of pharmaceutical solutions to public health problems. Through its multiple "biographies," misoprostol has generated partnerships between transnational stakeholders invested in reducing fertility and maternal mortality. At the same time, misoprostol's abortifacient capacity complicates safe abortion advocates' relations with NGOs and national health authorities that receive support from donors like USAID. Abortion stigma may delay misoprostol's integration into national LEM, clinical protocols, and pharmaceutical supply systems. Demand for generic brands of misoprostol in the private sector does not necessarily translate into access for low-income and rural women. As an abortifacient, misoprostol's connection to neo-Malthusian logics of population control threatens the gains won by FP 2020 in revitalizing global commitments to fertility reduction.

Misoprostol's legal obstetric indications, PAC and PPH, firmly position the medication in harm reduction approaches to maternal and reproductive health (Erdman, 2011; Hyman et al., 2013; Kulczycki, 2016). This has enabled partnerships with USAID, an enormously influential donor in global maternal and reproductive health that accounted for over two thirds of family planning funding between 2003 and 2013 (Grollman et al., 2018). In Senegal, for example, USAID funded a study in 2009 to test the feasibility of providing misoprostol for PPH at the community level (Ortiz et al., 2010). In 2011, USAID awarded Child Fund, an NGO, a $40 million grant over five years to expand health care provision at the community level, including the provision of misoprostol for PPH by TBAs (Ennulat, 2016). Due to anti-abortion funding policies such as the Helms Amendment and the GGR, USAID neither supports national health authorities in procuring misoprostol supplies, nor does it permit its contracting agencies to purchase the medication. Similarly, USAID supported research, training, and programming related to PAC in Senegal, but would not support the procurement of MVA because it is an abortifacient (Curtis, 2007; Suh, 2021).

In 2017, President Trump extended the GGR to organizations that receive US funding for infectious disease (Singh and Karim, 2017). More than ever, study participants were keenly aware of the need to keep MA activities separate from national partners who received funding from USAID. Some stakeholders, however, have been heartened by the injection of non-US sources of bilateral support for MA (and safe abortion more generally) in the region. Others have called for new forms of partnership that fund MOH directly rather than international NGOs. These kinds of partnerships would strengthen the capacity of national governments to procure and distribute technologies (SAD, 2019b).

Misoprostol stokes enduring tensions related to professional authority over reproduction: who can use the medication, where, and for what purpose. The medication's safety and effectiveness in preventing PPH and PAC have facilitated its integration into LEM throughout Francophone Africa. Yet, study participants pointed to gaps in health worker training and medication supplies in national health systems in countries where they worked. To a certain extent, these gaps reflect continuing debates about the role of TBAs in obstetric care (MacDonald, 2020). At the same time, the informal dispensing of misoprostol by doctors, nurses, midwives, and pharmacists suggests that formal health workers are actively facilitating safer, albeit illegal, abortions.

Starting with the 1974 Helms Amendment, and followed by the 1984 GGR, anti-abortion advocates have actively shaped the terrain of global reproductive health funding and policy (Crane, 1994; Barot, 2013). Misoprostol may offer a new frontier of scientific intervention for global anti-abortion efforts. By framing misoprostol as a poorly evidenced, sub-standard form of care for PPH, these actors aim to restrict access to abortion. For example, Maternal Life International is a Christian organization that, in addition to providing emergency obstetric care in various African countries (and Haiti), promotes couple-based natural contraception. In a 2011 letter to WHO, the organization explicitly expressed its opposition to the use of misoprostol for abortion, suggested that the "real agenda" of "misoprostol advocates" was "not evidence-based obstetrical care but rather unregulated medical abortion," and affirmed that ethical medical care necessitates "a proscription against abortion" (WHO, 2011a).

Study participants were eager to harness commonalities across Francophone countries, such as a tightly organized pharmaceutical market and the prominence of Islam (SAD, 2019b), toward a regional approach to expanding access to misoprostol, and safe abortion more broadly. While many were enthusiastic about misoprostol's potential to transform the landscape of reproductive health care in the region, they also described it as an exceptionally challenging place to do abortion-related work. Some bemoaned the reluctance they perceived on the part of the regional OP and national health authorities to engage with safe abortion. They were careful to keep MA "separate from" any national organizations that received USAID funding. In contrast to countries like Ghana and India, where MA was "flying off the shelves," they believed the region's burdensome pharmaceutical registration system, coupled with widespread abortion stigma, hampered procurement and distribution of these drugs.

And yet, some of the abortion stigma framed as exceptional to Francophone Africa appears to be relevant in other countries. Maxine described Ethiopia as a place where the MOH was "open" to engaging with abortion. Since 2005, Ethiopia has permitted abortion in cases of rape, incest, fetal malformation, or if the pregnant woman is under the age of 18. A woman's "word" is considered sufficient to establish her age or that she experienced rape or incest (Blystad et al., 2019). The national society of obstetricians and gynecologists played a prominent role in advocating for abortion law reform (Holcombe, 2018). Yet, a 2016 study of legal abortion provision at public and non-profit facilities showed that despite a favorable political climate, health workers continue to struggle with adjudicating between legitimate and illegitimate requests for abortion (McLean et al., 2019). John, who worked on MA in Francophone Africa, revealed that in a previous position with an NGO in a southern African

country, he had been warned directly by the MOH not to cross the line into legal advocacy for abortion. In India, where medication abortion is permitted in certified health facilities up to seven weeks and misoprostol and mifepristone are widely available at private pharmacies (Boler et al., 2009), an estimated 67% of abortions are classified as unsafe (Yokoe et al., 2019). In Ghana, where abortion is permitted for several indications, a 2016 study in the capital city of Accra showed that only half of pharmacies stocked misoprostol, with pharmacies in less affluent neighborhoods less likely to do so (Ganle et al., 2019).

Despite these inconsistencies, the language of exceptionalism remains a formidable tool in constructing Francophone Africa as a place particularly in need of resources and attention related to population. Critical development scholar Betsy Hartmann argues that the current focus on reducing fertility in SSA hinges on racialized perceptions of African fertility as "distinctive and dangerous" (2014). Population interventions are predicated on the "exceptional" nature of high fertility in SSA, despite a wide variation in fertility rates throughout the continent, and the existence of similar demographic patterns in other parts of the world during historical periods characterized by high rates of poverty and inequality (Hartmann, 2014). The OP, which many safe abortion advocates perceive as a unique opportunity to harness regional synergies, is predicated on Francophone Africa's exceptional demographic indicators.

FP 2020 and regional offshoots like the OP are the most recent interventions in a longer history of population interventions in SSA. For example, in 1980, Senegal was the first country in SSA to receive a structural adjustment loan from the World Bank and the IMF. Release of the third loan during the late 1980s was conditioned upon the establishment of a concrete population policy with support from USAID, Pathfinder International, and UN Population Fund (UNFPA) (Robinson, 2017). More generally, countries in SSA with high levels of structural adjustment debt are more likely to have articulated population policies (Robinson, 2015).

While Maxine describes population and climate change as a "European concern," population and development scholars have traced the "securitization" of climate change and population as an American concern since at least the mid to late 2000s (Hartmann, 2014; Sasser, 2018). Scarcity in natural resources like land and water due to climate change fuels conflict, which in turn propels migration from SSA to the global North. In the post-9/11 War on Terror, the region's emerging identity as a recruitment zone for organizations like Al-Qaeda has provided an additional geopolitical rationale for the expansion of US military intervention into Francophone Africa. None of the study participants viewed misoprostol, or MA more generally, as a tool of population control in Francophone Africa. Instead, they understood misoprostol as an important harm reduction approach to addressing the problem of maternal mortality. Yet, donors in the global North (including USAID) have long cultivated an interest in abortion as a technological strategy in the solution of population problems. If abortion and contraception represent two sides of the same neo-Malthusian coin, misoprostol is flexible enough to achieve both of these "jobs" within overlapping regimes of global reproductive governance.

Along with magic bullet interventions that generate statistical measures of cost-effectiveness, twenty-first century global health approaches have incentivized engagement with the private sector. In Senegal, for example, international NGOs have contracted private logistics operators to supply government health facilities with contraceptives. By closely monitoring the private operators' performance in delivering and taking inventory of contraceptives, this approach endeavors to prevent contraceptive stock-outs in the public sector (Duclos et al., 2019). Some of my study participants were keen to harness the private sector to increase access to misoprostol throughout the Francophone region. Private organizations, with support from international NGOs, do the work of registering and marketing misoprostol and other MA drugs. They believed the presence of multiple brands on the market generated competition between manufacturers, thereby keeping prices affordable for consumers. Sales of misoprostol provide concrete evidence of demand in the Francophone region. In 2018, DKT International, an international reproductive health NGO, sold over a million packets of misoprostol in Benin, Cameroon, the DRC, Côte d'Ivoire, Mali, and Togo (DKT International, 2018). In this sense, the market is key to getting life-saving drugs "into women's hands."

Given the lack of evidence that neoliberal health reform in SSA has improved maternal health outcomes (Thomson et al., 2017; Sommer et al., 2019), it is remarkable that the misoprostol revolution would hinge on its location in the private sector. It should come as no surprise that study participants with direct experience with the public health sector were more critical of a privatized, pharmaceuticalized approach to reproductive health. Laila, Ayo, Jacques, and Mariam, all African nationals, described unequal distributions of reproductive health care between private and public health facilities, wealthy and poor women, and rural and urban women. Privatized distribution of misoprostol reinforced the marginalization of community-based health workers like TBAs upon whom low-income and rural women often depend for maternal and reproductive health care. Although multiple generic brands of misoprostol may be available for purchase in formal and informal sectors of the health system, the drug may be unaffordable for low-income women, or altogether inaccessible for rural women who live far from a pharmacy. Even if a woman is able to purchase misoprostol, she may receive inaccurate information about how and when to use the drug, and what to do if complications arise.

Studies from middle- and low-income countries show that low-income women in particular are more likely to receive inaccurate information about misoprostol or inauthentic medication (Footman et al., 2018). In turn, such women may be more likely to experience complications requiring PAC. Although PAC has been widely accepted as a harm reduction strategy for unsafe abortion, in many developing countries PAC services are limited in quality and availability, especially at lower levels of the health system (Owolabi et al., 2018). In countries like Brazil (Zordo, 2016), El Salvador (Oberman, 2018), Senegal (Suh, 2021), and the United States (Eckholm, 2015), PAC serves as a doorway to criminalization if health workers suspect that a patient has illegally terminated pregnancy. Maternal mortality reduction strategies that prioritize access to drugs like misoprostol may thus exacerbate inequalities in

reproductive health outcomes and experiences among the very populations they aim to serve.

As a feminist advocate of reproductive justice, I support access to technologies like misoprostol that *empower* women through granting reproductive autonomy in contexts where legal abortion is highly restricted, and *benefit* them by reducing the risk of obstetric complications and death (Layne et al., 2010). Attempts to restrict misoprostol to "protect" women in SSA from the dangers of sub-standard care outside of hospitals conveniently overlook profound inadequacies in obstetric care in health facilities. As lockdowns and other disruptions related to the global Covid-19 pandemic have threatened access to health care worldwide, it is more important than ever to ensure women's access to life-saving drugs like misoprostol (Kumar, 2020). At the same time, privatized approaches to reproductive health amplify broader inequalities in access to resources according to age, gender, geography, and race. Neoliberal discourses of empowerment and self-actualization through rational consumption of health services or goods such as family planning or facility-based delivery obscure the gendered and racialized anti-natalism of twenty-first century approaches to maternal and reproductive health (Bhatia et al., 2019; MacDonald, 2019). While the presence of misoprostol in pharmacies and hospitals increases access to safe reproductive health care for those who can afford the drug, it also abandons the most vulnerable women to cope with discriminatory abortion laws and under-resourced public health systems while aspiring to responsible reproductive behavior.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Brandeis University Institutional Review Board and the Ministère de l'Enseignement Supérieure, de la Recherche, et de l'Innovation in Dakar, Senegal. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

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

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Filtering Inequality: Screening and Knowledge in Senegal's Topography of Hepatitis B Care

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Only a fraction of the estimated tenth or so of Senegalese who are chronically infected with hepatitis B virus (HBV) have been diagnosed. Of these, few have been assessed for their risk of progressing to potentially fatal liver disease (indicating need for treatment), and fewer still are taking antiviral drugs. A massive gap between those needing and getting treatment is widely acknowledged among experts. But given that HBV and its biomedical treatment options are largely invisible in bodies, health data, care practices, public messaging, or mass media, how can we observe, ethnographically, the effects of constraints on and inequalities in treatment? What are the stakes of access to drugs, when this access is not being sought out, claimed, or enacted? This article tackles these questions by examining how HBV is being enacted in Senegal, but not necessarily in relation to antiviral treatment. I first describe the emergence, over the past decade and a half, of an exclusionary topography of HBV diagnosis and treatment. I introduce the notion of "filtration" to describe the effects of this topography on the formation of potential "subjects of access." The diagnostic therapies and expertise required to determine need for treatment are expensive, urban, and largely privatized. Moreover, knowledge about HBV and its possibilities of care circulates in narrow and sparsely distributed channels. Only a tiny minority of persons are effectively "filtered into" care, while issues of access remain largely outside of public debate. I then move onto small-scale efforts, led by rural primary health workers and community associations, to raise awareness of and expand screening for HBV. Those driving information and screening either do not reveal that effective drugs exist or locate these beyond the reach of most of their audiences or patients. Why then do they do it? I examine the logics and effects of their work to identify the forms of inclusion, care, efficacy, and explanation these open up. At the same time, I seek to discern the indirect effects of unequal access to knowledge and resources in the ambivalence, uncertainties, and contradictions that pervade these efforts to inform, diagnose, and advise.

Keywords: Senegal, Hepatitis B, access to treatment, inequalities in access to healthcare, ethnography

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INTRODUCTION

"We have accessibility," said an infectious disease specialist as she opened the hepatitis B virus (HBV) session of a 2019 research meeting in Dakar. Quickly, she caught and corrected herself: "well, in any case, availability."

This slip states a seemingly obvious point: drugs "being there" is not the same as drugs getting to all those who need treatment. But how are we to identify those whose lives are marked by the gap between available drugs and their accessibility as HBV treatment? Public health discourse generally assumes that the potential subjects of HBV treatment are *already* out there, even if they are asymptomatic, as chronic HBV infection often is. They need only to be diagnosed. Identifying virus carriers requires a serological test for hepatitis B surface antigen (HBsAg). Not all carriers, however, are or will *ever* get sick from their infection. Current consensus is that only those at higher risk of developing severe, usually fatal cirrhosis and cancer should be treated. Identifying these treatment candidates requires further diagnostic testing and interpretation of viral activity, liver damage, and other indicators of risk.

Population infection rates estimated from sample surveys suggest that the majority of the world's HBV carriers are not diagnosed or linked into care, that is, effectively referred for treatment eligibility assessment followed by prescription and/or monitoring. Global advocacy for access to HBV treatment, which has emerged in and around the World Health Organization (WHO) and World Hepatitis Alliance (WHA) in the past decade, has focused on improving and demonstrating the feasibility of large-scale screening and assessment in resource-poor settings, where most HBV carriers live. Although drug prices and supply certainly remain a concern, the wide availability of generic antivirals for HBV (notably tenofovir disoproxil fumarate) has shifted attention to diagnosis. The experts convened to develop and review the WHO's first treatment guidelines, published in March 2015, focused in particular on developing diagnostic pathways that bypassed the high-cost equipment and expertise—including HBV-DNA quantification (i.e., PCR-dependent viral load testing), liver ultrasonography and specialist consultations—on which assessment protocols used in high-resource settings depend (WHO, 2015). The WHO also issued recommendations on screening strategies in different epidemiological settings, included where infection is widely distributed across the "general" population rather than concentrated in "high risk" groups (WHO, 2017). For public health, disparities between the massive number of people assumed to be infected and the much lower numbers who are screened, referred, and treated pose problems of *efficacy* (unprevented future morbidity and mortality) and of *equity* (exclusion from potentially life-saving treatment).

For ethnography, however, the scarcity of HBV diagnosis also poses a methodological problem, especially given the variable and delayed perceptibility of an infection that often remains asymptomatic or only vaguely symptomatic for most or all of carriers' lives.

Who are the potential subjects of HBV treatment, and how are they constituted as such? Where can we locate the gap between available treatment and its accessibility to those who have not or only partially been constituted as its subjects? How does this gap manifest around the limited and uneven presence of embodied and diagnostic knowledge as well as public communication and debate about HBV infections, pathology, and care?

In Senegal, HBV screening is performed systematically and for free only to donated blood,[1] although it is also part of the standard bundle of prenatal tests and thus is increasingly offered for a fee to pregnant women across the country. The equipment and expertise needed to assess treatment eligibility are concentrated in urban areas and are mostly available through private practice and test sites, or fee-paying services in teaching hospitals.

Moreover, public talk about HBV and its treatment—as advocacy, health messaging, or news coverage—is sparse. "Awareness-raising" has been small in scale as well as episodic. Examples include media coverage of a few, high-profile conferences on hepatitis held in Dakar as well as of annual "World Hepatitis Day" events. There are also occasional hepatitis-themed features or episodes, many serving as publicity for "neo-traditional" healers, on radio, television or internet channels. There have been no mass campaigns to inform that HBV infection is very common among unvaccinated adults (more than one in ten for those born before 2005) and can lead to fatal disease. Nor is information widely available about how and where HBV infection can be diagnosed, assessed, and treated. A qualitative study in rural Senegal found that only a third of nonexperts had ever heard of "Hepatitis B" (Boye et al., 2020). This study, and other questionnaire-based research, also points to gaps in the knowledge of healthcare practitioners such as nurses and generalist physicians, (Lawson et al., 2017; Jaquet et al., 2017a, b; Djaogol et al., 2019), suggesting a lack of investment in training. Many are thus unlikely to prescribe screening tests or refer for assessment.[2] In 2019, many experts in Senegal questioned the robustness of available seroprevalence data, and viral hepatitis was just being integrated into the national disease surveillance and reporting system. HBV thus has limited visibility not only as a bodily experience and as a test result, but also in clinical training, advice, and practice; in epidemiological data; in public health messaging; and in media coverage.

Given this invisibility, how is it possible to engage with inequalities in access without assuming that its potential subjects are "already out there," existing biologically by their (undiagnosed) viral infection and immune response? In this article, I propose to begin, empirically, by examining how HBV is being enacted in Senegal but *not necessarily as a*

[1]Blood for transfusion has been screened in Senegal since 1982 (Programme National de Lutte contre les Hépatites, 2018).

[2]Specialists complain about "ignorance" among lower-tier health workers, while some of the latter, I have found, report feeling inadequately trained. I heard of (and from) persons diagnosed as HBV positive who were told there was not biomedical treatment for HBV and referred for nonbiomedical care or, as will be detailed below, were given only dietary advice. Similar findings are reported for Burkina Faso by Giles-Vernick et al. (2016).

condition for antiviral treatment. I focus on the practices that bring HBV into being an object of knowledge and care in three types of settings, which form the core sections of this article: urban specialized HBV care, where treatment eligibility assessment followed by prescription are offered; the screening and advice provided by primary healthcare workers in one rural district; and two sets of "grassroots" initiatives to create collective awareness about HBV.

METHODS AND APPROACH

This article is based on fieldwork I conducted in Senegal in 2019. My broader research project concerns how aetiological knowledge about liver cancer has been produced and deployed in West Africa from the 1950s to the present. Given that chronic HBV infection was shown to be a risk factor in the 1970s–1980s and that antiviral drugs are, since the late 1990s, recognized to prevent infection-induced liver damage (cancerous and cirrhotic), my research included an ethnographic focus on HBV care in Senegal.

The three core sections of the article draw, respectively, on interviews and conversations with HBV specialists and experts; primary healthcare (PHC) workers in the rural health district of Nioro; and laypersons active in HBV screening and communication. The first group comprises approximately 20 internists, gastroenterologists, infectious disease specialists, epidemiologists, and virologists, mostly based in the capital city of Dakar. This covers a significant portion of the persons actively involved in HBV research and care in Senegal. I also attended several meetings on HBV care and research as well as conducted an extensive review of published research, policy documents, and media coverage. In February-March and July 2019, I spent four nonconsecutive weeks in Nioro, which is located in south-central Senegal between the regional capital of Kaolack and the Gambian border. I selected it on the basis of anecdotal reports of high liver cancer incidence, as well as its association with peanut consumption and farming given the identification of aflatoxin, a common contaminant of peanuts, as a cofactor of liver cancer. I interviewed 25 primary healthcare workers, including 11 nurses who managed village-level health posts (*infirmier chef de poste*, or ICP), 4 retired ICPs who had opened private clinics, and 10 midwives. A research assistant, Aissatou Diouf, was present during some interviews and participated in discussions. I also spoke with a range of other health actors at community, district and regional levels. Finally, I sought out and interviewed individuals who I heard had initiated HBV information and screening activities.

The interviews were semistructured and covered the history, practices, itineraries, landscape, and challenges of care provision for patients with HBV infection, liver cirrhosis, and cancer. They were either recorded or extensive notes were taken. All informants were provided with written and oral information about the project and gave explicit consent to participate and for interviews to be recorded (or not) and cited. Research authorization was also obtained in Senegal at national, regional, and district levels. Participants are systematically anonymized in this article, except for public figures who also agreed for interview content to be cited.

The Ethnography of Access to Treatment in Africa: Visibility and Inequality in HIV and HBV

Access to treatment has been a core focus of the anthropology of HIV/AIDS in Africa. From the late 1990s to the mid-2000s, antiretroviral drugs (ARVs) were available in limited quantity through private and personal channels, as well as in research trials and pilot treatment projects. Anthropologists revealed the effects, not only on bodies and survival, but also on social relations, political debate, and moral deliberation, of these uneven provisions and of the inequalities they generated. Nguyen (2010), for example, traced how, in Burkina Faso and Côte d'Ivoire, the performance of HIV-positive identities through associational involvement and public testimonials enabled some to gain access to scarce drugs, yet also gave rise to collective claims to treatment as a right based on a biological condition. At a moment when ARVs were getting cheaper in Uganda and being piloted in treatment programs, yet remained beyond reach for the majority, Whyte et al. (2004) described how unequal access created moral dilemmas and social tensions in clinical practice, family relations, and public debate. Desclaux et al. (2002) and Desclaux (2004) observed the effects of drug fees on patients enrolled in Senegal's pioneering public treatment program. They noted that even subsidized and sliding rates created inequality at two levels: in the affordability of treatment and in the burdens that finding money for treatment imposed on patients, who had to disclose their status in order to activate solidarity networks.

This body of work is rich in insights about the politicization of access and the subtle tensions and fault lines that treatment inclusion and exclusion can (re)produce. Such insights can guide the questions we pose about access to HBV care in Africa. Yet there are important differences in how HIV and HBV have been made visible as a threat to bodies, lives, and society, and as being treatable by antiviral drugs (even though some of the same molecules are used against both viruses). The prospect of ARV treatment increased and modified the visibility of HIV, for example through test uptake and disclosure of status. Yet ARVs entered into landscapes where HIV/AIDS had already been given a palpable presence through, for example, rumors of suspicious deaths (Fassin 1994), prevention campaigns that figured mass education and screening (with counselling, see Whyte et al., 2018), and patient associations, testimonies, and activism (Robins and Lieres, 2004; Nguyen, 2010).

Around what kinds of visibilities of HBV infection and care can we observe the effects of treatment (in)accessibility and its inequalities? There have been few qualitative or ethnographic studies of HBV in Africa (or elsewhere), with the exception of revealing but nonextensive studies in Côte d'Ivoire (Pourette and Enel, 2014), Burkina Faso (Giles-Vernick et al., 2016; Giles-Vernick and Hejoaka, 2020), Cameroon (Chabrol, 2018, 2019; Chabrol et al., 2019), and Senegal (Boye et al., 2020). These point to the challenges to access posed by the high cost of further HBV

care and lack of knowledge about HBV among both laypersons and health workers. They also show that the limited spaces and moments when HBV is made visible, for example when a diagnosis is made after blood donation, are located within topographies and trajectories marked by uncertainty about the meaning of infection and its invisibility as a collective presence (especially Giles-Vernick and Hejoaka, 2020; Chabrol, 2018, 2019). Building on this work, I seek to discern the *indirect* effects of the limited visibility of HBV and of access inequalities on broader (but far from universal) provisions of HBV diagnosis, information, and care.

I begin by mapping out the equipment, drugs, and expertise through which antiviral therapy is provided in Senegal. Yet I also attend to how the privatization of both specialized HBV care and communication limits the visibility of treatment beyond the narrow, urban, and exclusive circuits through which drugs and eligibility assessments can be accessed. In the following two sections, I turn to spaces where screening tests are performed, namely, in rural primary healthcare and through community action, but generally *not* in view of initiating trajectories into specialized assessment and treatment. Rather than dismissing testing without "linkage to care" as a therapeutic dead-end, as a public health perspective might, I propose to attend to these efforts as enactments of HBV with their own logics and effects. These open up unexpected forms of inclusion, care, efficacy, and explication that bypass inaccessible assessment and treatment. At the same time, these efforts are shaped by uneven distributions of information about HBV and other resources for care, and some of their actors are troubled by the restrictions on access to treatment they know or suspect lie beyond.

RESULTS

A Historical Topography of "Availability"

Most specialists trace the first expansion of HBV treatment in Senegal to a trial, "HEPADAK," initiated in 2003. Subjects were provided with access to manufacturer-donated lamivudine.[3] Before this, a handful of Senegalese purchased the less effective pegylated interferon abroad or in downtown Dakar, at the country's best-stocked private pharmacy. HEPADAK subjects were enrolled by specialists in four Dakar hospitals and private clinics (Vray et al., 2006), who were referred as HBV infected individuals by major blood banks. Confronted with difficulties in using biopsy to assess liver damage, project researchers negotiated additional funding to purchase and evaluate a trademarked liver ultrasonograph, a portable and noninvasive imaging technology, in Dakar (Mbaye et al., 2011). After the trial, the machine was made available at a cost to patients of 60,000 CFA/106 USD per test (until it broke down).

Trial researchers and the funder, a French public research agency, were committed to ensuring posttrial access to lamivudine. Negotiations with the Ministry of Health and National AIDS program allowed HBV patients to "dip into" donor-purchased stocks of HIV drugs, switching from lamivudine to tenofovir (both used for HIV) in 2010.[4] That such an arrangement was possible suggests that the number of individuals in specialist HBV care was low at the time and grew slowly afterward. The availability of HIV drugs for HBV patients does not seem to have been widely advertised (one specialist assured me it was not "a secret," but others noted the need to avoid donor scrutiny). In any case, even if the drugs were free, a full assessment of treatment eligibility cost, before 2014, upward of 150,000 CFA/264 USD, with tests to be repeated every six to twelve months for monitoring.[5] By 2014, however, HBV patients were blamed for causing ARV stockouts (Dakaractu, 2014). Still, as late as the end of 2017, it was estimated that only 893 individuals were taking drugs for HBV in Senegal (Programme National de Lutte contre les Hépatites, 2018).[6]

The cost of HBV treatment was briefly but forcefully put in the spotlight in the Senegalese media in 2011–2012. Having focused on vaccination since 1998, the country's pioneering National Hepatitis Program (PLNH), established by Aminata Sall Diallo, organized a high-profile pan-African meeting in Dakar to mark the first "World Hepatitis Day" in July 2011 (Sall Diallo, 2018). The conference issued a collective call to action, the "Appel de Dakar," which, notably, pleaded for drug price reductions (Sall Diallo, 2012). Sall Diallo also encouraged an articulate former soldier, Ibrahima Gueye, to speak out about his struggles to pay for treatment (e.g., Diatta, 2015a) and to form the patient association *Saafara Hépatites* in late 2011. Speaking to the media, which gave wide coverage to PLNH-organized 2012 World Hepatitis Day events, Sall Diallo and Gueye denounced the "excessive," "out-of-reach" and "horribly expensive" price of HBV drugs (e.g., RTS 2012; 2STV 2012; Senewebdirect 2012). However, the figures they gave were for pegylated interferon, which Gueye had been prescribed because of a coinfection with HBV (hepatitis "delta," a virus that requires HBV to replicate), and which was sold only by the best-supplied private pharmacies for 159,000 CFA/280 USD per week (a full course lasting a minimum of 48 weeks). They did not mention tenofovir, which was available in generic form, nor the

[3]Lamivudine was the first reverse-transcriptase inhibitor which, after being routinely used in HIV treatment, was approved for the treatment of HBV (by the FDA in 1998). It was welcomed as a significant improvement over pegylated interferon, which was only effective in some patients, administered by injection and reputed for painful side effects.

[4]Tenofovir disoproxil fumarate, initially commercialized as Viread, was approved by the FDA to treat HIV in 2001 and to treat HBV in 2008. Many patients treated with lamivudine developed drug-resistant HBV infections, so tenofovir was quickly adopted as the drug of choice.

[5]One hospital specialist told me, however, some patients presented with clinically evident cirrhosis and could thus be put on free antiviral therapy without further testing.

[6]The same document reports national prevalence rates of chronic infection at 9–11% (out of a population of about 15 and a half million). Even if only 5–10% of carriers require treatment, this suggests that only a tiny portion of these—or indeed, of those who test positive every year through blood donation screening (8,757 in 2017)—are accessing it.

fact that some HBV patients were already obtaining these from the HIV program.

Meanwhile, around 2012, the PROLIFICA study, which was the first to evaluate the feasibility of large-scale test-and-treat strategies in Africa with a view to informing strategies and advocacy for expanded access, was launched in various sites (Allain, 2016; Howell et al., 2016). One of these was Thies, a regional capital just over an hour's drive (without traffic) from Dakar. Unlike HEPADAK, which had collected subjects through existing, limited channels of diagnosis and care, PROLIFICA set up "community" screening in workplaces and villages. It also brought some diagnostic services and drug distribution beyond the capital, notably setting up a second liver ultrasonography machine (Touré et al., 2017; Cohen et al., 2019). Patients outside the trial could be assessed with the latter for 10,000 CFA/18 USD. The number of trial subjects enrolled, however, was relatively low: in 2019, a researcher spoke of a follow-up cohort of 460.

HBV-DNA testing capacity was set up in Dakar in 2013 or 2014. One machine was obtained by a military pharmacist, involved in research, who told me he had witnessed the "suffering" of patients from the high price and long wait associated with shipping samples for testing in France. So, he told me, he approached a PCR manufacturer and pleaded with them: "I'm passionate about hepatitis B, but [you] have to help us, give us the apparatus." They did, but operating costs, he says, mean he needs to charge 25,000 CFA/44 USD per test in the semiprivate lab he runs. Around the same time, the Dakar Pasteur Institute, a research institution that also provides private diagnostic and vaccination services, began offering HBV-DNA tests for 35,000 CFA/62 USD. In late 2016, the regional rep of a major European diagnostics firm announced the donation of a molecular testing platform (said to cost 120 M CFA: Diatta, 2016) to the Bacteriology–Virology Laboratory of *Hôpital Le Dantec*. The rep explicitly framed this as a private initiative to fill an accessibility gap in partnership with the public sector and was able to negotiate a price of 15,000 CFA/26 USD per test (he hoped subsidization would reduce this). In the first months of 2019, however, testing had stopped due to a reagent stockout. I heard that the rep held a monopoly on the supply of kits specific to the donated apparatus and had been too busy with politics to renew the order. At one meeting I attended, this donation-supply arrangement was criticized not only for failing HBV patients, but also for bypassing public procurement rules.

Even with these price drops, viral load testing is still seen by Senegalese experts as, in their words, the "bottleneck" or "Achilles' heel" of HBV care. This is generally the case in low-resource settings. Avoiding viral load testing, as well as expensive liver assessment such as ultrasonography, was an explicit goal in the development of WHO treatment guidelines (WHO, 2015). This reflected an explicit prioritization of a "public health approach" by which viral and liver assessment can be scaled up through simplification of tests and criteria and standardization of decision-making algorithms so that they can be used by nonspecialists.

Following this lead, the PNLH organized a meeting of Senegalese HBV experts circa 2015 with the goal of agreeing on a "national consensus" on testing, referral, and assessment protocols. This would enable the decentralization of HBV care beyond Dakar and major urban centers. By all accounts that I heard, the process failed. Some told me tensions arose between clinically oriented internal medicine specialists accustomed to working in hospital and private settings and infectious disease specialists who advocated for a public health approach modelled on HIV treatment. Whatever the reason, several meeting participants told me no agreement had been reached. A "national consensus" was published by the PNLH as a booklet but was never distributed (few knew of its existence).

In 2019, I heard many HBV experts in Senegal express doubts about the extent to which "gold standard" diagnostic assessment (such as used in high-resource settings) could be simplified and cost reduced. Many said they tried to "adapt," but that, as one hospital specialist exclaimed: "there are norms!" Some specifically questioned the WHO's "no-viral-load" criteria, which they thought would miss too many patients who needed treatment (see also Béguelin et al., 2018; McMahon and Dusheiko, 2018). Interviews, and the test prescriptions I have seen, indicate that most Senegalese specialists consider viral load measurement to be essential and that they often request a long list of both routine and harder-to-obtain tests. The cost of these tests adds up quickly: Gueye estimates a full assessment can cost from 100,000 to 300,000 CFA/175 to 350 USD, while the PLNH gives lower figures of 45,000–80,000 CFA/78–141 USD, probably for a "simplified" assessment (Programme National de Lutte contre les Hépatites, 2018).

In 2017, public drug procurement specifically for HBV treatment became operational as a result of negotiations between HBV specialists (including the PNLH) and the national pharmacy. The availability of this "HBV" tenofovir and its subsidized price of 5,000 CFA/9 USD for a month's supply was, as reported in a brief newspaper item, announced by the Minister of Health "on the sidelines" of a ceremony for the reception of four donated ambulances (Ndieng, 2017). I did not see any posters, pamphlets or webpages, whether in health facilities (including the national blood transfusion center, where many get diagnosed) or the PNLH website, providing information on where to get HBV tests, consultations, or drugs. Thus, persons diagnosed as HBV-positive are dependent on referrals to specialists (and on the information these specialists will then give them) and on personal networks. I came to participate in these by advising acquaintances who tested positive for HBV, but who had not been told where or why to obtain further care. Some may learn about *Saafara Hépatites* from the news, a specialist or the hospital blood bank with which the association works. Gueye, who has parted ways with the PNLH, fields frequent calls from patients who have not been told where to get various tests, what they are for, or what the results mean. He tries to keep up to date on test prices, drug stocks, and equipment breakdowns. Specialists say their HBV caseloads are growing due to increase in referrals from blood banks as well as, more recently, from prenatal care providers. I asked one whether he thought the availability of medicines was drawing people into HBV care. "No," he quickly answered, "I don't think people know."

In meetings and interviews I attended, the cost to patients of antiviral drugs was *not* a major topic of conversation. A couple of specialists admitted that it was still high "relative to incomes," and that a handful of patients resented the shift from free to fee-paying drugs. Most, however, insisted that patients were "willing

to pay" out of fear of getting liver cancer (a painful and rapidly fatal condition some may have witnessed in kin and neighbors). By contrast, I heard many express concerns about the lack of "communication" or "awareness-raising" about HBV. Some criticized the PNLH in private for its failure to do mass awareness-raising and screening, as well as to decentralize HBV care (beyond Dakar). Gueye has, in recent years, been openly critical of the program and of Sall Diallo's autocratic leadership: "there is only her," he said on TV (Dakar Matin, 2018; see also: Diatta, 2018). In response, Sall Diallo (2018) published an open letter detailing the program's history of tiny budgets (currently at 27 M CFA/48 K USD, and only 36 M CFA/63 K USD at its highest point).[7] This is the reason, she explains, why she has been forced to do all the "communication" herself: "to the extent that (my) image has been systematically associated with the fight against hepatitis in Senegal." In an earlier interview (Diatta, 2015b), she pointed out that donors fund mass communication about HIV/AIDS, malaria, and tuberculosis but not hepatitis. Because of this "global health governance," she has been left on her own to communicate about hepatitis "on television, on the radio, speaking to the written press. You all know me through these media." Thus, she implies, only the diseases that donors identify as priorities can become, through mass action, matters of public health. Meanwhile, her underfunded program and its target diseases remain associated with a thin and highly personalized presence in the public arena.

Colleagues in Senegal familiar with the history of HIV activism are mystified by the absence of vocal demands for free HBV care. But this lack of mobilization may, at least in part, be a product of the topography of care that has emerged from fragmented research, personal, and commercial initiatives and in the absence of public strategies and channels for distributing knowledge (from education about infection risk to systematic screening and referral practices) about HBV and HBV care. In this topography, potential subjects of HBV treatment are constituted, or not, by being "filtered" into or out of narrow circuits of care.

I propose filtration as an extension of Nguyen's use of triage (2010) to describe the paradoxical effects of limited ARV provision, whereby humanitarian efforts to "save lives" sort out those who may live from those left to die. Triage describes the selective allocation of scarce technologies (diagnostic and therapeutic), which, in the case of HBV care, is underpinned by the combination of high cost, urban concentration, and privatization. Some services are offered in private clinics and labs, while even in public institutions, patients are expected to bear a large portion of the costs of tests (which often depend on commercial technologies) and drugs, a fact that specialists largely accept as the normal state of affairs. By introducing filtration, I also want to draw attention to the additional, or rather amplifying, effects of sparse and uneven distributions of information and knowledge about HBV, whose channels are also, in a way, privatized. Communication about HBV is, due to lack of funding for awareness-raising, training, or even patient orientation, concentrated around public figures such as Gueye and Sall Diallo, or left to the initiative of individual practitioners. It is therefore highly personalized and small in scale. The result is that neither scarcity nor its modes of rationing have become topics of public or professional debate.

Filtration is a mediated process, in which potential subjects of treatment, their kin and clinicians, give advice and make decisions on the basis of incomplete and heterogeneous knowledge of the stakes of infection and the possibilities of care. In this mediation, obstacles such as cost, distance, and lack of knowledge are difficult to clearly delineate and may be impossible to disentangle. Some who may be able to arrange, even if at considerable sacrifice, to pay for lifesaving drugs are uninformed of their condition or of how it can be managed. Practitioners, some of whom are poorly informed about available treatment options, may selectively mete out such information to avoid futile, interrupted quests for care. What does seem clear is that filtration increases the likelihood that those to whom drugs are eventually prescribed—after having been successively filtered into care by screening, persuasive and well-informed referral and full assessment, as well as ability to pay and travel—will in fact be willing to pay for them. Meanwhile those who have been filtered *out* of care and who have not been (fully) enacted as subjects of treatment (or even of HBV) are unlikely to demand access or to criticize its inequalities. In the following section, I examine how filtration is initiated at points of primary healthcare, in a rural area where HBV screening tests are expanding yet very few are referred for assessment and treatment.

Lateral Care

"I like hepatitis B too much!" exclaims Dr. T. "I mean I like the follow-up of hepatitis B, not," he clarifies, laughing, "the patient." Dr. T. is not a doctor but the nurse who heads a rural health post (ICPs are commonly addressed as "doctor") in the district of Nioro, which is near the Gambian border and whose main town is about an hour's drive from the regional city of Kaolack. He is describing his plan to set up a system to register and monitor his HBV patients, as he did for diabetes and hypertension. He also describes previous HBV initiatives.

In 2013–2014, during a community health education project for malaria, he "integrated"—a deliberate term of contrast with "vertical" disease-specific actions—hepatitis B (alongside diabetes and hypertension) in a series of public events such as conferences and plays. As the demand for HBV screening increased, Dr. T., again as a "personal initiative," procured a stock of rapid tests for his health post from the District Health Centre's Laboratory. He also organized blood drives, primarily as an HIV-screening strategy—which the district mandated each post to develop—but with the knowledge donor blood would also be tested for HBV.

Among Nioro's PHC workers, Dr. T. appears as exceptionally enterprising; the only one to report having organized information and screening events (although another midwife-ICP pair said they had planned similar activities). Yet he was not the only one

[7]By contrast, HIV/AIDS control received 10–14 billion CFA per year in 2013–2018, of which about a third was managed by the national AIDS program (and a quarter to a fifth contributed by the Senegalese state, the rest made up of donor funding) (annual reports available on: https://www.cnls-senegal.org). Budgets for malaria control were of 18 billion CFA for 2016 and nearly 13 billion for 2017 (http://www.pnlp.sn/wp-content/uploads/2016/08/PNLP_PSN_VFF_03-02-2016.pdf).

to be concerned about HBV. HBV screening is increasing in the district, as a result of occasional blood drives organized by youth or religious associations and its recent routinization in prenatal testing. The high proportion of positive results has made the infection visible as a public health problem to many PHC workers.[8] Most ICPs have also experienced the heavy emotional burden of diagnosing or providing end-of-life care to patients with advanced liver disease. This explains, in part, why some ICPs, like Dr. T., are keen to expand screening and some midwives think it is important to persuade women to pay for a prenatal HBV test. But where does screening lead? Below I describe how practitioners, in their words, advise patients who test positive. I first examine whether and how they refer for further care, noting, in particular, their expressions of *ambivalence* about the uncertain benefits, or the high costs, of additional consultations, testing and treatment. Instead of, or alongside, referrals, PHC workers nearly always provide advice for self-care, mainly through diet. I explore this dietary advice as a form of *lateral care*, a term of contrast with the public health model of a "continuum of care"—from screening through referral, further assessment, treatment, and/or monitoring, or palliative care—that supposes a linear trajectory organized around access to diagnostics and drugs. Nonreferral and dietary advice are lateral in the sense of eschewing options that PHC workers are either poorly informed about or know to be unaffordable to the majority of their patients. Yet they also manifest preventive logics anchored in situated understandings of available resources, social relations, emotional care, and liver cancer aetiology. In concluding this section, I reflect on how lateral care both responds to and reproduces inequalities in patients' capacity to treat HBV.

Referral Ambivalence

The prospect of antiviral treatment figures ambiguously, alongside the therapeutic power of diet, in Dr. T's advice to those who test positive:

> N.T.: . . . what do you tell people to convince them that it's important to do the follow-up. . .?
>
> Dr. T: Well! *It depends*, eh, it depends . . . on age . . . on sex too, it depends on the patients you have. Because there are people who are educated, who know something about it . . . but for others . . . you tell them clearly that there is a disease inside you, well, sometimes . . . it can manifest itself, but *it can also not* . . . we explain to them, the treatment how it goes, the diet you need to follow . . . *Especially the diet, because sometimes there is a lack of means, with respect to the correct treatment*. . .
>
> [. . .]
>
> N.T.: And you tell them that in some cases it's possible to treat, that there are medicines. . .?
>
> Dr. T: Yes, of course, of course! Because there are people even if they haven't had treatment . . . *well it's a treatment*, in quotation marks, who just followed a diet and were ok. Well, I don't know if it was the test that wasn't . . . well or not, but there are people who followed a diet and who came back with a negative test [repeats this several times, as if this is amazing but true]. And, well, those people, we consider them to be cured. There are also people who follow another treatment . . . an antiviral treatment, who do their viral loads to see the evolution of the disease. There are really advances concerning treatment!" (emphasis mine)

Although he seems to identify antivirals as the "correct treatment," Dr. T. concedes that this option is not open to all chronic carriers. Conversely, he describes "diet" as effective, but also as a fallback for when "there is a lack of means." What he is hinting at here, I think, is that he modulates how he communicates the stakes of HBV as part of sorting out candidates for referral for treatment, from the rest, for whom, playing on the uncertainty of HBV effects, he reassuringly insists that the virus may never "manifest" at all and that diet is therapeutic. Another ICP, Dr. P., is more forthcoming about how he tailors his advice:

> "You know, when you're in front of a person, an intellectual, the way of communicating differs from [that] with an illiterate person . . . you can confuse a person. Us, we know the quality of the person in front of us . . . with illiterate people . . . they don't get nuance, and when you explain certain things, it makes them scared, it terrorises them, they fear death . . . it's very complicated!"

His tone here is admittedly patronizing, suggesting doubt in the intellectual as well as emotional capacity of the "uneducated" to handle the implications of HBV infection. But for Dr. P., as for Dr. T., differential ability to "understand" HBV seems to be tangled up with unequal ability to pay for follow-up care. As Dr. P. also put it: "*some* understand very well, and *sometimes* have the means to go get followed up" (emphasizes mine). Dr. D., a former ICP now in private practice, describes himself as the most energetic and successful HBV referrer in the district. He is adamant that persuasive referral depends on conveying just how high the stakes of infection and treatment are: "I tell [them] if you don't treat, you will have cancer . . . I don't mince my words [*je ne lésine pas sur les mots*]!"

These three ICPs are the only PHC workers who told us that they refer at least some HBV positive persons to the regional hospital in Kaolack specifically to be assessed for antiviral treatment. They seem better informed than others: they know treatment is available, but also that it entails frequent travel to the city and expensive tests. Some of their patients may be able to afford this, and, indeed, it is notable that they practice in some of the district's larger towns, serving populations among which some can be described as members of, or have close connections to, a religious, farming, or political elite. Though none of these ICPs explicitly stated that they referred some but

[8]Some ICPs, however, did not report administering HBV tests or advising carriers.

not others, Drs. T. and P. are quite clear that they selectively provide the information by which patients can be *persuasively* referred. This information is not only complex but also, as Drs. P. and D. insist, emotionally charged. By juxtaposing ability to pay for treatment with capacity to understand and handle the stakes of HBV, Drs. T. and P. may be hinting that they judge the latter as a proxy for the former. Yet they may also be implying that informing patients who cannot afford treatment about the potentially fatal outcomes of infection and the availability of lifesaving drugs would *create* a situation of cognitive and emotional incomprehensibility. Selective referral may thus be a manifestation of ambivalence about initiating trajectories into further care amid widespread poverty and lack of communication about HBV.

Ambivalence about referral can also be discerned in midwives' response to HBV tests. The latter oversee the lion's share of HBV screening at PHC level. A minority (2 of 11) reported providing *only* dietary advice, without referral, as did a few ICPs. Most midwives, however, described referral to the GP at the district health center in Nioro as standard practice. Yet they are unaware that treatment is available and about the steps required to obtain it. This may limit their motivation and ability to refer *persuasively*, since they cannot tell their patients why, exactly, they should consult the GP. Several stated they felt inadequately trained to deal with HBV infection.[9] They also suggested the GP would simply confirm the screening test result and reinforce dietary advice. A few thought further testing might be done; indeed, basic tests of liver enzyme function can be performed at district level. None, however, spoke of further referral to the regional level, which is required for treatment eligibility assessment and prescription. At least two doubted the GP referrals they provided were followed-up on. Moreover, all said they told women to wait until after they had given birth to see the GP or put off referring until a postnatal visit. Most midwives also told us their primary concern was to reassure women who tested positive and who, being pregnant, should be protected from strong emotion. They do this by stressing that the virus may remain "dormant" and that following a diet, which they advise starting during pregnancy, can suppress or even clear the infection. My overall impression from midwife interviews was that most referred without much conviction, if at all.

Referral ambivalence, whether enacted as selective referral, nonreferral, or "half-hearted" referral, can be seen as a force of filtration that pushes the majority of HBV carriers away from trajectories into further care and the possibility of treatment. The poor training of health workers as well as the lack of public information about HBV has indeed been identified as a "barrier to linkage to care" in other African settings (Giles-Vernick et al., 2016; Shimakawa et al., 2017). Yet referral ambivalence is also haunted by the prospect of futility that trajectories will be stalled or interrupted, wasting time and money, generating anxiety about the uncertainty of prognosis and the value of care (see Giles-Vernick and Hejoaka, 2020). As Whyte et al. (2004) suggest, there is mutual interaction between unequal access to drugs and broader patterns of socioeconomic inequality. Access may not only reflect ability to afford treatment, but also be shaped by assumptions, for example among health workers, about what care will entail and how it will be understood and prioritized as well as paid for by specific patients. In a way, referral ambivalence can be seen as stemming from an impulse to protect patients from the consequences of unequal access, an impulse that may appear as humane, paternalistic, or unfair. At the same time, it entrenches—particularly when some are selected for referral and not others—existing inequalities in access to resources, knowledge, and care. To understand the reasoning underlying (non-)referral, however, it is important to consider how PHC workers see dietary advice as a form of care.

Dietary Self-Care

Regardless of whether or how they refer, nearly all PHC workers report giving dietary advice to those who test positive for HBV. The details vary, but the common thread is to reduce fat intake. Some specify foods to avoid, such as butter, meat, and, most often, peanuts. A few add other "hepatotoxic" substances, notably paracetamol and herbal remedies. For specialists in Europe or Dakar, there is no evidence of *any* effect of dietary restrictions on the outcome of chronic HBV infection. They interpret the widespread "belief" in diet—which appears to cut widely across space and education levels (e.g., Giles-Vernick et al., 2016; Erlinger, 2020; ul Haq et al., 2012)—as the stubborn vestige of now outdated expert opinion. They do, however, recognize an enduring logic: that digestion of overly fatty foods burdens or "tires" the liver, thereby rendering it more vulnerable to infection-related damage.

This is one of the reasons we heard from Nioro PH workers for avoiding fat and oil; these could "accelerate" hepatitis-related disease progression. But we were also told that fatty diets could "cause" HBV *infection,* as could the consumption of aflatoxin-contaminated peanuts. Peanuts are a ubiquitous source of both protein and fat in regional diets, while aflatoxin is the metabolic byproduct of a fungus to which peanut plants and kernels are prone, particularly in Senegal's climate. For many PHC workers in Nioro, diet is not simply an ancillary measure; they describe it, like Dr. T. did, as a treatment that can keep infected people healthy and in some cases even eliminate the virus altogether. Dietary advice does not therefore seem to be offered merely as a better-than-nothing alternative to referral under conditions of limited knowledge about and access to antiviral treatment.

Dietary efficacy is located, in Nioro, within a dense prognostic and aetiological tangle, where sparse fragments of biomedical evidence (limited screening, rare further assessment, scarce epidemiological data) are projected against experiential knowledge of foodscapes, landscapes, and disease. Let us return to Dr. T.: he did seem to position diet as a lesser and cheaper alternative to antivirals, which he calls the "correct" treatment. Yet he went on to explain that the reason for very high rates of HBV infection in the region was "due to dietary habits, with the use of peanuts, we've noticed that people don't use the good kernels, the good kernels are used for seed, and also

[9]Midwives were trained to administer birth dose HBV vaccine, which was introduced in 2016, but many said they were not taught to emphasize vaccination for babies of those who tested positive.

for sale. So generally, the bad kernels are used . . . so naturally in the Saloum [the geographical region] there are many cases [of hepatitis]." By "bad kernels", Dr. T. means those with signs of damage or mold, indicating they are likely to be contaminated by aflatoxin.

Current biomedical evidence shows that chronic consumption of aflatoxins is, like chronic HBV infection, a risk factor for liver cancer and that both can act in synergy as cofactors (Kew, 2013). Without specifically referring to epidemiological data and aetiological knowledge, most PHC workers in Nioro expressed concerns about pervasive aflatoxin exposure as a cause of liver cancer. Peanuts are the main crop grown in Nioro and a major source of both cash and food. While historically grown for export, a growing portion of the harvest has gone to local consumption and trade since the 1980s or 1990s. Recent regulatory changes along with surplus production have stimulated the growth of domestic commercial sales of kernels as well as oil, paste and flour, which are processed on a small scale in towns and villages (Clavel et al., 2013).

Peanuts saturate Nioro's landscapes: fields fill the rolling hills; bigger towns are crowded with piles of pods, machines to shell them, warehouses to store them, and trucks to drive them away; the smell of simmering peanuts sauces and roasting kernels and the sounds of pressing and grinding waft along their streets, while piled plastic drums of unrefined peanut oil mark weekly markets; and regional cuisine is made up of a long list of peanut-based dishes. Primary healthcare workers "know" the interaction between peanuts (as fatty or as toxic) and HBV infection not through epidemiological data, but through a juxtaposition of intensities: positive test results and cases of liver cancer alongside the omnipresence of peanuts in the landscape and foodways. As midwife K.—who had hoped, like Dr. T., to organize a communication and screening event—puts it:

> Hepatitis is a problem . . . here . . . Because Saloum . . . peanuts, there are a lot here [she repeats this]. So people eat fatty food all the time. All they eat is peanuts. Lunch, dinner, all peanuts. Cooking . . . *mafe* [a peanut-paste based dish], how many times to they cook *mafe* during the week? *Ceere bi* [millet couscous] they make it [with a peanut sauce], how many times? *Mbaxalou saloum* [a regional specialty made with peanut flour]. . . Their oil too, it's made from peanuts. So their whole consumption is based on peanuts. It's because of this that there is an excessive rate of positive antigens here. Liver cancer, yes, there's a lot of it.

For many ICPs and midwives, this entanglement underpins the efficacy of dietary management of HBV. For some, a fat- and/or peanut-restricted diet (a few specify further to avoid *bad* peanuts) can slow or halt the damaging effects of chronic infection. This view overlaps, even if it is not perfectly aligned, with biomedical evidence of synergistic relations between aflatoxin and HBV. As mentioned above, emphasizing the efficacy of diet is also a way of reassuring positive individuals, particularly pregnant women. Those who were most emphatic about diet are those, like Dr. T., who say they have seen it reverse antigen test results. Midwife W., who advises patients to avoid peanut paste and paracetamol and to reduce oil and butter, has also seen "women who come back with a negative HBs antigen after, after the diet [she repeats this]," as has Midwife K., who concluded: "so you see the value of educating them in relation, especially, to the diet they have to follow!"

For Nioro's PHC practitioners, then, access to HBV care is not an "all" (i.e., referral culminating in antiviral therapy) "or nothing" proposition. They may filter a few into further care through selective referral. But others who have been diagnosed as positive are not filtered out of care altogether, even if the dietary treatment offered has limited efficacy on biomedical terms (still, given potential reduction of synergistic interaction between risk factors, may be somewhat protective). A few, like Dr. T., further recommend HBV positive individuals to self-monitor for a prickling sensation in the upper-right abdominal quadrant and sometimes prescribe liver enzyme tests to check for indicators of liver damage, or abdominal ultrasounds (which must be done at regional level), for signs of cancer. These forms of self-care through diet and vigilance are opened up not just by "ignorance" and poor training, but also by the aetiological entanglements of liver disease with peanut-filled diets, the uncertainty and variability of HBV infection outcomes, and lack of access to further diagnostic assessment (and, probably also, also by inaccurate rapid screening tests which may give false positive followed by negative results).

Yet individuals are also filtered into, or out of, dietary self-care. Most midwives noted it was a challenge to get women to pay for prenatal testing. The price of the HBV test was fairly low, at 2,500 CFA/4.4 USD (although it had recently nearly doubled).[10] It was, however, integrated with a test bundle costing 12,000 CFA/21.1 USD. Midwives complained many could not afford this or that they reported their husbands refused to pay for it. This suggests that poverty combines with gender inequality to filter some out of HBV screening (as well as other tests important to a safe pregnancy and childbirth). There may also be gender, age, and socioeconomic factors of likelihood to donate blood; in Dakar, these include being male, over 40, and attaining higher levels of education (Duboz et al., 2010).

Capacity for dietary change is also unequally distributed. Households in Nioro rely heavily on peanuts and oil (including unrefined peanut oil) as a relatively cheap and abundant source of protein, calories, and taste. Furthermore, eating is a communal process with gendered and generational hierarchies, while meal preparation is time, labor, and fuel consuming. Even the more precise and potentially more useful advice to eat (rather than sell) only "good" peanuts may entail loss of much-needed income. Only those with privileged access to resources—as part of wealthier households and/or because of their position *within* households (see Foley, 2009)—might be able to act on dietary advice. When I pressed ICPs and midwives on the feasibility of cutting out oily foods and peanut products, they usually laughed, indicating that obviously, for a majority of their

[10]Testing kits could also, according to Gueye, be procured at a much lower cost. Most health posts did not have testing kits, even though tests used at the district level are suitable for point-of-care testing.

patients, this was a ridiculous suggestion. Several pointed specifically to gendered constraints: one ICP told me women (the vast majority of those screened) retorted: "well what will I eat then?" Even if they wanted to follow the advice, he explained:

> They cannot. And, here in the Saloum, women aren't really taken into consideration, not really [. . .] So that they can decide absolutely nothing [. . .] Men are the ones who make the decisions. So if you are a homemaker, in your home you say, I'm not going to eat [. . .this or that] you risk having all the problems in the world [he repeats this, for emphasis]!

Another midwife reported a woman being brought in by her family because she refused to eat anything at all after testing positive for HBV. Indeed, for many, the only way of heeding the advice given, mostly, recall, to pregnant women, is to go without. Moreover, self-care turns responsibility for HBV management onto individuals and households (Petersen and Lupton, 1996), and away from claims on collective, or perhaps state, obligations for protection, whether through better food regulation or greater access to diagnosis and drugs. In the end, then, even the lateral expansion of HBV care centered on dietary management generates filtered and therefore stratified access.[11]

Making Collective HBV

Neutralizing Aetiology

The Nioro district lab technician told us of HBV screening activities organized by a village association led by a "very dynamic youth." Back in Dakar, I met with Saliou, a busy freelance consultant. There were two factors behind the initiative, he told me. First was his own sense of obligation to "do something" in his home village, to which he wanted to maintain his attachment and where expectations were high given he obtained a Ph.D. from a North American university and his father played an important role in national politics. Not wanting to go into politics, as village elders pressed him to, he opted to launch a "citizen action movement" which would work in various domains, including health. The second factor (he had not lost the thread of his two-part structure even after a half-hour of talking and eating), was an intense, cumulative experience of deaths in the village due to what some labelled liver cancer. "There is not a single house[hold] in the village that hasn't lost a young person [to the disease]," he told me. This triggered not only grief, but also pervasive fear (a "psychosis") and divisive accusations of witchcraft. He recounted asking himself: "Will we let this disease destroy us? Let inaccurate beliefs dictate our actions?" By organizing conferences about HBV and offering screening tests, which began in 2017, the movement would thus recast the deaths as arising from HBV infection that was highly prevalent in the village and a cause of liver cancer.

The purpose of raising HBV "awareness" in this village, which I will call Keur Laye, was, as in PHC settings, not primarily to launch trajectories toward further diagnostics and antiviral drugs. As in the health posts, those found positive in Keur Laye were reassured their diagnosis was not "synonymous with liver cancer" and were given dietary advice. In the first year, Saliou also paid for liver enzyme testing. But in addition to opening up this space of lateral (or merely minimal) posttest care, HBV knowledge in Keur Laye was valued for establishing new causal explanations for a shared history of misfortune, thereby shifting attributions of responsibility in a collective "moral imagination" (Livingston, 2005). In this final section, I turn to the intended effects, particularly on understandings of shared risk and responsibility, of HBV knowledge distribution, first in Keur Laye, and then in the work of patient advocate Ibrahima Gueye (who was also one of the speakers invited to Keur Laye).

Aissatou Diouf and I went to Keur Laye to meet with members of the movement. Gathered in a circle in a courtyard at dusk, they described how the repeated deaths of mostly young men, occurring after rapid weight loss and abdominal swelling, had affected this village of about a thousand inhabitants. As far as he could remember, said the eldest of the group, more than forty had died since 1976, others said one or two every year. Most of the victims were men, and all were young, in their twenties and thirties, so their deaths "really hurt." Members of the movement were also young men. They spoke of the blood drive (the first screening session having been organized as such to qualify for free testing and reduce stigma) as an "awakening." Before was a time of ignorance, when recurring illness and death were attributed to possession or evil eye, and there was a lot of "fighting" (which I suspect is an understatement) in the village. With the blood screening, "many cases were revealed, that's when we knew that it is hepatitis that brought this problem." Or, as another put it: that all this time, it was "just hepatitis." Back in Dakar, Saliou had told me (he was not in Keur Laye that evening) villagers had come to him after Gueye's well-attended conference to say they felt "relieved of a pressure. The situation had been real tense because of the disease." "The HBV initiatives had succeeded," he suggested, because they had managed to "demystify, to render banal [*banaliser*] the disease."

The young men of Keur Laye were not the first to tell me of the association between liver disease and witchcraft accusations. Former heads of medical districts in Dakar, as well as several Nioro ICPs, explained that deaths occurring after rapid wasting and abdominal swelling were often attributed to someone—often a jealous woman or witch—having given the victims "something to eat" in order to take possession of them. Occult aetiologies for similar symptoms have also been noted by anthropologists in other regions of Senegal (Foley, 2009; Boye et al., 2020). The health workers I spoke to, in Nioro and Dakar, worried about these witchcraft accusations not because they saw them as unscientific, but due to their consequences: wasted money on divination, sacrifices, and remedies; consumption of remedies

[11]Anthropologists of HIV treatment programs have also noted that access to food, even when drugs are provided for free, becomes a site of treatment inequality, given that patients are educated that they must eat well in order for ARV treatment to work effectively. See, e.g., Kalofonos (2010), Prince (2012).

meant to expel the ingested occult substance, but which instead accelerated disease progression; and above all the durable divisions and tensions that such accusations kindled within and between households: "It dislocates relations . . . dislocates families!," exclaimed one former ICP, who told us of tensions within his own family that persisted years after his mother's death from liver cancer. Another ICP recounted a case in which the accused—the wife of the victim's best friend—had been beaten and locked up with the victim. The ICP had intervened, giving the accusers a "sermon" about the diagnosis of liver cancer, after which the case was "settled amicably" through monetary compensation and divorce.

Members of the movement described HBV screening as successful in neutralizing a collective causal narrative around deaths, thereby alleviating the tensions that had arisen from occult and interpersonal explanations. Yet they also admitted that knowing about HBV, and one's status, was not easy. Saliou told me that, initially, a "rival" group had discouraged people from getting tested, calling his movement "irresponsible" for "not doing anything" for those diagnosed as positive. Others also spoke of the difficulty of following dietary advice. One asked poignantly how, when he could barely cover household expenses, he could help his HBV positive wife stay healthy. Probably because they hoped I might help mobilize resources, but perhaps also because the recurring deaths and information/screening sessions had led them to frame HBV as a *collective affliction*, members of the group emphasized the need for—even a sense of entitlement to—outside help. In other words, they rejected an individualization of responsibility for HBV self-care. Yet the help they asked for was for good food, not for further diagnosis or drugs.

Saliou, however, was troubled by the knowledge, albeit vague, that with greater resources he and his movement might be able to offer more, biomedically, to those screened as positive. Ibrahima Gueye, he said, had "brought treatment up, but not in detail" during his conference in Keur Laye, so Saliou was unsure of what exactly further care would entail. The high cost of this care seems to make antiviral treatment practically unmentionable in many settings, even during HBV awareness-raising and screening activities. Both Saliou and Gueye blame the state for limits and gaps in HBV care and communication. Calling the state "irresponsible," Saliou exclaimed: "what we are doing, it's the government that should be doing it!"

An Exposed Nation

Ibrahima Gueye has called for greater state subsidization of HBV care, particularly of diagnostic tests, including, recently, free screening (Diatta, 2018). Yet I never heard him framing access to cheaper, free, or public HBV care, including treatment, as a *right* (human, civic or otherwise). We met several times during my fieldwork; I also heard him intervening in a research symposium and collected newspaper articles and YouTube videos of his media presence. My overall impression was that he brings up the need for more "awareness raising" [*sensibilization*] about HBV more often, and with greater emphasis, than that for greater *access* to care. Much of his advocacy work, with other members of *Saafara Hépatites* (of which he is the nearly exclusive public face), focuses on screening and information. This includes World Hepatitis Day, conferences in villages and in prisons (which Gueye was doing in 2019 in collaboration with a prisoner welfare NGO), and newspaper and television interviews, in which Gueye emphasizes the scale of exposure in Senegal and the need to get tested.

Gueye's efforts thus seem to work *within,* rather than against, a topography of unequal access to largely privatized HBV care. By informing people about the risk they face and what they can do about, more may decide to pay for care. He insists, for example, on the possibility of vaccination for those who test negative. This is a reason he gives for why even those who cannot afford specialized care should get tested. A course of three vaccine doses for adults is subsidized and costs 5,000 CFA/9 USD (infant HBV vaccination is free). The epidemiological logic of adult vaccination is debatable, given low rates of susceptibility in Senegal. Epidemiological data indicates that most adults who test negative for HBsAg antigen are already immune (e.g., Coursaget et al., 1993). However, antibody testing is more expensive than vaccination, so many Senegalese specialists recommend the latter as potential protection regardless of immune status. Getting vaccinated as an adult is, in both epidemiological and economic terms, a private endeavor. "Yes, that's a bit expensive," Gueye admitted of the vaccine price, "but if people are well informed, they can pay. It costs less than this watch, this phone, this dress. . ." he went on, pointing to objects around us. Similarly, on a Dakar-based YouTube channel (Yesdakar, 2019), he said: "some people will say I don't have 5,000 for the test, I don't have 5,000 for the vaccine, but we pay 150,000 for a phone. . .".

Gueye's emphasis on willingness to pay for *relatively* affordable HBV screening tests and vaccines may index a more general acceptance of (or resignation to) the privatization of HBV care and resulting inequalities. "Personally," Gueye told me, "I'm against free care [*la gratuité*]. Subsidization, sure, but there has to be a minimal price . . . there's always someone who pays, who will pay tomorrow . . . people get used to it." I heard specialists speak similarly about charging for antiviral drugs. Desclaux (2004) describes how the initial design of Senegal's HIV treatment initiative rested on assumptions—among both local professionals and entrenched in international health policies—about the inherent value of user fees, which would foster a sense of "dignity" as well as responsibility (translating as adherence) among patients and activate "traditional solidarity networks." The acceptance of user fees for HBV care may similarly reflect a broader "internalization" of the logics of the health reforms initiated under structural adjustment, whereby only the most cost-effective mass measures such as infant vaccination can count as public goods, and other

care is either dispensed as "charity" or at least partly privatized by cost sharing (see, e.g., World Bank, 1993; Foley, 2009). Intensified global health investments in the mid-2000s, along with demands for care as a *right* (as HIV treatment was reframed, Desclaux, 2004), have expanded the scope of public health—but HBV care continues, as Sall Diallo often points out, to be excluded from this scope. Discussions about access continue to revolve around affordability; that is, *how much* "users" will pay rather than *who* should bear the price of care (and who may profit from it, for example, in the commercial economy of testing equipment, supplies, and services).

While Gueye's "awareness-raising" individualizes responsibility for care, it also seeks to deindividualize and destigmatize responsibility for infection by insisting on the collective nature of *exposure*. He likes to illustrate this point by evoking an image familiar to many Senegalese adults of schoolchildren lined up to be vaccinated with a jet-gun. As the host of a 2012 talk show laughed, presumably at her own memory of this image, Gueye pressed on: "one single needle, five hundred people [. . .] the reason I bring this up [is to emphasize that] hepatitis, it concerns us all, everyone is at risk" (Senewebdirect, 2012). To me, he said, "I show the scar on my arm. People see it and tell themselves they too might be affected." Sall Diallo also points to widespread risk; "hepatitis concerns us all" was a slogan she circulated, along with the figure of an 85% exposure rate (i.e., nearly universal contact resulting in immunity or infection. Others, such as Coursaget et al., 1993, put it at over 90%). Nevertheless, PNLH declarations and activities have emphasized "risk groups" such as health and sex workers.[12] Gueye refuted this on television: "the *whole population* is at risk, the numbers show it!" (2STV 2019)

Sall Diallo appears unworried about stigmatizing HBV; for example, she frequently and bluntly reminds audiences that sex is a mode of transmission. By contrast, Gueye treats sexual transmission as a delicate issue. He explained his strategy to me:

> I cannot be said that it does not exist. It can exist. But I bring it up last, starting upstream. When someone is positive, they cannot know when they were infected. The first possibility is that they were born with it. That's to reassure [. . .] for the majority here in Africa, that's it. In any case, it lifts a weight. I summon the past first.

Evoking uncertainty about infection source, early-life transmission, and serial childhood vaccination are, for Gueye, ways of conveying HBV as a neutral and widely shared exposure; a risk for which individuals cannot be held responsible. This is a strategy to counter stigma and the kinds of tensions he has witnessed around HBV diagnoses: for example, of men seeking to cast out their infected wives. His goal, he states, is "that the person does not feel responsible." Gueye sees stigma as an obstacle to both (individualized) care-seeking and collective mobilization.

The work of Keur Laye's movement and of Gueye and *Saafara Hépatites* communicates to audiences that HBV circulates widely among them and that they should not be held responsible for their status, nor should they accuse each other of transmission or of causing swollen-stomach deaths. HBV knowledge is treated as having the power to reconstitute social relations around shared infection, risk, disease, and loss. In neither case has this emergent sense of HBV as a collective burden been explicitly linked to arguments for redistributing the costs of care through collective, public mechanisms. Yet the potential is there: reframing HBV as collective misfortune, in which some must bear the bodily effects of its variable outcomes but should not necessarily be made to bear the financial and logistical costs of mitigating these, may serve as a basis for making claims to free and public care as a right.

CONCLUSION

Further research is needed to determine whether and how clinical interactions, as well as other modes of communication about HBV, may filter individuals in or out of care and thereby mediate access inequalities. My research has been limited to what actors involved in the provision of HBV information and care *say* about what they do and why. There is more to be learned through observation of clinical and educational practices and by tracking their effects on patients and audiences, as well as on trajectories of testing and care (likely in combination with information-sharing and decision-making among kin networks). Yet my focus, via HBV actors, on the topography of specialized care and HBV communication, alongside screening and information efforts that largely fail to join up with this topography, opens up a vista onto uneven provisions of *both* HBV technologies and knowledge and a glimpse of interactions between them. This has allowed me to identify filtration—which arises from these interactions—as a mechanism that produces inequalities in access to care and, at the same time, renders these inequalities less visible and less open to contestation.

By attending to the indirect effects of access inequalities on enactments of HBV, I have sought to illuminate complex entanglements among HBV knowledge/communication, "means" (to pay for care), privatization, gendered and socioeconomic disparities, explanatory models of causation and efficacy, and assumptions about who can and should bear the costs of care. Access is not determined only by who knows about, or can pay for, what kind of care. "Filtration" describes this nonlinear, dynamic entanglement by which

[12]I heard other Senegalese experts speak of risk groups as well as sexual, iatrogenic, and parenteral transmission among adults. Others, however, assert that infection is distributed throughout the "general" adult population, while epidemiological data suggest that sexual transmission is absent or negligible given pervasive childhood exposure to HBV in Africa.

different sites and mechanisms of inequality are mutually enacted and constitute—or not—potential subjects of HBV care.

To conclude, I want to highlight two themes amid this dense tangle: privatization and gender. HBV has been pointed to as a neglected issue in global health (e.g., Lemoine et al., 2012) despite its heavy burden of morbidity and mortality. My research suggests this neglect, at the level of what PNLH director Sall Diallo calls "global health governance," which gets reproduced in national healthcare policy and practice,[13] hinders not just action on, but even the articulation of, HBV as a *public* health issue. For one, there are few resources to detect and communicate the scale of infection at the national level and thus frame it as a collective problem. In addition, the distribution of scarce resources for care both assumes and reinforces private responses to (the risk of) infection and illness. Infected individuals are expected to pay, in part or in whole, for diagnostics, drugs, or "therapeutic" diets. The provision of most of these services, as well as communication about HBV, have been left to personal and/or commercial initiatives, with little or no public oversight. Even the nominally public but underfunded PNLH manifests as a highly personalized presence. This results in uneven and fragmented distributions of both HBV care and information about it, so that subjects of treatment are formed in spaces of privileged access that remain largely invisible and uncontested. Moreover, widespread emphasis on personal responsibility for exposure (or at least, a lack of effort to *deemphasize* risk behaviors such as sex) and for care, including self-care, deflects attention from potential collective models of viral circulation and protection. There are sites of tentative conceptualizations of HBV as a shared problem that should be tackled collectively through public channels, but these have yet to give rise to vocal demands for access to treatment.

The privatization of HBV and its care partly overlaps with its gendering. As the PHC practitioners we interviewed point out, expectations that individuals can and should pay for HBV screening tests and that dietary restriction is an effective and accessible form of self-care, are both challenged by and reinforce gendered household dynamics. More research is needed on the gendered implications of focusing screening efforts on pregnant women, especially given widespread assumptions about the sexual transmission of HBV. Gueye, for example, has hinted that diagnoses of HBV often provoke suspicion, rejection, guilt, and confusion due to these (unfounded) assumptions. Yet epidemiologically validated emphasis on perinatal and early childhood HBV exposure as both frequent and risky (more likely to lead to cirrhosis and cancer) also draws attention to mothers as transmitters of an infection that tends to kill more men. How do HBV data and models shape understandings of gendered relations of care, pleasure, and harm? Similar questions can be asked of occult forms of swollen-belly death: in all the stories I heard, the accused were always—often jealous—women.[14]

Points and processes of filtration—whether as orientation into lateral care (diet or nonbiomedical healers), unpersuasive referrals or too-expensive, unexplained test prescriptions—arise from *partial* expansions of access to diagnosis and drugs. Increasing the availability of screening tests, viral load testing or antivirals are likely to have unintended effects if not accompanied by a *public* strategy for their coordination, and the fair distribution of resources, including information, and costs. A focus on filtration, rather than on the proportion of treatable individuals getting treatment, provides a fuller and more nuanced view of what happens in the gap between the availability and accessibility of biomedical technologies.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because interview content may include personal or identifiable data even if anonymized. Requests to access the datasets should be directed to n.tousignant@ucl.ac.uk.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the UCL Research Ethics Committee (Office of the Vice-Provost (Research)) and Comité National d'Éthique pour la Recherche en Santé (Senegal, Ministry of Health). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

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[13]This happens in both direct ways, through lack of donor funding for HBV action, and indirect ways, when as national priorities are set to capture available resources.

[14]Livingston (2005) notes that women were also often accused of responsibility for children's disabilities in Botswana. Elsewhere in Africa, witchcraft accusations have often been linked to tensions in gendered roles and relations (e.g., Drucker-Brown, 1993).

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frontiers in Pharmacology

ORIGINAL RESEARCH
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Health Insurance and Out-Of-Pocket Expenditure on Health and Medicine: Heterogeneities along Income

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Background: Achieving universal health coverage is an important objective enshrined in the 2015 global Sustainable Development Goals. However, the rising cost of healthcare remains an obstacle to the attainment of the universal health coverage. Health insurance is considered an option to reduce out-of-pocket (OOP) expenditure on health and medicine. Nevertheless, the relationship between insurance and the OOP along welfare distributions is not well understood. This study investigates the heterogeneous association between health insurance and OOP expenditure on health and medicine, along income, using data from the Kingdom of Saudi Arabia.

Methods: This study used data of 8655 individuals drawn from the Saudi Family Health Survey conducted in 2018. The study adopts Tobit models to account for possible corner solution due to individuals with zero expenditure on health. We minimize the confounding effects of non-random selection into the insurance program by estimating the Tobit equations on a sample weighted by inverse propensity scores of insurance participation. In addition, we test whether the health insurance differently relates to OOP on health and medicine amongst people with access to free medical care as opposed to those without this privilege. The study estimates separate models for OOP expenditure on health and on medicines.

Results: Health insurance reduces OOP expenditure on health by 2.0% and OOP expenditure on medicine by 2.4% amongst the general population while increasing the OOP expenditure on health by 0.2% and OOP expenditure on medicine by 0.2%, once income of the insured rises. The relationship between the insurance and OOP expenditure is robust only amongst the citizens, a sub-sample that also has access to free public healthcare. Specifically, the insurance reduces OOP expenditure on health by 3.6% and OOP on medicine by 5.2% and increases OOP expenditure on health by 0.4% and OOP expenditure on medicine by 0.5% once income of the insured increases amongst Saudi citizens. In addition, targeting medicines can lead to greater changes in OOP. The relationship between insurance and OOP is stronger for medicine relative to that observed on health expenditure.

Conclusion: Our findings suggest that insurance induces different effects along the income spectrum. Hence, policy needs to be aware of the possible welfare distribution

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impacts of upscaling or downscaling the coverage of insurance amongst the populations, while pursuing universal healthcare coverage.

Keywords: insurance, medicines, out-of-pocket expenditure, health, saudi arabia (KSA), income

INTRODUCTION

The economics textbook expectation is that health insurance, provided at actuarially fair price with full coverage, induces risk-averse individuals into participation, with the quest of reducing unanticipated financial risk (Wagstaff and Lindelow, 2008). By implication, health insurance should, therefore, reduce out-of-pocket (OOP) expenditure on health. However, empirical evidence reveals different outcomes. In some contexts health insurance indeed reduces OOP expenditure (Ahmed et al., 2020; Harish et al., 2020; Sriram and Khan, 2020) while increasing the OOP expenditure in alternative settings (Li et al., 2020; Okoroh et al., 2020; Ying and Chang, 2020). These contradictions invite the question whether policy should expand or contract the provision and coverage of health insurance in the best interest of citizens. The question is more relevant now than before since countries embarked on increasing universal Health Coverage (UHC) upon the adoption of the Sustainable Development Goals in 2015.

Several countries established health insurance as one of the mechanisms for attaining UHC (Buttorff et al., 2015; Fang et al., 2019; Matsushima et al., 2020). However, the effectiveness of the insurance in increasing proper healthcare access for all depends on the behavior responses and health expenditure implications of different subsections of the targeted populations (Kraft and VD Schulenburg, 1986). For instance, if health insurance compels healthcare providers to shift the patient's demand curve to the right due to asymmetric information, the affluent would increase OOP expenditure. The poor might only reduce OOP as the insurance covers their medical cost while having less income to attain the supplier induced demand services. This makes understanding of the different effects of health insurance along welfare spectra vital for UHC attainment. This study, therefore, aims to estimate the heterogeneous effects of health insurance, along income, on OOP expenditure. The study uses data from the Kingdom of Saudi Arabia (KSA), one of the countries that has been implementing a health insurance scheme for about two decades.

Saudi Arabia is a suitable case study to understand the relationship between health insurance and OOP expenditure. Despite being a high-income country, the KSA (just like other countries in the Arabian Gulf region) has some low-income healthcare attributes which make its context applicable to results from neither high- nor low-income effects of insurance literature. Firstly, the country provides free healthcare to its citizens through public health facilities which increases pressure on public healthcare provision (Al-Hanawi et al., 2018a). Secondly, about 56% of its workforce are expatriates who do not access the free healthcare and therefore rely on insurance and OOP expenditure (Alkhamis, 2018). Therefore, results from the KSA could reveal not only the heterogeneous relationship between insurance and OOP expenditure but also how this relationship can be modified under strained free healthcare system. To the best of our knowledge, this study is the first to be conducted in an oil dependent country that finances healthcare using the finite natural resource (Al-Hanawi et al., 2018b). Considering the potential threat of continued fall in oil prices, countries beyond the KSA that also finance healthcare using the natural resource, would benefit from our results, whether to consider insurance as an effective means of insuring sustainability of healthcare financing while pursuing universal health coverage.

This study contributes to prevailing debate on the relationship between health insurance and OOP expenditure on health by not just examining the direction but also how income mediates this relationship of interest. If the relationship differs based on the level of income, then, this study provides the much-needed direction that policy can choose strategies from while being fully aware of the distribution impacts of the course of action. In addition, we demonstrate whether the analysis of the relationship between health insurance and healthcare access should account for welfare distribution to provide reliable estimates. Considering that medicines expenditure forms the largest component of OOP expenditure (Wirtz et al., 2012; Zullo et al., 2017; Ghosh et al., 2019), this study further examines a particular relationship between health insurance and OOP expenditure on medicine, besides the general OOP expenditure on health outcome.

Healthcare Access and Health Insurance in Saudi Arabia

The KSA provides free access to healthcare services through the public health facilities to both Saudis and non-Saudis working in the government sectors. Furthermore, the KSA provides free healthcare services to the general public, which exorbitantly raises the cost of financing healthcare in the kingdom exacerbated by the rapid demographic changes, an aging population, changing disease pattern, and increased prices of medical technology (Almalki et al., 2011). Public health provision in the KSA is of high quality. However, it has faced efficiency challenges due to the overwhelmingly large number of people that it caters for (Al-Harajin et al., 2019). These public healthcare bottlenecks lead to increased OOP expenditure amongst some citizens. Unsurprisingly, most private healthcare services are provided to Saudis who are eligible for free healthcare services through the public sector (Walston et al., 2008). Besides, the kingdom has over 75% of private sector employees as expatriates, accounting for 56% of the gross Saudi workforce (Alkhamis, 2018). These attributes pose a further strain on the KSA healthcare resource envelope.

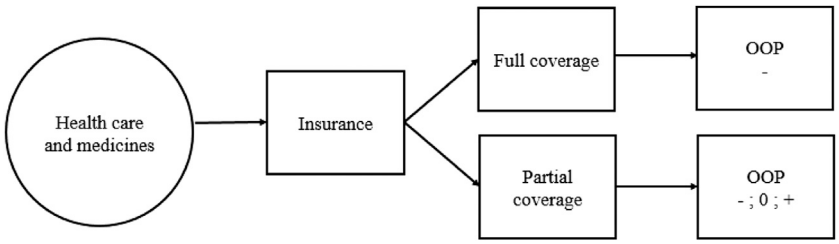

FIGURE 1 | Conceptual framework for the economic decision to incur out of pocket expenditure.

In response, the Saudi government enacted the Cooperative Health Insurance Law in 1999 that established a mandatory health insurance scheme for private sector employees in 2002 (Al-Sharqi and Abdullah, 2013; Alkhamis et al., 2014). The scheme aimed to force private sector employers to cover healthcare costs for their employees (Saudi and non-Saudi) in a quest to relieve pressure off public health services by pushing the private sector employees to private healthcare providers (Al-Hanawi et al., 2018a). Under the scheme, the insured obtain healthcare services from private healthcare facilities, and the employers pay a full amount for the premium that, however, differentiates coverage packages across employees' profiles (Alkhamis, 2018). It is worth noting that the general population including the public sector employees are also allowed to access private health facilities and pay out-of-pocket or purchase private health insurance packages to safeguard their income and wealth against unanticipated health shocks from illnesses. Currently, the scheme has 27 insurance companies catering for 11 million beneficiaries, that access private healthcare (Rahman, 2020).

The Council for the Cooperative Health Insurance (CCHI) coordinates and manages the provision of health insurance in the KSA. The CCHI determines all minimum healthcare needs and treatments that are provided for under a unified insurance benefit package (Alkhamis, 2018). While some top-ranking employees enjoy comprehensive coverage from their companies and institutions, some workers have partial coverage. Those under partial coverage incur co-payments for their medical bills because the unified package remains insufficient (Aidam et al., 2016).

Against this backdrop, both citizens and expatriates in the KSA remain at risk of increased OOP expenditure. The question remains whether, besides easing pressure on public facilities, policy should expand access to health insurance to move toward equitable access to healthcare. The policy stance also remains a dilemma particularly because of the missing consensus on the direction of the relationship between health insurance and OOP expenditure in the healthcare access literature. In this study, we uncover the possible heterogeneous direction of the relationship; how different levels of income mediate the relationship between health insurance and OOP expenditure.

Conceptual Framework

The economic question we set out to answer is: "How does participation in health insurance relate to OOP expenditure on health, along different income levels?" Part of the answer can be found in literature (Gnawali et al., 2009; Nguyen et al., 2011; Zimmer, 2011; Roos and Schut, 2012; Cantarero-Prieto et al., 2017; Dong et al., 2018) that examines the effects of health insurance on healthcare utilization. While available literature deals with whether health insurance leads to either positive or negative or no effects at all, we depart from that focus to examine the possible outcomes subject to the income levels of the insured. Our hypothesis is that individuals that subscribe to health insurance should experience a reduction in OOP expenditure and increase consumption of prescribed care conditional on income that allows them to join this high level of healthcare.

Theoretically (as shown in **Figure 1**), an individual anticipating financial risk due to uncertain healthcare costs should purchase health insurance based on incentives that their health insurance package provides consistent with their risk. A more generous package, that is actuarially fair and offers full coverage, should attract risk-averse individuals (Wagstaff and Lindelow, 2008). The perceived benefit is the comfort that whether one is ill or not, their finances are secured since insurance takes full care of the medical costs. These are individuals who will most likely reduce OOP expenditure once they are insured and could have no desire to use the savings in higher level healthcare consumption.

In the event of non-generous, partial coverage, risk perverse individuals may purchase health insurance. However, unlike the risk averse, these individuals' behavior may not be predicted. If they use the savings from reduced expenditure from health in alternative means, OOP will reduce (negative sign). Alternatively, they may still incur OOP only to a level offsetting the saving from usage of health insurance (zero change). This will result in no significant net change in OOP. A third option is where these individuals demand expensive care which they cannot afford in the absence of health insurance (positive sign). The overall effects of health insurance on OOP become positive.

In practice, the increased demand for expensive healthcare could emerge from health-seeking effects of health insurance combined with opportunistic behavior of providers with asymmetric information (Ying and Chang, 2020). Insurance increases number of medical visits that individuals make to healthcare providers (Al-Hanawi et al., 2020). Healthcare providers use their superior asymmetric information advantage to prescribe medicine that is not covered by the insurance (Bernal et al., 2017). Consequently, the insured spend more resources on medical care than they would without the health insurance. Nevertheless, the insured would do so, only when they have

TABLE 1 | Variable definition, specification, and summary statistics (*N* = 8655).

Variable	Definition	Mean	Std. Dev
OOP expenditure on health	Continuous	747.018	1194.665
OOP expenditure on medicine	Continuous	394.113	889.001
Health insurance	Dummy (1 insured; 0 uninsured)	0.298	0.457
Monthly income	Continuous	11,443.920	10,639.740
Nationality	Dummy (1 saudi; 0 non-saudi)	0.770	0.421
Age	Continuous	36.514	21.090
Gender	Dummy (1 male; 0 female)	0.525	0.499
Marital status	Dummy (1 married; 0 unmarried)	0.590	0.492
Below primary school	Dummy (1 below primary school; 0 otherwise)	0.200	0.400
Primary school	Dummy (1 primary school; 0 otherwise)	0.139	0.346
Intermediate school	Dummy (1 intermediate school; 0 otherwise)	0.157	0.364
Secondary school	Dummy (1 secondary school; 0 otherwise)	0.308	0.462
Higher education	Dummy (1 higher education; 0 otherwise)	0.196	0.397
Health status[a]	Dummy (1 good; 0 otherwise)	0.759	0.428
Wealth index[b]	Continuous	0.026	1.768

[a]*for health status (subjective health) good comprises good and very good and otherwise (bad) encompasses mediocre, bad, and very bad.*
[b]*Note: the study constructs the wealth index by running PCA on household assets that include energy source, water source, house construction materials, availability of mosquito nets, and type of the housing facility.*

the resources required to procure the prescription. Therefore, the relationship between health insurance and OOP expenditure conditional on income levels remains an empirical question which this study intends to answer using data from the KSA.

MATERIALS AND METHODS

Data and Variables

This study draws secondary data from the 2018 Family Health Survey (FHS) conducted by the General Authority for Statistics (GaStat) in the KSA (GASTAT, 2018). The FHS is the first collaborative stage between GaStat and several entities in the health sector in the Kingdom such as the Ministry of Health, the Saudi Health Council, as well as the private and academic sectors. The FHS is a field survey conducted every three years by GaStat and it falls under the classification of education and health statistics. The FHS collects information by visiting a representative sample of the population across all 13 administrative regions in the KSA. An important element to our study is that the health status section of the survey includes a question on whether an individual is covered by health insurance or not. Further, the respondents also report on OOP health expenditures that they incurred. A follow up question asks the amount of OOP that the individual spent, particularly on medicine. The survey also contains rich information on demographic and socioeconomic status.

Given the richness in health-related information and representativeness, the FHS is ideal for examining the heterogeneous relationship between health insurance and OOP along different levels of income. The FHS collected a total sample of 15,265 responses randomly selected across the 13 administrative regions of the KSA. This study limits the analysis to respondents who have complete information on all the variables of interest. Therefore, this study's analysis is based on a sample of 8,655 respondents after dropping those with non-responses to healthcare related questions and covariates.

The main outcome variables for this study are OOP expenditure on health and OOP expenditure on medicine. **Table 1** provides the specific definitions, means and standard deviations of the outcome variables and all other independent variables used in the study. OOP is measured as a continuous variable in Saudi Riyal (SR) (1 US$ = 3.75 SR). On average, OOP expenditure on medicine forms 53% of the total OOP expenditure on health in the sample. The main independent variable used in this study is health insurance. Health insurance is captured as a binary variable with 1 if respondent is covered by health insurance and 0 if otherwise. In our selected sample, 30% of the respondents have health insurance. The second independent variable used in this study is income. The income is a continuous variable and measured in SR.

In terms of socioeconomic background, we include age of the respondent and the wealth index of their household as continuous variables. The wealth index is constructed by running a Principal Components Analysis (PCA) on household asset dummies (1 capturing those that possess an item and 0 otherwise) that include access to different energy sources (electricity and gas), water source (public network, tanks, bottled, filters and a well), house construction materials (concrete), availability of mosquito nets, and type of housing facility (villa house). Gender was coded as a dummy variable, with 1 for male and 0 for female. Marital status was captured as dummy variable, with a value of 1 for married and 0 for unmarried (including never-married, single, widowed and divorced). Nationality was coded as a binary variable, with 1 for Saudi and 0 for non-Saudi (expatriate). Household income is used as a continuous variable. With regard education level, it was grouped into five categories and was coded as follows: 1 for below primary school (those who can just read and write and the illiterate), and 0 for otherwise; 1 for primary school education and 0 for otherwise, 1 for intermediate school and 0 for otherwise, 1 for secondary school and 0 for otherwise, 1 for higher education (including those with university degree or postgraduate degree) and 0 for otherwise. We also include health status (subjective

health) with 1 for those who perceive themselves in a good health (good and very good) and 0 for those who do not think they are in a good health status (bad, very bad and mediocre).

Empirical Strategy

This study examines how health insurance relates to OOP expenditure on health and on medicines along different levels of income. We therefore build econometric models that specify OOP as a function of insurance, income, and the interaction between insurance and income. The model can be presented as follows.

$$InY_{ij} = \beta_0 + \beta_1 Insurance_i + \beta_2\left(Insurance_i \times lnincome_j\right) + \beta_3 lncome_j + \beta_4 X_{ij} + \varepsilon_{ij} \quad (1)$$

In **Eq. 1**, Y is the outcome representing either OOP expenditure on health or OOP expenditure on medicines for individual i in household j. **Eq. 1** captures the average effects of insurance on OOP by β_1 assuming that β_2 is insignificant. A positive β_1 coefficient would imply that insurance increases OOP while a negative coefficient shows a reduction in OOP due to the insurance. Controlling for income (through the log of income variable and the β_3 coefficient), β_2 captures the difference in OOP due to insurance along income. Income is logged in this study for two reasons. First is to ensure that it is normally distributed because income is always skewed to the right in survey data which was also the case in our sample. Second, logging income together with OOP allowed us to interpret the results of the study as direct percentage changes. The average effects of insurance on the gross value of OOP are then equal to $(\beta_1 + \beta_2)$.

If insurance induces equity in healthcare access signaled by a homogenous reduction in spending, β_2 will be insignificant. Alternatively, if insurance leads to income gaps in healthcare access β_2 will be significant. Precisely, a negative sign could imply that within the sub-sample of the insured OOP reduces with increased income. Thus, the insurance package is comprehensive enough that even the rich reduce out of pocket-payments for sophisticated care. A positive sign could entail that insurance increases awareness of self-health (that can also result from supplier induced demand), which however, is not fully covered by the package. The rich use this knowledge to procure additional healthcare, increasing the healthcare access gap between them and the poor.

In **Eq. 1**, we also include other OOP covariates, to reduce the effects of omitted variables biasing the relationship of interest. At individual level we control for age, gender, marital status, and the level of education. At household level we include wealth index, which is a summary of the assets acquired by a household in which an individual resides. We capture the error term of **Eq. 1** with ε_{ij}.

Functional Form

Notably, the anticipated effects of health insurance are conditional on the individual incurring OOP expenditure. In healthcare systems that also provide free healthcare services, some people may incur no OOP. Modeling the relationship between insurance and OOP without accounting for the zero OOP expenditures leads to corner solutions unless the estimator adopts an appropriate functional form. We, therefore, estimate **Eq. 1** using the Tobit model censored at zero, to evade the corner solutions. An additional concern is about the systematic differences between the insured and the uninsured which we minimize using the Inverse Propensity Scores Weighting technique.

TABLE 2 | Marginal effects from logit estimates on factors that affect participation in insurance.

	(1)	(2)
	Insured	**Standard errors**
Saudi national	−0.583***	[0.015]
Age	0.002***	[0.000]
Male	0.081***	[0.011]
Married	0.087***	[0.014]
Primary school	0.095***	[0.021]
Intermediate school	0.071***	[0.020]
Secondary school	0.127***	[0.019]
Higher education	0.146***	[0.021]
Health status	0.036**	[0.015]
Wealth index	0.060***	[0.003]
Pseudo-R^2	0.329	
Observations	8655	

*Significance levels: *** p <0.01, ** p <0.05, * p <0.1. Standards errors in parentheses.*

Inverse Propensity Scores Weighting

The variable health insurance is potentially endogenous since characteristics that affect participation in insurance could simultaneously relate to OOP. An example is the case of adverse selection. Sick people incurring high OOPs may self-select into insurance. This could over- or underestimate the true effects of insurance on OOP. Since some of these confounding factors are unobservable to a researcher, the estimates could be biased. Formally, this would entail that the error term in **Eq. 1** correlates with the coefficient of insurance. We minimize these confounding effects by weighting our Tobit estimations with inverse propensity scores.

To construct the weights, we first estimate a logit model of insurance participation as follows:

$$Insurance_{ij} = \alpha_0 + \alpha_1 M_{ij} + \mu_{ij} \quad (2)$$

The explanatory variables, M_{ij}, in **Eq. 2** are those used is **Eq. 1** except the income. μ_{ij} is the error term. We generate propensity scores of insurance participation conditional on observed characteristics using estimates presented in **Table 2**. We follow previous literature (Hirano and Imbens, 2001) to weight each observation in the treatment group by 1 and those in the control group by a fraction of 1 minus the propensity score as follows:

$$w_i = \frac{\widehat{p}(M_i)}{\left(1 - \widehat{p}(M_i)\right)}, \; 0 < \widehat{p}(M_i) < 1 \quad (3)$$

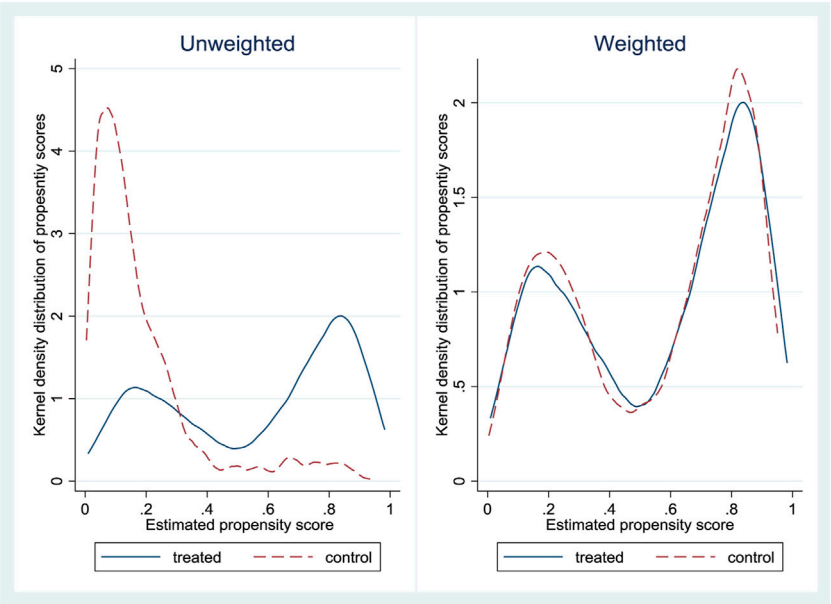

FIGURE 2 | Kernel density distribution of propensity scores for the insured (treated) and uninsured (control).

The Inverse Propensity Scores Weighting (IPW) reduces confounding effects by shifting the distribution of the untreated group's covariates to match that of the treated. The weights, w_i , create a sample where the distribution of covariates is independent of the treatment status.

RESULTS

Inverse Propensity Scores Weighting Results for Insurance Participation

Although our interest is to understand the heterogeneous effects of health insurance on OOP expenditure, we begin by validating our methods. **Table 2** presents the marginal effects of selection into health insurance from a logit model. The chances of obtaining insurance reduces for non-citizens. This is consistent with the notion that the Saudi health insurance is aimed at covering private sector workers, who are mostly expatriates. Being married, male, educated, and having a good self-assessed healthy status, increases the probability of obtaining insurance. Notably, relatively rich households obtain insurance in comparison to the less well off. The salient picture is that all the included covariates significantly relate to selectivity into health insurance.

We then predicted propensity scores of the participation from the logit estimates and compute inverse propensity weights. **Figure 2** shows kernel density distribution of the OOP covariates among the treated group of the insured (bold line) and the control group of the uninsured (dotted line). The first plot (left panel) shows the unweighted distribution of the covariates and the second plot (right panel) displays the distribution of covariates that is weighted by the IPW. In the unweighted panel, we observe that the treatment and control groups overlap imperfectly, while the weighted panel reveals more unified distribution of covariates. The IPW pools the distribution of the treated and untreated covariates into more comparable groups and reduces selectivity into insurance bias on observable attributes.

Descriptive Statistics

Table 3 presents the equality of means, using t-tests, between the insured and the uninsured when using the IPW and when not using the weights. The table also includes income, OOP expenditure on health and OOP expenditure on medicine. Columns 1 to 3 present unweighted results. The insured have high average income while they spend less on OOP expenditure on health relative to the uninsured. This provides a preliminary picture that insurance associates with reduced OOP expenditure on health. The two groups do not differ on medicine related OOP. All covariates remain statistically significant and maintain the signs observed in the insurance participation equation results that are in **Table 2**. Columns 4 to 6 of **Table 3** show weighted differences. Income and OOP expenditure on health remain high and low respectively for the insured relative to the uninsured. Weighted results show that insured individuals spend, significantly, more on medicine OOP relative to the uninsured. Amongst the covariates of OOP only male (positive), those with below primary school education (positive) and individuals with higher education (positive) remain significant after weighting. The loss in significance for the majority covariates, after weighting, emphasizes the reduction in bias on observable attributes by the IPW.

TABLE 3 | Differences in means between the insured and the uninsured samples.

	Weighted			Unweighted		
	(1)	(2)	(3)	(4)	(5)	(6)
	Insured	Uninsured	*t*-test	Insured	Uninsured	*t*-test
Income	12,308.140	11,077.910	1230.230***	12,308.140	10,387.100	1921.038***
Health OOP	609.900	805.090	−195.190***	609.900	693.110	−83.208**
Medicine OOP	404.850	389.570	15.286	404.850	350.270	54.582*
Saudi national	0.400	0.930	−0.523***	0.400	0.410	−0.009
Age	38.220	35.790	2.424***	38.220	39.450	−1.232
Male	0.610	0.490	0.122***	0.610	0.540	0.069***
Married	0.710	0.540	0.175***	0.710	0.690	0.021
Below primary school	0.232	0.125	0.108***	0.147	0.125	0.022*
Primary school	0.145	0.124	0.021**	0.145	0.124	0.021
Intermediate school	0.153	0.167	0.0138	0.181	0.167	0.014
Secondary school	0.305	0.315	0.0098	0.319	0.315	0.005
Higher education	0.270	0.165	0.105	0.270	0.208	0.062***
Health status	0.840	0.720	0.120	0.840	0.840	0.007
Wealth index[a]	0.470	−0.160	0.628***	0.470	0.440	0.025
Observations	2575	6080		2575	6080	

Significance levels: *** p *<0.01,* ** p *<0.05,* * p *<0.1.*

[a]*The wealth index reveals that insured individuals are wealthier than the uninsured. However, weighting removes the wealth differences between the insured and the uninsured.*

In **Table A1** of appendix, we examine the differences in OOP expenditure split by income categories and nationality. We also include means, standard deviations and 95% confidence intervals. The sample is first disaggregated by median income, which was 8900 SR in the sample. Those above the median incur more OOP on health (1009 SR) than those below the median (485 SR). The trend is the same with OOP on medicine with those above the median spending more (530 SR) than those below median income. Concerning nationality, Saudis spend more on OOP on health (842 SR) than non-Saudis (425 SR). Similarly, for OOP on medicine, Saudis spend more (450 SR) than non-Saudis (206 SR).

Factors that Affect OOP Expenditure on Health and OOP Expenditure on Medicine

Table 4 presents factors that relate to OOP expenditure on health and OOP expenditure on medicine. The estimates include income, insurance, the interaction between income and insurance and covariates (control variables) of OOP. However, in the interest of brevity we limit the results description to the coefficients of interest (income, insured and insured*income) and exclude the covariates. The first 2 columns present results on OOP expenditure on health. Column 1 shows the homogenous relationship between income and insurance on OOP. Income increases expenditure on OOP. The health insurance reduces OOP. This is the primary expected role of insurance in cushioning participants from unanticipated health spending. Column 2 includes the interaction between income and insurance. Income maintains a positive relationship with OOP, and insurance remains negatively related to OOP. The interaction between income and insurance is positive and significant. The result reveals that within the subsample of the insured, income increases OOP.

Column 3 of **Table 4** presents results of the homogeneous relationship between income, insurance, and OOP on medicine. OOP increases with income. The coefficient is larger (0.572) compared to the general insurance in column 1 (0.537). Insurance reduced OOP but with a coefficient (0.408), that is less than that for the OOP expenditure on health (0.448). The result shows that medicine is the largest driver of OOP expenditure on health. Column 4 presents results that include the interaction between income and insurance. The findings show that in a subsample of the insured income increases OOP. The coefficient of interaction is larger (0.218) for the OOP on medicine compared to that of OOP expenditure on health in column 2 (0.178). The interacted results for both OOP expenditure on health and OOP on medicine together reveal that the increase in OOP that is driven by insurance centers on medication. The results show that among the insured, high income increases the chance that an individual meets the costs of the increased health care demand. Thus, partial insurance coverage fails to completely offset inequality in healthcare access.

Robustness Checks: Relationship Between Insurance and OOP Expenditures by Nationality

Saudi Arabia presents a unique case of the healthcare provision. The kingdom provides free access to healthcare to citizens through public healthcare facilities but not for expatriate workers. At the same time, the KSA has one of the largest numbers of expatriate workers. The expatriates rely on OOP and health insurance. Therefore, the aggregated results presented above may mask heterogeneous information by nationality. The expectation is that insurance should be relevant to the expatriates who have limited healthcare alternatives. If insurance is relevant for the citizens only, then the public free healthcare system is less effective in providing the demanded health care to its citizens.

TABLE 4 | Marginal effects of factors that affect OOP expenditure.

Variable	(1)	(2)	(3)	(4)
	OOP-Health	OOP-Health	OOP-Medicine	OOP-Medicine
Income (log)	0.537***	0.443***	0.572***	0.457***
	(0.031)	(0.047)	(0.030)	(0.042)
Insured	−0.448***	−2.036***	−0.408***	−2.357***
	(0.043)	(0.441)	(0.039)	(0.438)
Insuredincome (log)		0.178***		0.218***
		(0.048)		(0.048)
Saudi national	0.160***	0.175***	0.166***	0.182***
	(0.048)	(0.048)	(0.041)	(0.041)
Age	0.002	0.002	0.005***	0.005***
	(0.002)	(0.002)	(0.002)	(0.002)
Male	−0.204***	−0.201***	−0.139***	−0.134***
	(0.039)	(0.040)	(0.036)	(0.036)
Married	−0.120**	−0.112**	−0.155***	−0.145***
	(0.049)	(0.049)	(0.046)	(0.046)
Primary school	0.163**	0.158**	0.015	0.009
	(0.066)	(0.066)	(0.065)	(0.066)
Intermediate school	0.151***	0.143***	−0.082	−0.092
	(0.055)	(0.055)	(0.057)	(0.056)
Secondary school	0.029	0.024	-0.087	-0.090
	(0.057)	(0.057)	(0.056)	(0.056)
Higher education	−0.050	−0.054	−0.198**	−0.204***
	(0.091)	(0.091)	(0.078)	(0.078)
Health status	−0.212***	−0.185***	−0.158***	−0.126***
	(0.046)	(0.049)	(0.047)	(0.047)
Wealth index	0.018	0.010	0.029	0.018
	(0.012)	(0.012)	(0.012)	(0.012)
Pseudo R^2	0.0905	0.0927	0.0994	0.1021
Pseudo-log likelihood	−7165.184	−7148.340	−6935.431	−6913.946
Observations	8,655	8,655	8,490	8,490

*Note: Standard errors in parentheses. Significance levels: ***p <0.01, **p <0.05, *p <0.1*

Table 5 presents the relationship between health insurance and OOP expenditure on health split by nationality. Across all models, income relates positively to OOP. Columns 1 and 2 present estimates for the Saudi citizens and show that OOP reduces with insurance. Consistent with the aggregated outcomes, insurance interacted with income increases OOP. Columns 3 and 4 show results for the sub-sample of expatriate workers. While insurance maintains to reduce OOP expenditure on health, there is no relationship between OOP and the interaction between insurance and income. **Table 6** repeats these results using OOP on medicine. The findings remain consistent with those of OOP expenditure on health.

DISCUSSION

The results from this study contribute to a long-standing debate on whether health insurance reduces or increases OOP expenditure on health. We model the heterogeneity of the relationship between the insurance and OOP along income to untie this debate. Indeed, our results show that at low levels of income health insurance reduces OOP. Nevertheless, within the insured, income increases OOP. These outcomes support previous studies (Ahmed et al., 2020; Harish et al., 2020; Sriram and Khan, 2020) that established that health insurance reduces health spending through risk pooling. We further clarify that these expenditure-reducing effects of insurance accrue at the lower tail of income distribution. Hence, if the objective of policy is to cushion the relatively poor, then health insurance is a key.

Further, these findings raise a red flag on inefficiencies of healthcare provision induced by possible information asymmetries between healthcare providers and the clients under insurance. Previous evidence shows that health insurance increases health seeking behavior (Jowett et al., 2004; Blanchet et al., 2012; Robyn et al., 2012; Jin et al., 2019). As the insured make more visits to healthcare providers, they discover more about their health and a set of services required to maintain good health. Nevertheless, providers take advantage of the availability of the insured to prescribe care that is not covered by the insurance (Bogg et al., 2016). The choice of what part of the prescription is more essential than the other remains private information of the provider. This encourages supplier-induced demand and rising costs of medical expenditure that one would not have incurred in the absence of insurance.

The result that these rising costs due to health insurance are amongst the relatively rich also highlights persistent inequalities in the quality of and access to healthcare. Thus,

TABLE 5 | Marginal effects of the relationship between health insurance and OOP expenditure on health.

	(1)	(2)	(3)	(4)
Nationality	**Saudi**	**Saudi**	**Expatriates**	**Expatriates**
Variable	**OOP**	**OOP**	**OOP**	**OOP**
Income (log)	0.595***	0.402***	0.477***	0.440***
	(0.035)	(0.032)	(0.039)	(0.072)
Insured	−0.347***	−3.630***	−0.487***	−1.093
	(0.039)	(0.550)	(0.074)	(0.756)
Insured*income		0.350***		0.071
		(0.059)		(0.090)
Age	0.007***	0.007***	−0.001	−0.001
	(0.001)	(0.001)	(0.003)	(0.003)
Male	−0.026	−0.036	−0.341***	−0.346***
	(0.041)	(0.041)	(0.064)	(0.064)
Married	−0.102	−0.123***	−0.119*	−0.118
	(0.053)	(0.055)	(0.068)	(0.069)
Primary school	0.236***	0.247***	0.129	0.128
	(0.077)	(0.076)	(0.094)	(0.094)
Intermediate school	0.173***	0.177***	0.149***	0.144*
	(0.068)	(0.068)	(0.074)	(0.075)
Secondary school	0.179***	0.202***	−0.041	−0.043
	(0.065)	(0.065)	(0.078)	(0.078)
Higher education	0.223	0.254	−0.133	−0.140
	(0.071)	(0.072)	(0.131)	(0.134)
Health status	−0.102**	−0.091*	−0.279***	−0.262***
	(0.049)	(0.048)	(0.072)	(0.078)
Wealth index	0.011	0.008	0.015	0.009
	(0.013)	(0.013)	(0.021)	(0.022)
Observations	6,666	6,666	1,989	1,989

*Note: Robust standard errors in parentheses. Significance levels: ***p <0.01, **p <0.05, *p <0.1.*

if these extra services are essential for good health and they are only attained conditional on high income, then health insurance increases inequalities of access to good health. This is against the anticipated notion that insurance reduces healthcare inequality by making more services accessible to the liquidity constrained, moving them closer to the well-off. Perhaps insurance should be made more generous to cater for the improved demand that it creates if equity in healthcare is to be achieved.

In addition, the results from this study highlighted that free public healthcare systems do not eliminate increased spending on private health services. Particularly, we showed that the relationship between health insurance and OOP and the relationship between health insurance and OOP along different levels of income, are significant amongst people with access to free public healthcare who also happen to be citizens of Saudi Arabia. Free public health care is characterized by several bottle necks such as long waiting lines and limited amount of resources available to provide adequate health care to the population (Alkhamis et al., 2014). Hence, the finding that the heterogenous relationship between health insurance and OOP is only robust amongst Saudi citizens, could be reflecting the significance of these public healthcare provision challenges. Further, we show that these relationships are stronger on medicines relative to OOP expenditure on health. The result could also highlight the possible shortage of medicine in public the healthcare system.

Besides, the relationship between health insurance and OOP expenditure is insignificant amongst expatriate workers in this study. The result could be due to the nature of healthcare access for the expatriates. These workers are not allowed to use free public healthcare services and their employers are mandated, by law, to purchase health insurance for the expatriates to access private healthcare services (Alkhamis, 2018). Unlike public facilities, private facilities are not congested, hence, people have short waiting times. The convenience of using insurance in the private facilities reduces need to opt for quicker but paying services that are already covered by the insurance. Expatriates only pay for services that are not covered by insurance. The absence or presence of insurance should not alter demand for such services. This is confirmed by the positive relationship between income and OOPs by the expatriate workers. Therefore, OOPs amongst expatriates is responsive to income changes but not insurance. Arguably this could be through changes in demand on health care services that are outside the insurance package.

Only a handful of studies have examined the heterogenous effects of health insurance on OOPs. All of them evaluate insurance schemes that were initiated by government as is the case with the KSA scheme. In Mexico (Wirtz et al., 2012), the insurance is found reducing OOPs on medicine with effects of within a range of 1.4–1.7%, that is lower than the 2.2% found in our study. The heterogeneity studied in Mexico is, however, on different types of insurance packages rather than along different levels of income that we examine. Results from China partly support our

TABLE 6 | Marginal effects of the relationship between health insurance and OOP on medicine.

	(1)	(2)	(3)	(4)
Nationality	**Saudi**	**Saudi**	**Expatriates**	**Expatriates**
Variable	**OOPMED**	**OOPMED**	**OOPMED**	**OOPMED**
Income (log)	0.722***	0.430***	0.461***	0.488***
	(0.040)	(0.037)	(0.039)	(0.067)
Insured	−0.242***	−5.188***	−0.517***	−0.075
	(0.040)	(0.613)	(0.063)	(0.678)
Insured*income		0.527***		-0.051
		(0.066)		(0.080)
Age	0.012***	0.012***	0.001	0.001
	(0.001)	(0.001)	(0.002)	(0.002)
Male	−0.062	−0.080	−0.227***	−0.224***
	(0.042)	(0.042)	(0.055)	(0.056)
Married	−0.258***	−0.291***	−0.091	−0.093
	(0.054)	(0.057)	(0.065)	(0.065)
Primary school	0.126	0.145*	−0.012	−0.011
	(0.083)	(0.081)	(0.092)	(0.091)
Intermediate school	0.175**	0.182**	−0.204***	−0.200***
	(0.074)	(0.074)	(0.074)	(0.074)
Secondary school	0.264***	0.303***	−0.250***	−0.249***
	(0.071)	(0.072)	(0.076)	(0.076)
Higher education	0.278***	0.326***	−0.371***	−0.365***
	(0.074)	(0.076)	(0.110)	(0.113)
Health status	−0.186***	−0.170***	−0.110	−0.122*
	(0.053)	(0.052)	(0.071)	(0.074)
Wealth index	0.010	0.005	0.036	0.041**
	(0.015)	(0.014)	(0.020)	(0.020)
Observations	6,563	6,563	1,927	1,927

*Note: Robust standard errors in parentheses. Significance levels: ***p <0.01, **p <0.05, *p <0.1.*

findings (Wagstaff and Lindelow, 2008). Even though health insurance is found increasing OOP for both the poor and the rich, the increase is more pronounced amongst the rich. The authors argue that the contributory nature of the schemes make high quality services only affordable for the affluent. In Rwanda (Woldemichael et al., 2016), a health insurance is found increasing OOP on outpatient services for the rich while reducing OOP expenditure on health and on medicine. In relation to our findings, the results outside Saudi Arabia reveal that the heterogenous effects of insurance on OOP are context specific: they depend on the coverage of the schemes and income differences between the insured. In the case of KSA that implements a uniform compulsory scheme for non-citizens, OOP generally reduces with insurance, while increasing amongst the rich who are insured.

It is important to note that our study has possible limitations. First, since the data is self-reported it could suffer from recall bias particularly for exact amount of OOP and income. Second, there was a considerable amount of missing information on some health indicators that limited the sample size for analysis. This could be a serious problem where the non-responses are non-random which was not necessarily our case. Third, we only interpret our results as associations not causations recognizing the possibility that selection into insurance could be due to other factors such as risk aversion, that are not observable to a researcher. Fourth, we cannot observe how the heterogeneous relationship between insurance and OOP changes overtime because our data is cross-sectional. However, these findings light up important insights on the direction of association between health insurance and OOP, that it varies conditional on income. Therefore, policy should be aware of the likely implications of promoting health insurance coverage on OOP for people with different income levels; the insurance reduces OOP across the entire population but raises the OOP amongst people with high income (when income increases).

CONCLUSION

The study used data from the KSA to show that insurance reduces OOP expenditure on health amongst its participants while increasing the expenditure along rising income amongst them. The results highlight possible supplier-induced demand that insured individuals encounter in setups where insurance coverage is less generous. Further, they show that advanced care remains only accessible subject to income, hence, insurance may not be a panacea for equitable healthcare access. The heterogeneities along income are only robust amongst Saudi citizens (who have free public healthcare access) illuminating the significance of healthcare burdens experienced by free healthcare systems. The relationship between insurance and OOP is stronger on medicine, pointing toward the need for policy to target medicine within the healthcare package if welfare is to register remarkable savings on insurance. Accounting for these heterogeneous relationships

between health insurance while also maintaining a robust public healthcare system could therefore go a long way in propelling countries toward attainment of universal healthcare coverage, while being conscious about the potential welfare distribution impacts of the insurance on health spending.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analyzed during the current study are not publicly available due to privacy, confidentiality, and other restrictions. Access to data can be gained through the General Authority for Statistics in Saudi Arabia. Requests to access these datasets should be directed to Customer support of the General Authority for Statistics, email: cs@stats.gov.sa.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published and agree to be accountable for all aspects of the work.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

APPENDIX

TABLE A1 | Differences in Out-of-Pocket expenditure by income and nationality.

	Mean	Std Error	95% CI
OOP expenditure on health			
Below median income	485.440	8.006	469.746–501.135
Above median income	1009.990	23.800	963.336–1056.644
OOP expenditure on Medicine			
Below median income	257.996	4.617	248.946–267.045
Above median income	530.956	18.359	494.968–566.944
OOP expenditure on health			
Non-Saudi national	425.829	12.155	402.003–449.655
Saudi national	842.855	16.089	811.317–874.393
OOP expenditure on Medicine			
Non-Saudi national	206.659	6.707	193.512–219.806
Saudi national	450.046	12.161	426.207–473.885

Note: median income in the sample is 8900 Saudi Riyals (Equivalent to US$ 2373,33).

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