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The politics of COVID-19 vaccination in middle-income countries: Lessons from Brazil

Elize Massard da Fonseca [a,b,*], Kenneth C. Shadlen [c], Francisco I. Bastos [d]

[a] Sao Paulo School of Business Administration, Getulio Vargas Foundation, Rua Itapeva, 474, Sao Paulo, SP, 01332-000, Brazil
[b] Latin America and Caribbean Center, London School of Economics and Political Science, Houghton St, London, WC2A 2AE, United Kingdom
[c] Department of International Development, London School of Economics and Political Science, Houghton Street, London, WC2A 2AE, United Kingdom
[d] Laboratory of Health Information, Oswaldo Cruz Foundation, Av. Brasil 4365, Rio de Janeiro, RJ, 21045-900, Brazil

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ABSTRACT

As the world struggles to meet the challenges of vaccination against COVID-19, more attention needs to be paid to issues faced by countries at different income levels. Middle-income countries (MICs) typically lack the resources and regulatory capacities to pursue strategies that wealthier countries do, but they also face different sets of challenges and opportunities than low-income countries (LICs). We focus on three dimensions of vaccination: procurement and production; regulation of marketing registration; and distribution and uptake. For each dimension we show the distinct challenges and opportunities faced by MICs. We illustrate these challenges and opportunities with the case of Brazil, showing how each dimension has been affected by intense political conflicts. Brazil's procurement and production strategy, which builds on a long trajectory of local production and technology transfer, has been riddled by conflicts between the national government and state governments. The regulatory approval process, based around one of Latin America's most highly-regarded regulatory authorities, has also been subject to acute inter- and intra-governmental conflicts. And with regard to distribution and uptake, in the face of high uncertainty, even with a solid health infrastructure, Brazil encounters difficulties in promoting vaccine delivery. The research also reveals the importance of coordination among these dimensions, in Brazil and beyond. Pandemic preparedness and response must include sharing knowledge of how to produce vaccines and recognition of the crucial linkages between procurement, regulation, delivery, and uptake that are necessary for ensuring access to these products.

1. Introduction

The COVID-19 pandemic has brought attention to the challenges in securing access to vaccines on a global scale. Historically, populations in the Global South have been more likely to suffer from inadequate or delayed supplies of drugs, vaccines, and other essential medical products. Yet the factors that affect countries' access are not uniform. In this paper we focus specifically on the challenges faced by middle-income countries (MICs), which are frequently omitted from global initiatives to enhance access and affordability.

We focus on three dimensions that affect countries' abilities to use COVID-19 vaccines to curb the pandemic: procurement and production; regulation of marketing registration; and distribution, that is, delivery and uptake. Each dimension is highly politicized. While procurement and production of pharmaceutical products always involves complex trade norms and interests, risk regulation is no less contentious. MICs are still building regulatory capacity in the pharmaceutical sector, and uncertain scientific evidence around COVID-19 vaccines makes the challenges even more daunting. Finally, distribution is burdened by challenges in the context of scientific uncertainty and increasing vaccine hesitation, which can be fueled by the actions of denialist political officials. In such conditions, even solid health infrastructures may struggle to promote vaccination delivery.

We illustrate these challenges with the case of Brazil, discussing the obstacles that have emerged in each dimension, and showing how local processes have been affected by intense political conflicts, impeding coordination among them. While the national government's lackluster – and largely denialist – response to the pandemic has received considerable attention (Fonseca et al., 2021; The Lancet, 2020), scratching below the surface reveals a more complex set of decisions and initiatives.

* Corresponding author. Sao Paulo School of Business Administration, Getulio Vargas Foundation, Rua Itapeva, 474, Sao Paulo, SP, 01332-000, Brazil.
E-mail addresses: elize.fonseca@fgv.br (E.M. Fonseca), K.Shadlen@lse.ac.uk (K.C. Shadlen), francisco.inacio.bastos@hotmail.com (F.I. Bastos).

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Brazil's response to COVID-19 also builds on a record of successful responses to infectious diseases (e.g. HIV/AIDS, Hepatitis-C, Tuberculosis) and a strategy to orient national innovation and industrial policies toward meeting the demands of the national health system (Flynn, 2015; Nunn, 2008; Shadlen and Fonseca, 2013). Indeed, it is the combination of President Jair Bolsonaro's seemingly minimal ambition to mobilize a serious response to COVID-19 and other actors in the health community – and beyond – to do so, and the conflicts generated by these contrasting ambitions, that make the Brazilian case a fascinating one to study.

Although procuring COVID-19 vaccines, subjecting them to regulatory scrutiny, and distributing them widely are global issues that create generalized challenges, the steps that countries take nationally can mitigate or exacerbate these challenges. To understand this, it is necessary to begin exploring the reasons and mechanisms that underlie government responses and their lessons for public health practitioners and scholars in preparation for the next pandemic, or a resurgence of COVID-19. Our aim is to draw lessons from Brazil, which have implications for MICs more generally. We use the term "middle-income" to refer to countries classified by the World Bank as such, but also in a broader sense, in that we are referring to a set of countries that lack the abilities to respond to COVID-19 as wealthier countries can, but in general have resources, regulatory capacities, and healthcare infrastructures that distinguish them from the world's poorest countries.

Our study is grounded in qualitative, configurative research, a particularly useful approach given the need for in-depth, constantly updated data collection and analysis to understand countries' responses. As the current situation does not allow for the collection of primary data (field visits and semi-structured interviews), we base our analysis on systematic document-based research from January 2020 to April 2021, including government reports, media sources, and webinars. We also conducted online interviews with six key players engaged in the COVID-19 vaccine discussions and policies in Brazil. This study was also informed by the authors' decades of research on health industry policies, including studies on policies for antiretroviral drug production, pharmaceutical regulation, and technology transfer agreements for drug development.

The remainder of this article is organized in six sections. After providing a review of the challenges and opportunities presented to MICs in three key dimensions, in Section 3 we briefly provide background on political institutions and pandemic response in Brazil, so to contextualize the current case. We then examine each of the three dimensions in the case of Brazil. In Section 4 we analyze the intergovernmental disputes around strategies to promote technology transfer agreements to manufacture COVID-19 vaccines locally, in Section 5 we examine the politics around regulatory issues, and in Section 6 the challenge of distributing COVID-19 vaccines in Brazil. Finally, in the conclusion (Section 7), we outline lessons for global health and an agenda for future studies.

2. Procurement, regulation, and distribution of COVID-19 vaccines in MICs

The COVID-19 pandemic requires countries to devise strategies for procuring vaccines, for approving vaccines for local use, and for distributing the vaccines to their populations. This section reviews these three dimensions, showing how each takes on specific forms in the case of MICs.

2.1. Procurement and production of vaccines

To procure COVID-19 vaccines, countries can participate in global initiatives, they can make arrangements directly with the vaccine developers, and they may also be involved in conducting earlier-stage research with an eye towards developing new vaccines. Each of these presents distinct sets of challenges and opportunities for MICs.

One way for countries to procure vaccines is via COVAX, a pooled procurement mechanism that aims to de-risk vaccine purchasing by reaching agreements with a wide range of developers.[1] Although COVAX includes a facility to use donor funds to provide vaccines at close to zero-cost to 92 poor countries, many MICs are ineligible. Instead, MICs (as well as high-income countries) seeking to participate in the pooled procurement scheme do so as "self-financed countries," purchasing doses that COVAX secures from the developers.

Because of COVAX's limitations, both in terms of the amount of doses available and the timing of when the doses will be delivered, countries of all income levels have also negotiated directly with vaccine developers for supplies (Torjesen, 2020; Wouters et al., 2021). Some high-income governments did this early in the pandemic, before late-stage clinical trials had progressed, arranging to purchase abundant stocks of diverse portfolios of vaccines. Globally, the flurry of purchases accelerated in late 2020, as more information on efficacy became available. Yet countries purchasing vaccines at this point were competing over scarce doses, as much of the leading producers' initial output had already been committed. Faced with this scenario, MICs increasingly turned to vaccines developed by Chinese, Indian, and Russian labs (Taylor, 2021).[2]

One opportunity that MICs can exploit to secure greater access to vaccines is local production.[3] That is, they can partner with originator companies to produce vaccines locally, rather than importing, thus expanding coverage. To the extent that vaccine developers seek to establish distinct regional production networks they may turn to local partners with production capabilities. AstraZeneca, for example, has established vaccine manufacturing partnerships with local labs across the globe (Taylor et al., 2021).[4] Depending on their industrial infrastructure, MICs may have opportunities to participate in the production of COVID-19 vaccines.

But local production is easier said than done. Even where pharmaceutical manufacturing capacity exists, rapid production of COVID-19 vaccines at sufficient scale also depends on extensive transfer of technology and knowledge from the originators to the local partners, including non-codified, tacit knowledge that is not contained in patents or other public documents (O'Sullivan et al., 2020; Price et al., 2020). Yet technology transfer has enormous political and legal challenges, on account of the complexity of the information, the involvement of large teams of experts, and the need to align manufacturing and regulatory processes.

Finally, and to a lesser extent, MICs can invest in research of new COVID-19 vaccines. Although many MICs have scientific capabilities for basic research that could eventually lead to new vaccines, the extent of resources required to achieve these results, both in terms of the amounts of funding needed and the consistency of funding over time, make this challenge exceptionally daunting. As indicated, new vaccines have emerged from China, India, and Russia. These cases are an exception in that sense, deserving case studies on their own.[5]

2.2. Regulation

Vaccines, like other medical technologies, need to be authorized for

[1] https://www.gavi.org/vaccineswork/covax-explained (accessed April 24, 2021).

[2] https://launchandscalefaster.org/covid-19/vaccineprocurement (accessed April 27, 2021).

[3] As countries with high levels of virus prevalence and appropriate healthcare infrastructures are good sites for late-stage clinical trials, countries could also potentially condition authorization of trials on access to doses (Apuzzo and Gebrekidan, 2020). Space considerations prevent us from discussing this approach in this paper.

[4] https://public.tableau.com/profile/duke.global.health.innovation.center#!/vizhome/ManufacturingDataperVaccine/ManufacturingandPurchasespervaccine (accessed April 24, 2021).

[5] Cuba, a low-income country, has multiple vaccines in development too (Burki, 2021; Faiola and Herrero, 2021).

use in each country where the owner intends to commercialize its product. Pharmaceutical companies typically seek approval for new products with the US Food and Drug Administration (FDA) or the EU's European Medicines Agency (EMA), known as stringent regulatory authorities; approval from a stringent regulatory authority is then used as a basis for approval in other countries with less-established regulatory systems (Braine, 2005). However, the COVID-19 pandemic has compressed the regulatory processes: with new vaccines sought by all countries, urgently, companies have submitted data to obtain market approval simultaneously on a more global basis. The result is that national regulatory authorities (NRAs) in developing countries, which tend to be underfunded and lacking broad legal mandates to assert control over the safety, efficacy, and quality of medical products (National Academies of Sciences Engineering and Medicine, 2019), face unfamiliar challenges.

A crucial aspect of the regulatory approval process is determining and evaluating vaccines' efficacy, i.e., the percentage reduction in risk of infection, hospitalization, or death among vaccinated persons relative to unvaccinated persons, which is measured during clinical trials. To guide national regulators, the WHO established a target product profile for COVID-19 vaccines specifying minimum characteristics, including 50% efficacy—similar to influenza vaccines (World Health Organization, 2020a, b).

Countries' regulators must decide whether and how to comply with the WHO guidance, and if they should develop new tools to meet the exceptional circumstances brought by the pandemic. Low-income countries are likely to use the WHO Emergency Use Listing Procedure to approve COVID-19 vaccines (World Health Organization, 2020a). MICs may do the same, but they may also rely on the guidelines of international harmonization networks, or create their own rules and procedures.

The COVID-19 pandemic thus allows us to understand more about the regulation of pharmaceutical products in MICs, a topic that has been understudied. Broadly, regulators confront the risks of acting too slowly or too quickly. In the case of HIV/AIDS medicines in the USA, for example when the slow approval of breakthroughs antiretroviral drugs delayed the entry of these life-saving medicines, patients demanded new standards of efficacy, which resulted in the establishment of regulatory policies to fast-track certain products (Vogel, 2012). Yet quick approval of pharmaceutical products can be problematic too, allowing the entry of sub-standard or unsafe products into the market, and thus damaging the legitimacy of – and popular support for – the regulatory process (Carpenter, 2004, 55). We investigate these two processes – the slow or quick approval of COVID-19 vaccines and the political demands around approval - but also look for other mechanisms that could influence vaccine regulation in the MICs. For instance, the choice for relying on assessments conducted by another NRA or trusted institution when registering a COVID-19 vaccine.

2.3. Distribution: delivery and uptake

The third dimension, distribution, refers to both delivery and uptake. Or, put differently, bringing the vaccines to the people and bringing the people to the vaccines. Here, healthcare infrastructures are of critical importance. Regardless of whether countries import drugs or produce them locally, they need logistics and transportation infrastructure, as well as warehouses and clinics, to distribute and store medicines. While in low-income countries the delivery is often the responsibility of donor organizations – for instance, Gates Foundation will get the vaccines to where they have to go[6] - in MICs that responsibility lies with the healthcare system.

The WHO framework for the allocation and prioritization of the COVID-19 vaccination serves as a base on the prioritization of groups for vaccination within countries while supply is limited (World Health Organization, 2020b). Defining populations that could form the appropriate target groups is a problem faced by all countries, rich and poor. When considering the politics of vaccine distribution, we need to acknowledge that allocation is not just a matter of priority and ethics, but also politics. Who defines the priority list and how? Who will go first and why? Across the globe we have seen anecdotal information about groups trying to bypass the determined order of COVID-19 vaccinations. Some of these instances appear to be due to an inadequate definition of high-risk health professionals (e.g., should clerks working in COVID-19 hospitals be considered high risk?), while others show a clear pattern of catering to the rich and government elites.

Complementing the challenge of delivering vaccines is the challenge of uptake, as governments throughout the world, rich and poor, must confront the problem of vaccine hesitancy. Concerns about vaccines are related to the speed at which these products have been developed and approved, with doubts amplified by misinformation campaigns and anti-vax movements (Wouters et al., 2021). People's decisions about vaccination depend on many factors, including trust in government (Miyachi et al., 2020), which can be a challenge for countries where their leaders are sowing doubts of the quality of the vaccines based on the geographic location of their developers. Vaccine hesitancy is listed by the WHO as one of ten threats to global health, which should be carefully addressed by government leaders and not nurtured.

3. Contextualizing Brazil's response to COVID-19

Brazil has been one of the countries most affected by COVID-19, both globally and in the Latin American and Caribbean region. In January 2021, a more contagious coronavirus variant (P.1) surged in the city of Manaus, which was followed by an abrupt increase in COVID-19 hospital admissions. In March 2021, as Brazil witnessed a new spike in the pandemic, state and municipal governments were compelled to close non-essential businesses (and in some places, implement lockdowns) (Andreoni et al., 2021).

The Brazilian government's response to the virus has been controversial, and brought widespread criticism (The Lancet, 2020). President Jair Bolsonaro was elected in 2018 through an alliance between economic liberals and social conservatives. Bolsonaro's response to COVID-19 reflects his ongoing prioritization of business interests (not to 'stop' the national economy), his alliance with former US president Donald Trump (and in particular the shared hostility against China), and his conflict with the presidential-hopeful and governor of Sao Paulo (Fonseca et al., 2021). Important resistance to Bolsonaro came from state governors, particularly from Sao Paulo, the country's wealthiest and most populous state, who gained the authority to respond to the pandemic in the absence of a coordinated national response. A Congressional inquiry launched by Brazil's Congress to investigate the Executive's response to COVID-19, including questions about the vaccination strategy, shed light on the presumptive mismanagements of the Ministry of Health (MoH) (Marcello, 2021).

Brazil is a federal, multi-party presidential regime, with three levels of elected governments – municipal, state, national. Brazil has one of the largest public health systems in the world, covering 75% of the population, while 25% are secured through private health insurance (Paim et al., 2011). The MoH is responsible for coordinating health policies such as vaccination, while states and municipalities are responsible for healthcare provision. States have greater autonomy in healthcare provision, including in developing their vaccination campaigns if they wish (or need) to do so. The fact that Brazil is a continental sized country marked by deep social, economic, and cultural inequalities poses challenges to responding to the pandemic and to the process of vaccination (Castro et al., 2021).

In the remainder of this paper we explain how political conflicts have affected Brazil's COVID-19 response in the three dimensions that are the

[6] https://www.gatesfoundation.org/ideas/articles/coronavirus-vaccine-development-gavi (accessed March 7, 2021).

focus of our analysis: procurement and production, regulation, and distribution. Before doing so, however, and as a baseline for the subsequent analysis, we provide background about Brazil's approaches and historic successes in each of these dimensions.

Not only does the MoH have experience purchasing drugs in bulk for the national health system, the countries' state-owned research institutes and public laboratories have ample experience internalizing innovative vaccine production through technology transfer agreements (Benchimol, 2017). Indeed, roughly 75% of the vaccines used in the National Immunization Program (PNI, Portuguese acronym) come from public laboratories (Interfarma, 2017). Looking beyond vaccines per se, since the 1990s, soon after HIV/AIDS treatments were launched in wealthier countries, Brazil strategically invested in local production of antiretroviral drugs, an approach that came to be regarded as a remarkable global health example in the fight against the epidemic (Flynn, 2008; Nunn, 2008). More recently, the MoH has promoted ambitious technology transfer program for drug and vaccine development. This program has helped establish the expertise and absorptive capacity to allow local firms to engage with the developers of COVID-19 vaccines (discussed in Section 4).

Complementing Brazil's advances in production is the strengthening of the regulatory environment. The national regulator, ANVISA, was created in 1999, in the context of scandals over falsified and unsafe medicines. With the strong support of the MoH, Congress approved the creation of ANVISA as an independent agency, a model that grants it administrative and financial independence, and the stability of its directors (Piovesan and Labra, 2007). Since the late 1990s, the MoH and ANVISA have reformed what had been a corrupt and inefficient drug regulation system, such that Brazil's regulatory structure is regarded as the most stringent in Latin America (Pan American Health Organization, 2021).

Historically, Brazil has had a remarkable track-record in vaccinations, notwithstanding the country's size and divisions. The National Immunization Program (PNI) provides vaccines, exclusively funded by public resources, to the entire population. The logistics are impressive. In 2017, PNI distributed 300 million doses of vaccines and serum (ibid). PNI has 38,000 immunization rooms distributed in more than 5500 municipalities and it can reach 50,000 rooms during vaccination campaigns (Ministerio da Saude, 2020). Such campaigns mobilize 114,101 health professionals (three per room). In addition, citizens can also access vaccines, at any time of the year, at one of the 10,000 Basic Health Units.

4. Procuring and producing COVID-19 vaccines in Brazil

Although Brazil had been excluded from initial discussions of the WHO's response to COVID-19 on account of President Bolsonaro's controversial statements and actions (Moreira, 2020), in September 2020, Brazil signed an agreement with the COVAX Facility to procure doses covering 10% of the population. With an income-level that makes the country ineligible for the receipt of donor-funded vaccines, Brazil participates in COVAX as a "self-financing country." Self-financed countries can purchase doses covering up to 50% of their populations, through either "Committed Purchase" or "Optional Purchase" arrangements.[7] Brazil opted for the latter, thus retaining control over which vaccines it accepts from Covax, but at a higher price. Accordingly, Brazil committed USD 148,8 million upfront in 2020, with an additional USD 316 million) due when exerting its purchasing option (Franco, 2020).

The main feature of Brazil's vaccine procurement strategy was to couple purchases with agreements for technology transfer and local production. Indeed, COVAX was always a back-up; Brazil's purchased a small amount of doses through the pooled procurement scheme, as the MoH was banking on the local production and technology transfer strategy, which, if successful, would allow the country access to a larger number of doses, at lower prices. Yet these arrangements have been hampered by acute intergovernmental (and intragovernmental) disputes, and technical and legal problems.

In June 2020, as the Oxford vaccine research progressed, the MoH and AstraZeneca (AZ) reached an agreement that would allow Biomanguinhos, the biotechnological branch of the federal research institute, Oswaldo Cruz Foundation, to produce the vaccine locally. The arrangement included a first stage of the technology transfer, with AZ supplying the drug substance and Biomanguinhos undertaking the fill-finish steps to complete the manufacturing process for an initial 30 m doses (and then, if approved, another 70 m doses). Then, the second stage of technology transfer, involving internalization of the entire production process, including sharing of the crucial cell lines, would enable Biomanguinhos to manufacture the drug substance too, and thus the entire vaccine.

Both stages of the agreements required Biomanguinhos to adapt its manufacturing facilities and processes, and to retrain its personnel, to meet AZ's production standards. According to the Biomanguinhos director, Mauricio Zuma, the capability gains from the initial technology transfer arrangements would include improvements to quality control processes, although the primary technological advancements would come in the second stage, with Biomanguinhos manufacturing the drug substance itself (Personal Communication). AZ's vaccine uses a non-replicating viral vector, a genetically engineered virus that mimics SARS-CoV-2. Although Biomanguinhos already has the technology for cell culture in bioreactors, used to scale up industrial production, it will learn how to apply its existing capabilities to the viral vector technique.

These capability gains are important, not just for the production of a specific COVID-19 vaccine, but for subsequent products as well, accelerating the timescale for vaccine production. Mauricio Zuma, who characterized the benefits that accrue to Biomanguinhos from the technology transfer arrangements with AZ as "priceless" puts it as such: "There are speculations that Sars-CoV-2 is potentially mutable, requiring a new vaccine. A different vaccine in the future. If that's the case, we would be better equipped to give a rapid response by our own means and staff. This is a crucial point of this tech transfer" (CNN Brazil, 2020).

Yet technology transfer is easier said than done. The initial process was delayed, on account of technical problems with the machines and delayed delivery of key inputs. Nor has the second stage progressed smoothly. With the agreement signed in May 2021, AZ could send the cells that Biomanguinhos required to make the vaccine locally (Jansen, 2021). The transferral of the biobank to the local producer is the core step of the technology transfer, which required a long negotiation over the precise terms of the agreement (Vasconcelos, 2021).

Another crucial procurement and production initiative consisted of the state government of Sao Paulo and Butantan, a local public laboratory, reaching an agreement in June 2020 with China's Sinovac Biotech to conduct Phase III clinical trials of its novel vaccine candidate (Reuters, 2020). The Sinovac vaccine uses inactivated SARS-CoV-2 virus, a well-known technological approach used in polio and flu vaccines, one that Butantan had experience with from the production of rabies and dengue vaccines (Batista, 2020). Similar to the arrangements described above with Biomanguinhos, here too the initial stage features the local laboratory importing the drug substance and completing the manufacturing process locally, with an expectation that Butantan will also move to producing the drug substance. And, here too, Butantan did not have capacity for manufacturing this vaccine at scale, so it needed to convert existing facilities and also construct facilities.[8]

Because the agreement with Sinovac is a state government initiative

[7] https://www.gavi.org/vaccineswork/covax-explained (accessed April 24, 2021).

[8] See a webinar organized by the South Center with the experience of Butantan https://www.youtube.com/watch?v=H6dmVvxRiOo (accessed April 24, 2021).

and Butantan is owned by the Sao Paulo government, the governor does not have the authority to promote a comprehensive procurement strategy for Brazil's healthcare system. Initially, the purchasing commitment involved coverage in the state of Sao Paulo, with the possibility of expanding it nationally, at the discretion of the MoH. The governor of Sao Paulo, a political rival of the president, gained visibility for the partnership with Sinovac, which marked a stark contrast to Bolsonaro's agenda. Thus, local production of the Sinovac-Butantan vaccine (and regulatory approval and distribution, as we shall see in the next sections), was affected by inter-governmental conflict.

In addition to the procurement and production agreements with AZ and Sinovac, a number of state governments, as well as a local private firm, União Quimica, have also conducted negotiations for the Russian Sputnik vaccine (Moreira and Machado, 2020). Although União Quimica's initial request for emergency approval in early 2021 was denied by ANVISA due to incomplete data, the MoH agreed to purchase 10 million doses, pending regulatory approval.

Although technology transfer for local production has been an important feature of the Brazilian approach, such arrangements are not available for all vaccines. In the case of Pfizer, which has adopted a more centralized approach to global production, exporting to the world from a handful of sites in Europe and the USA, the MoH was unable to secure a commitment to local production or technology transfer.[9]

In fact, not only were technology transfer and local production not possible, but even the purchase of the vaccine was fraught with complications. Initial contract discussions that had begun in July between Pfizer and the MoH stalled, on account of disagreements over the amount of doses, the designated jurisdiction for resolving disputes, and, importantly, Pfizer's insistence that it would be protected against any claims that citizens might file if they experienced adverse events (Al Jazeera, 2021). Frustrated by the holdup, actors within the office of the Presidency bypassed the MoH and proceeded to negotiate directly with Pfizer, and in March 2021 a contract for 100 m doses was completed (on Pfizer's terms, enabled by a change in Brazilian legislation that gives Brazilian states and municipalities responsibilities for adverse events).[10] However, because the Pfizer vaccine was the first to receive market authorization by a stringent regulatory authority, and it also conducted clinical trials in Brazil, the Brazilian Congress and media questioned the slow procurement of this vaccine (Câmara dos Deputados, 2020).

Delays in local production at both Biomanguinhos and Butantan, and in procuring vaccines from Pfizer, led state governors, Congress, and civil society actors to pressure the MoH to pursue contracts with additional suppliers (e.g. from Russia) and the regulatory agency to expedite its review process (Vargas and Barcellos, 2021). Indeed, to start vaccination in early 2021, the MoH had to import six million doses of the AZ vaccine that it had intended to produce local, and make a deal with Butantan despite the hostility of President Bolsonaro to the Governor of Sao Paulo and the alliance with Sinovac. Throughout the first six months of 2021, the Ministry of Health signed agreements with Pfizer, Janssen, and Bharat Biotech (producer of Covaxin, despite lack of transparency on the clinical trials).

Finally, in terms of researching for a new product, there are several projects under development in Brazilian universities, including technologies such as virus like particles, synthetic products, and replicating viral vector – some have progressed to begin clinical trials (Hallal, 2021). However, investment in science and technology has been reduced considerably during the Bolsonaro presidency (Andrade, 2019). Brazil's research investment (total 60 million for the development of Versamune-CoV-2FC. Clearly, such amount is not sufficient for vaccine research.

5. Regulating vaccines in a polarized political context

Brazil agreed to the international consensus that vaccines proven to be at least 50% effective should be accepted during the pandemic (TV BrasilGOV, 2020). ANVISA is responsible, among others, for regulating clinical trials, pre- and post-marketing surveillance, and regulating imports of experimental products not yet approved in Brazil. Before the pandemic, ANVISA did not have rules on expedited marketing approval or reliance on other agencies for marketing authorization. Therefore, in February 2020, Congress approved legislation authorizing ANVISA to register products that received marketing approval from national regulatory agencies in other countries (full registration, not emergency authorization, as the latter is an abbreviated, temporally process). The law was then altered in April to rely on approvals from four NRAs that Congress designated as qualified to decide on the market entry of health products: the FDA, the EMA, the Pharmaceutical and Food Safety Bureau (Japan), and the National Medical Products Administration (China).[11]

Second, in September, to accelerate the marketing approval of vaccines, ANVISA established a new resolution allowing companies to make continuous submissions of information about the development of their vaccines as it becomes available throughout the course of the trial. Third, in July 2020, ANVISA created an evaluation committee for clinical studies, records, and post-registration changes of drugs for the prevention or treatment of COVID-19. Authorization of clinical trials would be assessed in 72 h.[12] Finally, in November, ANVISA created a new instrument to allow emergency use authorization of vaccines. When asked for ANVISA's motivation for developing such a regulatory instrument, the General Manager of Medicines and Biological Products, Gustavo Santos, explained that Brazil has been learning from other regulatory agencies, such as the FDA and International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) (Agência Nacional de).

Emergency authorization is a way of accelerating the availability of vaccines according to certain risk-benefit requirements (Agência Nacional de). COVID-19 vaccines licensed under emergency use cannot be distributed to the entire population and will only be available for government-funded programs. Initially, the emergency use would only be authorized for products whose clinical trials phase 3 were conducted in Brazil, where the agency holds information about safety and efficacy, and the clinical trials timeline. Therefore, as of December 2020, only four developers were entitled to request emergency approval (Sinovac, AstraZeneca, Janssen, and Pfizer). After a strong criticism from Russia's Gamaleya Institute, Congress, and the media, ANVISA revised its procedures to accept clinical trials conducted abroad (Vargas, 2021). The new legislation, creation of rolling review mechanism, and emergency authorization illustrate the processes of regulatory reliance – partly a decision taken in Congress, but also by ANVISA's regulatory specialists.

Therefore, vaccine developers seeking authorization in Brazil would have three options: rolling review approval and final license (the route used by Pfizer, which received marketing approval in March 2021), emergency use (e.g., AZ and Sinovac, authorized in December 2020, and Janssen in April 2021), or use the Congress route, claim the right to commercialize their product in Brazil as it was authorized in one of the 4 agencies listed in Law 14,006/2020 (as the writing of this article, April 2021, no firm has used this option).

Despite ANVISA's reputation for being one of the stringiest agencies in Latin America (Pan American Health Organization, 2021) and the

[9] https://launchandscalefaster.org/covid-19/vaccinemanufacturing (accessed April 24, 2021).

[10] Pfizer's contract was publicly available for ten days on the MoH website.

[11] Of these 4, the first three are recognized as stringent regulatory authorities by the WHO; note also that the WHO, which has its own prequalification process, was not included on the list. Noteworthy, in March 2021, ANVISA expanded the list to include other agencies: https://www.legisweb.com.br/legislacao/?id=410753 (accessed June 8, 2021)

[12] https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2020/submissao-de-ensaios-clinicos-novas-orientacoes (accessed April 26, 2021).

effort to expedite COVID-19 trials and vaccine approval according to the highest international standards; the agency became caught up in political conflict, both between the executive and legislature and between the national and subnational governments.

Bolsonaro advocated to slow the regulatory approval process, exclaiming that "the population will not be guinea pig" (Baptista, 2020) and insisting that "Brazil will not rush to approve the vaccine" (Lima, 2020). The president's concern with regulatory affairs began in late October 2020 as Butantan was getting ready to import the active substance and other materials from China for local production of Sinovac's vaccine. Bolsonaro's support for a careful – and slower – regulatory process had less to do with avoiding entrance of drugs that are unsafe or ineffective, than a political strategy to delay the availability of the product sponsored by his political opponent in Sao Paulo.

A critical moment for regulators was the interruption of Sinovac/Butantan clinical trials in November 2020. A series of miscommunication between Butantan and ANVISA further deepened a debate that was already highly politicized. Butantan reported a severe and unexpected event in the trial but did not provide supporting documents. In the face of uncertainty, ANVISA, relying on the precautionary principle (risk assessment judgment), suspended the trial (ANVISA, 2020). The president took this opportunity to further fuel the dispute with the governor of Sao Paulo, mocking the vaccine's safety (Gullino, 2020).

ANVISA was well positioned to respond promptly to the COVID-19 crisis. However, the agency had its processes questioned and used in political discussions. ANVISA also faced criticism from vaccine developers (mainly Pfizer and the Gamaleya Institute) and society about the criteria for emergency use. Given ANVISA's cautionary regulatory processes, Brazil granted its first emergency authorization to Sinovac/Butantan and AstraZeneca/Biomanguinhos in January 17, almost a month after other MICs. Several newspaper articles compared Brazil's vaccine authorization/approval with other Latin American countries such as Chile, Mexico, and Argentina – some vaccines registered in these countries (e.g. Sputnik-V, SinoPharm) had little information about clinical trials. In April 2021, ANVISA rejected a request of state governors to import Sputnik, arguing that the vaccine has "inherent risks" and "serious" defects, including lack of information ensuring safety, quality, and effectiveness (Brito and Ivanova, 2021). ANVISA eventually approved the exceptional and temporary import of Sputnik and Covaxin, with the conditions that immunization will cover no more than 1% of the population, will be restricted to certain individuals, who will be informed that the vaccine does not hold regulatory approval (Neumam, 2021). The six state governments that purchased Sputnik will be responsible for rolling it out locally, required to conduct effectiveness evaluation studies while doing so. The MoH will be responsible for distributing Covaxin. Imports of both vaccines can be suspended if ANVISA rejects their application.

Regulatory approval is a crucial antecedent to vaccination. Therefore, regulatory decisions had decisive implications for the timing of vaccination and the products available for distribution in the country.

6. Delivery and uptake of COVID-19 vaccines in Brazil

Brazil began its COVID-19 vaccination rollout on January 17, 2021, almost a month after its neighbors in Latin America and other MICs, which caused strong societal and congressional pressure on ANVISA and the MoH (Cancian, 2021). Notably, despite the delay, as soon as the first vaccine was authorized, Brazil quickly caught up with other MICs (Fig. 1). Here, we unpack some of the politics distribution, including planning the vaccination campaign (defining priority populations), coordinating distribution, and ensuring confidence in the vaccine.

Brazil's COVID-19 vaccination strategy was shaped directly and indirectly by political conflict. The MoH's initial strategy stipulated that immunization would start with health professionals, elderly population, patients with comorbidities, and other people with increased vulnerability. Within this approach, consistent with the WHO's framework for the allocation and prioritization of the COVID-19 vaccination (World Health Organization, 2020b), the MoH suggested 29 priority groups, which amounted to 49.6 million people. This list quickly expanded, however, as additional societal groups, e.g. education professionals, truck and industry workers, requested they too be treated as "priority" (Lopes and Carvalho, 2021), and by February 2021 the "priority"

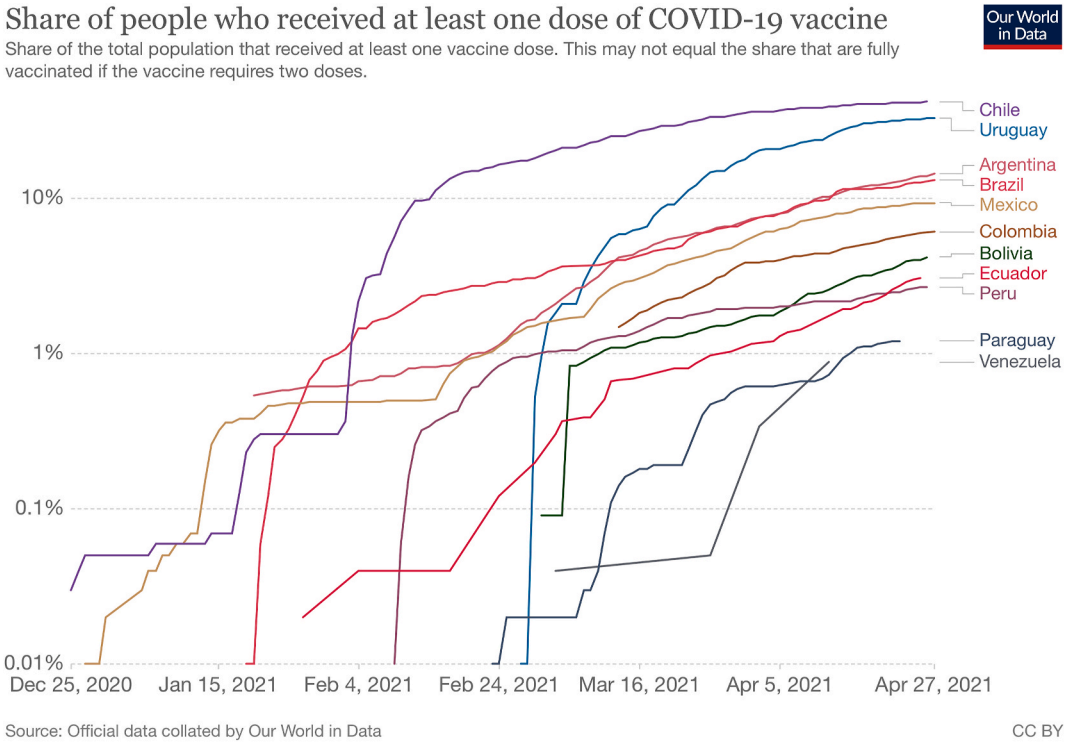

Fig. 1. Share of people who received at least one dose of COVID-19 vaccine.

population went increased by more than 50%, to 77.2 million people (Werneck et al., 2021).

Once vaccination commenced, it also became evident that the national plan was not detailed enough to allocate doses efficiently. For instance, it did not define who, exactly, are the healthcare workers that are entitled to the vaccine. Therefore, state and municipal governments had to operationalize the MoH's guidelines locally, establishing their own priority list and logistics. Several states altered the priority list to include state security forces and education professionals, leaving behind vulnerable groups such as patients with comorbidities (Lopes, 2021).

Nor, critically, did the national vaccination plan stipulate in advance which products would be distributed, a problem that is linked to the procurement/production and regulatory issues discussed in the previous sections. Although Pfizer vaccine was the first approved worldwide, until December the MoH was silent about the possibility of procuring Pfizer, or any other product apart from the Biomanguinhos-AZ and Butantan-Sinovac vaccines. And even the inclusion of the latter occurred only after intense dispute between the Sao Paulo and federal governments, and intervention by the Supreme Court. As discussed above, Bolsonaro was emphatic that Brazil would not use "the Chinese vaccine" (Schuch, 2020) and attempted to impede ANVISA's approval for local use. The Sao Paulo government, however, began negotiations with state and municipal governments around the country to supply the vaccine directly to them, a decision that was authorized by the Supreme Court if the federal government failed to properly conduct the vaccination program (Falcão and Vivas, 2021). It was only in the face of vaccine under-supply and this ruling that the Bolsonaro government agree to reach a deal to include the Butantan-Sinovac product in the national vaccination strategy.

The confrontational position adopted by President Bolsonaro, the disputes with state governors, and some of his public statements on the dangers of vaccines have potential implications for vaccine confidence too, and thus population's willingness to receive vaccines. The common reasons for vaccine hesitancy in Brazil are issues with confidence in the efficacy/safety of the vaccine and concerns about adverse effects (Brown et al., 2018; Sato, 2018). In cross-national research on COVD-19 vaccine confidence, Brazil ranks high. According to a set of random surveys in late 2020 of adults in 32 countries, Brazil was 7th among 32 countries in terms of willingness to take a COVID-19 vaccine (Wouters et al., 2021). Yet longitudinal analyses tell a different, and more worrying, story, of declining vaccine confidence. In December 2020, 73% of Brazilians declared that they intended to get vaccinated, aa reduction of 16% when compared to the August poll. In March 2021, there was an increase and 84% declared intention to get a COVID-19 vaccine (Datafolha Instituto de Pesquisa, 2021) It is difficult to determine the causes of this change, but it's certainly plausible that increased hesitancy seen in late 2020 is associated with controversial political statements at the highest level. In December, Bolsonaro declared that he would not take the vaccine and 'if you turn into a crocodile, it's your problem,' referring to alleged, possible side effects of Pfizer's vaccine (Daniels, 2021). Indeed, the President's response to the pandemic has leveraged misinformation as a political strategy, promoted pseudoscience, and undermined the MoH (Lasco and Curato, 2019).

This scenario is particularly problematic as Brazil has failed to control the pandemic. A year after the first case was diagnosed, Brazil was still facing a surge in cases and deaths, with several variants of concern in circulation (Castro et al., 2021), failure to mitigate the spread and expand vaccination could further aggravate the burden.

7. Conclusion

The historical alignment of the health system with public production facilities has made Brazil well-equipped to engage in tech transfer of COVID-19 vaccines. Most important, Brazil's strategy for ensuring access to COVID-19 vaccines is a hopeful combination of tech transfer, international and local procurement initiatives, and investments on local research of a new vaccine. However, stumbling blocks and limited coordination between production/procurement, regulation, and distribution affected Brazil's COVID-19 vaccination strategy. Even if the country had committed to Pfizer in August 2020, Pfizer only received regulatory approval in February 2021. Similarly, although technology transfer promised to allow Brazil to secure greater access to vaccines, local production vacillated given technical, legal, and supply problems. To further complicate, conflicting relations between governors and the president have influenced what could have been a coordinated, successful strategy. Political disputes between the president and the governor of Sao Paulo have influenced the planning of the national vaccination campaign and sowed needless doubts of the quality of the vaccines. Furthermore, these disputes have not only marred the organizational reputation and trustworthiness of ANVISA, an agency that until recently was increasingly gaining credibility in health regulation, but also sowed doubt about and distrust in COVID-19 vaccines. Such suspicions can have far-reaching consequences for public health that will be difficult to reverse. Yet, we can take lessons from Brazil's strategy now and for future crises preparedness.

The pathway for gaining access to COVID-19 vaccines in Brazil invites us to reflect on (and revisit) the politics of ensuring access to pharmaceuticals in MICs. We acknowledge that it is far too soon, still in the middle of the pandemic and at the incipient stages of vaccination in Brazil, to draw conclusions. However, we point to some directions for future research.

Brazil demonstrates that sharing knowledge about vaccine production is crucial for ensuring affordable access to these products in MICs. It also suggests that the integration of health and industrial policy is crucial for addressing urgent health problems, such as the demand for COVID-19 vaccines. Increasing investment in industrial development alone is not sufficient. It is the dynamic interaction of both realms, R&D and health systems, that matters (Santiago, 2020). Such integration cannot be built quickly during pandemic times. It requires long-term investments to develop knowledge in strategic sectors for national security, which can be applied during public health emergencies. We urgently need to reformulate pandemic preparedness to include not just pooling procurement but also sharing knowledge about the production of life-saving pharmaceuticals. This is crucial for countries that are excluded from global initiatives to enhance access to vaccines in low-income countries but also lack the capacity to purchase large amounts of vaccine doses. Surprisingly, the *UN Research Roadmap for the COVID-19 Recovery* was silent about any reformulation of the current research and development model. Therefore, we call for a better integration of the UN's Sustainable Development Goals (particularly SDG 9, infrastructure and industrialization, and SDG 3, health and well-being) and for the inclusion of technology transfer strategies in pandemic preparedness guidelines.

The dispute over COVID-19 vaccine authorization in Brazil draws attention to the importance of examining the politics of pharmaceutical regulation in the Global South. The politics of regulation is a field that has developed in the U.S. and European contexts (Vogel, 2012), but we have yet to fully understand its dynamics in emerging economies. During public health emergencies, countries face pressure to rapidly approve lifesaving products, and expertise in fast-track mechanisms for doing so is crucial. However, many LMICs have yet to develop capacity in pharmaceutical regulation, and some do not even have an adequate national health regulatory authority to put forward such regulations (Khadem Broojerdi et al., 2020). In Africa, for instance, Tanzania and Ghana are the only countries acknowledged by the WHO to have well-functioning regulatory systems for medical products (World Health Organization, 2018). There is extensive variation in drug regulation in the Global South (Fonseca and Shadlen, 2017), and comparative political studies could provide valuable contributions toward explaining the local political dynamics that shape drug approval processes in these countries, particularly during public health crises when regulatory coherence is key.

Because the incentives and institutional baseline of Global South countries differ from those of industrialized economies, scholars will need to develop new concepts and approaches to answer these questions. COVID-19 regulation efforts in Brazil suggest some avenues for investigation: First, there should be further study of the political economy of drug regulation. Second, there should be further investigation of health authorities' risk assessment criteria and regulatory functions for marketing approval of new products (Light, 2010; Vogel, 2012). And third, as drug regulation is becoming increasingly harmonized through common standards set by international agencies and regulatory networks such as ICH, the Pan American Network for Drug Regulatory Harmonization, the International Pharmaceutical Regulators Programe (Silva and Tagiari, 2016), there is increasing need to understand regulatory convergence and how MICs translate such norms into domestic regulatory standards.

Finally, planning the distribution of vaccines in conditions of uncertainty is challenging. Health infrastructure is key to getting vaccines to people; however, COVID-19 has taught us that government capacity alone is not sufficient to ensure pandemic preparedness. The contestations about vaccine approval, procurement, and coordinated national plan in Brazil further illustrate the importance of considering politics when responding to pandemics. For instance, trust in government and policy experts is crucial for persuading the public to accept a COVID-19 vaccine (Wynen et al., 2020). In addition, although international guidelines assist in creating a more equitable distribution of vaccines, decisions about uptake are conditioned on agreements made at the production and procurement stage and the marketing authorization norms defined by each country. For instance, at first, according to the ANVISA norms, only four vaccine developers would be entitled to emergency use authorization because they are the only ones conducting clinical trials in Brazil. Congressional legislation on COVID-19 has increased the possibility of vaccine uptake in Brazil. However, distribution will depend on the capacity of the health system to deliver certain products (e.g., Pfizer's vaccine will be challenging to distribute). Therefore, the case of Brazil illustrates well the crucial linkages between production, regulation, delivery, and uptake that are necessary for ensuring access to COVID-19 vaccines in MICs.

Author contributions

Conceptualization and Data curation (EMF and KS); Funding acquisition (EMF and FIB); Investigation and Methodology (EMF and KS); Roles/Writing - original draft (EMF and KS); Writing - review & editing (EMF, KS, FIB).

Declaration of competing interest

The authors declare no conflict of interest.

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