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Facing the Pandemic of Antimicrobial Resistance

Current Actions and Future Challenges in Antibiotic Stewardship, Access, and Innovation in Brazil

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Abbreviations

AMR	antimicrobial resistance
ANVISA	Brazil's national health regulatory authority
API	active pharmaceutical ingredient
CAP	Price adequacy coefficient
CMED	Drug Market Regulation Chamber
ERP	external reference price
GLASS	Global Antimicrobial Resistance and Use Surveillance System
IRP	internal reference price
MoH	Ministry of Health
NHS	National Health Service (UK)
PDP	Partnerships for Productive Development
RENAME	Brazil's national list of essential medicines
SUS	Brazil's unified health system

Key findings

- Almost 140,000 people die with a drug-resistant bacterial infection in Brazil every year. This burden of antimicrobial resistance (AMR) is likely rising, due in large part to shortcomings in access, stewardship, and innovation for antimicrobials.
- Brazil's existing Productive Development Partnerships system could be modified to reduce incentives for overselling and leveraged to improve antimicrobial procurement in Brazil and possibly across the region. This policy option would also support local manufacturing goals set by the Brazilian government.
- Brazil can further address antimicrobial market challenges in its AMR response by modifying pricing policies for new antibiotics, scaling up priority regulatory review processes, expanding AMR stewardship policies, leveraging AMR data for decision-making, and increasing access to diagnostics for antibiotic-resistant infections.
- With the largest pharmaceutical sector in Latin America and the Caribbean and one of the largest in the world, Brazil could lead the way in addressing the access and stewardship gaps for critical antimicrobials.

Executive summary

While some high-income countries are considering specific actions to address the growing burden of antimicrobial resistance (AMR), efforts among low- and middle-income countries are less common. This paper analyzes current efforts in Brazil, a middle-income country, to improve antibiotic stewardship, access, and innovation.

We carried out a desk review of current active efforts, national policies, and procurement processes within the Brazilian Unified Health System (SUS) related to antibiotic access, stewardship, and innovation. We complemented this analysis with 11 expert interviews. All interviewees are currently working within the Brazilian health sector and have direct knowledge of and/or decision-making authority on AMR-related initiatives.

Our desk review and interviews highlighted the importance of three institutions. First, ANVISA, the national health regulatory authority, oversees new drug approvals and is responsible for health surveillance. Second, the Drug Market Regulation Chamber (CMED) regulates drug pricing in Brazil. And third, the Ministry of Health (MoH) manages public health policies and purchases highly specialized health products for SUS.

To further strengthen antibiotic access, stewardship, and innovation in Brazil, we suggest leveraging existing infrastructure. Our proposed model builds upon the traditional Partnerships for Productive Development (PDP) model, in which contract arrangements between the MoH and an official laboratory aim to transfer and absorb the technology and the production of a health product from a private pharmaceutical company over 10 years. The traditional PDP model offers incentives for the partners involved, which include pharmaceutical companies, public laboratories, and SUS. It provides pharmaceutical companies with indirect access to SUS; official local laboratories with advanced technological expertise; and SUS with potential access to new, more affordable products. The PDP model could support the innovative capabilities of local laboratories through the technology transfer process, which is likely to have spillover effects in the development of new drugs.

Our proposed model, the annual fee PDP, recommends minor changes to the traditional PDP. Like subscription models promoted in Sweden and the United Kingdom, the annual fee PDP involves fixed annual payments to pharmaceutical companies in exchange for access to their drugs. Such a measure would delink revenues from sales volumes, hence reducing pharma companies' incentive to oversell their drugs, while also justifying investments to register new antibiotics which are not yet available in Brazil. We conclude our analysis with a discussion of the appropriate scope, implementation, and political palatability of the annual fee PDP.

1. Background

Brazil is the most populous country in the Latin American and Caribbean region and the eighth-largest economy in the world. Its Unified Health System (SUS) offers all people in Brazil access to complete healthcare services and drugs without a copayment. SUS provides services, ranging from primary healthcare to comprehensive hospital services and complex treatments, and is financed with tax revenues. According to IQVIA, Brazil is one of the 10 largest pharmaceutical markets worldwide and the largest in Latin America and Caribbean—and is expected to remain so for at least the next four years (IQVIA 2022). According to the national association of pharmaceutical companies, SINDUSFARMA, Brazil sold almost $20.7 billion in pharmaceuticals in 2022.[1]

Brazil's large pharmaceutical market is complemented by a very strong, in-country production capacity through a unique network of public laboratories. These laboratories have the capacity to manufacture a significant quantity of medicines and other health technologies. The medicines are, in turn, sold through the private market and to SUS through traditional auctions. They are also sold through an innovative purchasing system known as Partnerships for Productive Development, or *Parcerias para o Desenvolvimento Produtivo* (PDP) in Portuguese (discussed in Section 2.1). The network includes the Oswaldo Cruz Foundation (FIOCRUZ), the most prominent science and technology health institution in Latin America, and a world leader in the production of yellow fever vaccines. FIOCRUZ also produces several rapid tests, including those to detect HIV, chikungunya, COVID-19, dengue, and Zika, among others.

Yet, the country faces a mounting burden of antimicrobial resistance (AMR) going forward. Every year in Brazil an estimated 222,000 people die from a bacterial infection. It is thought that 62 percent (138,000) of these deaths are due to antibiotic-resistant infections—an estimated 33,000 of which are directly attributed to AMR.[2] According to official information from local antimicrobial sensitivity tests, in 2021, the resistance rate of *acinetobacter baumannii* bacterias to Carbapenems antibiotics (like imipenem or meropenem) was 86.7 percent—meaning less than 14 percent of isolates examined were susceptible to this drug—above the worldwide rate estimated by the World Health Organization's (WHO) Global Antimicrobial Resistance and Use Surveillance System (GLASS) of 69.0 percent.[3] In addition, according to a recent report by the WHO, Brazil holds the highest antibiotic usage rate in the Americas, with 22.8 daily doses per thousand people, substantially higher than Bolivia (19.6), Paraguay (19.4), Canada (17.1), Costa Rica (14.2), and Peru (10.3) (WHO 2018). Another study found that Brazil is the least prepared country of the G20 to combat AMR (IDSA 2021), despite commitments made in the National Action Plan to fight AMR, enacted in 2018.

1 Available on https://sindusfarma.org.br/mercado/indicadores-economicos visited on March 10, 2023.
2 Available on https://www.tropicalmedicine.ox.ac.uk/gram/research/antimicrobial-resistance-visualization-tool tool visited on April 27, 2023.
3 Available on https://app.powerbi.com/view?r=eyJrIjoiZDIwZjYyMzUtMmYxZS00MTRjLTk0NWMtZWE2ZDUzOGRjOTVjIiwidCI6ImI2N2FmMjNmLWMzZjMtNGQzNS04MGM3LWI3MDg1ZjVlZGQ4MSJ9 and https://worldhealthorg.shinyapps.io/glass-dashboard/_w_d2d13bda/#!/ visited on March 10, 2023.

In this paper, we analyze how Brazil's policies and current purchasing systems are affecting local access, innovation, and stewardship of new innovative antibiotics. We highlight policy areas that need special attention and make recommendations for strengthening Brazil's response to the AMR pandemic. To develop the study, we conducted a desk review of national policies and SUS's current antibiotic procurement process, to identify the main processes and challenges. This analysis was complemented with insights from interviews with key informants—representatives from government agencies, industry associations, and academia—selected from a stakeholder map. The map identified key influencers relevant to listing, procuring, and reimbursing antibiotics in Brazil. We identified over 850 stakeholders and categorized them according to their level of influence in the decision-making processes of listing, pricing, and procuring drugs in Brazil. We focused on 37 stakeholders with a very high or high level of influence and interviewed 11 of those. In the second stage, we identified opportunities to improve the current antibiotic purchasing system to help the country be better prepared to deal with AMR. This study is part of an ambitious agenda that seeks to contribute to the understanding of new models through which low- and middle-income countries can better address the challenges posed by AMR.

The next section presents key challenges that Brazil is facing and current actions its key institutions are taking to tackle each, identified through an analysis of the desk review and key informant interviews. We also highlight opportunities to improve antibiotic stewardship, access, and innovation in Brazil. Section 3 presents our main recommendations to foster antibiotic stewardship, access, and innovation in Brazil, and Section 4 concludes with a summary and discussion of the paper's key findings.

2. Key challenges, current actions, and opportunities for improvement in antibiotic stewardship, access, and innovation in Brazil

2.1. Traditional purchasing mechanisms do not provide sufficient incentives to introduce new antibiotics to Brazil, but Partnerships for Productive Development and annual fee models could create new incentive structures

Procurement of antibiotics by SUS, the major source of health care in Brazil, takes place at three levels: national, state, and municipal. The Ministry of Health (MoH) is responsible for procuring medicines at the national level, while the State or Municipal Health Offices are responsible for procurement at the state and municipal level, respectively. At the national level, SUS provides coverage of all medicines listed in the National List of Essential Medicines (RENAME). There are also some drugs for which responsibility for supply is shared by the national, state, and municipal levels. Still, states and municipalities have the autonomy to choose which medicines to buy according to their local epidemiological characteristics.

Irrespective of the administrative level, procurement must take place through electronic auctions. Electronic auctions can foster participation favoring competitiveness and potentially reducing the prices of purchased drugs. The auction's final price must comply with the national price caps

(see Section 2.2), including a minimum mandatory discount known as the price adequacy coefficient (CAP). Since December 2020, the CAP has been 21.53 percent.[4]

Traditional purchasing mechanisms like auctions are effective in fostering competition and reducing prices, but they do not provide sufficient incentives to drug providers to introduce new antibiotics to the Brazilian market or to invest in antibiotic research and development. Company revenues depend on the volume sold, and low volumes are encouraged to protect new antibiotics. Additionally, price caps further limit the ability of companies to compensate for the low volume of sales with higher prices. Hence, the current system for purchasing antibiotics under-incentivizes innovation and motivates overuse.

Partnerships for Productive Development. Brazil has overcome similar problems in other areas—including accessing highly effective antiretroviral therapy in the late 1990s at a lower cost (Nunn et al. 2007; Rodrigues and Soler 2009)—by increasing local production. One model Brazil has developed to address these market concerns is an innovative purchasing system known as Partnerships for Productive Development—or *Parcerias para o Desenvolvimento Produtivo* (PDP) in Portuguese.

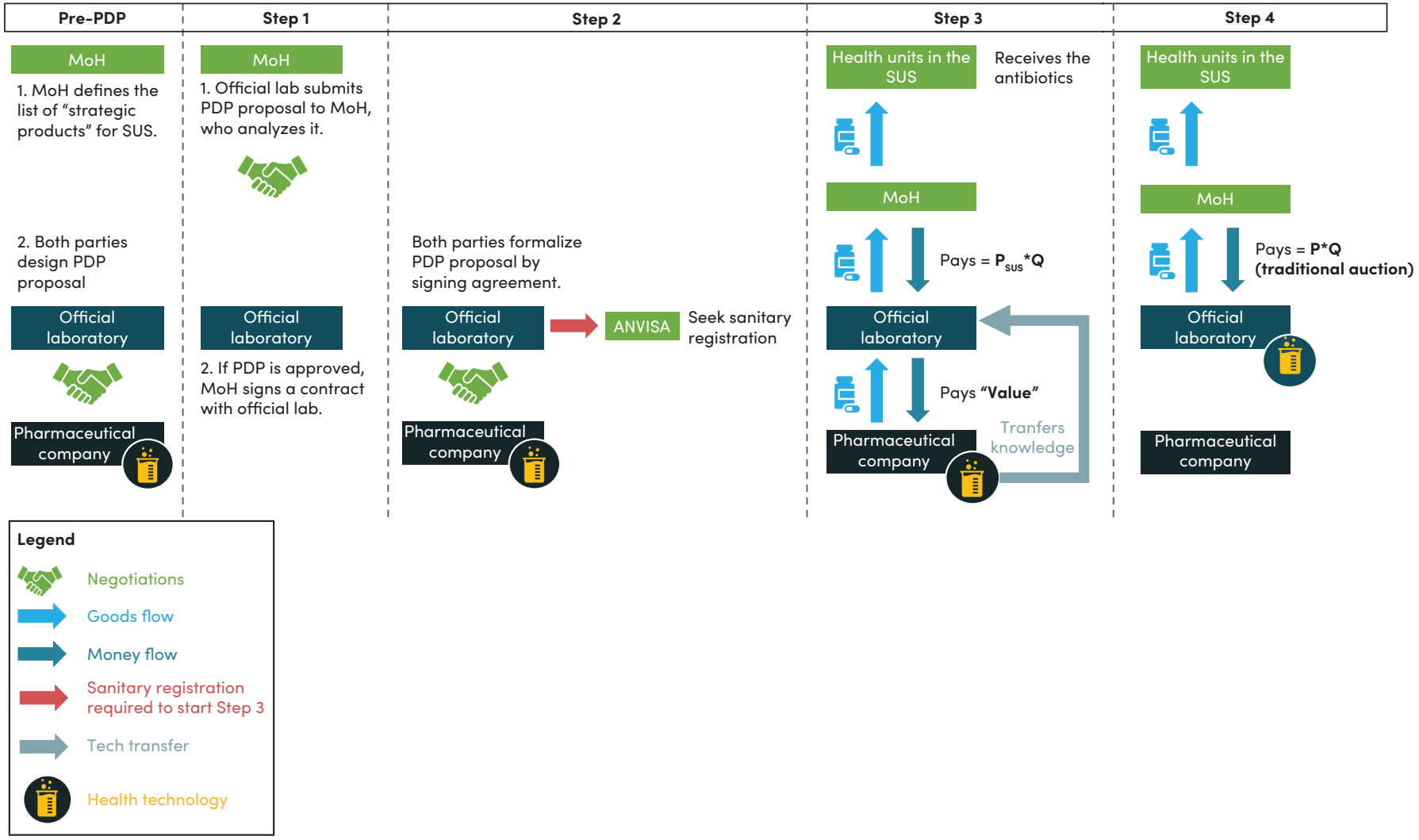
PDPs began in 2009 as a way of using MoH's central procurement system and SUS purchasing power to bring new drugs to Brazil, stimulate local production, and decrease the cost to SUS of accessing certain treatments. Ordinance 2.531/2014 governs PDPs. Under a PDP, the MoH purchases a health product (e.g., a medicine) from a public laboratory, which purchases a health technology from a pharmaceutical company. PDPs aim to *gradually transfer* and *absorb* the technology and production of a health product from a drug provider to an official lab, within 10 years.[5] As of December 2022, there were 66 active PDPs, the majority of which are related to antivirals, anticancer, and immunosuppressant medicines. There is only one PDP related to antimicrobials, specifically to treat tuberculosis (the combination treatment of ethambutol/isoniazid/pyrazinamide/rifampicin—one of the earliest PDPs launched in 2009).

The technology must be *gradually transferred* to an official laboratory from a national or international company that owns the technology. The official lab proposes the PDP to the MoH and should be qualified to supply SUS during the period of technological absorption. The supply to SUS is carried out through the official laboratory, which gradually starts producing the medicine. At the beginning, depending on the agreed terms set between the official lab and the pharma company, the active pharmaceutical ingredient (API) may be decreasingly imported from abroad or supplied by a local pharma company that holds the technology. Accordingly, the technology transfer usually begins with packaging, then bottling, production, and, finally, the formulation of the drug's API by the official laboratory. In Figure 1, we describe the four steps of every traditional PDP.

4 Resolution CMED N. 5 of 2020. Available on https://www.gov.br/anvisa/pt-br/assuntos/medicamentos/cmed/legislacao/resolucoes_cte visited on March 10, 2023.

5 In the case of synthetic medicines, health technology is the capacity and needed knowledge to manufacture the API at a large scale.

FIGURE 1. The traditional Partnership for Productive Development (PDP) of Brazil



Sources: https://www.gov.br/saude/pt-br/composicao/sctie/cgcis/pdp/etapas-do-pdp visited on December 15, 2022; Ordinance 2.531 of 2014 available at https://bvsms.saude.gov.br/bvs/saudelegis/gm/2014/prt2531_12_11_2014.html visited on December 15, 2022; CGU (2019), and Varricchio (2017).

PDPs also involve *absorbing* the production of the health product. At the end of the PDP, the official lab successfully takes up sole responsibility for manufacturing the health product. By the end of the PDP, the official lab can continue to supply SUS through the traditional auction mechanism. The pharma company may still supply the private market.

The PDP model offers incentives for pharmaceutical companies, official laboratories, and SUS. PDPs provide pharmaceutical companies with a secure pathway to SUS that does not follow the electronic auctions. PDPs provide local official labs with technological expertise, and the potential to supply SUS. Finally, completed PDPs provide SUS with access to a broader range of more affordable health technologies.

In a traditional PDP, the purchasing price arises from a negotiation between the MoH and the official lab. Prices must decrease over the lifespan of the PDP and be based on previous prices paid by the MoH for purchasing the same medicine and on a price cap negotiated by the Drug Market Regulation Chamber (CMED). Although the official laboratory's revenue depends on the price per unit and the number of units sold to the MoH, the official laboratory and the pharma company have more flexibility when they negotiate the payments' timing and conditions. Some price arrangements could be more attractive to the pharma company than to the official lab. In principle, they could, for example, negotiate a price per unit or a fixed annual payment. This flexibility opens the possibility for the official lab to purchase a technology transfer by paying a fixed amount to the private company or by sharing revenues per unit sold to SUS with the private company.

Subscription Models. Two high-income countries (Sweden and the United Kingdom) are advancing in the application of innovative purchasing mechanisms for antibiotics. These aim to create new incentive structures that will enable drug providers to invest in the development and commercialization of new antibiotics.[6] Subscription models—an innovative purchasing mechanism sometimes known as the "Netflix model"—consist of fixed, annual payments to a drug provider for a set period, in return for access to a previously negotiated supply guarantee. Crucially, the fixed payment delinks the drug provider's revenues from sales volumes. In this sense, the drug provider's revenues do not depend on the number of antibiotics sold. Instead, subscription models decrease the incentive to oversell the drug because every additional unit manufactured would decrease profits. Pilots of subscription models have been applied worldwide to different groups of drugs, from treatments for hepatitis C to HIV and diabetes (Trusheim, Cassidy, and Bach 2018). Several other countries are moving towards implementing such a system for antibiotics specifically, including Canada, Japan, and the United States, whose plan is outlined below.

In 2020, Sweden adopted a partially delinked subscription model. The aim is to guarantee access to any newly patented antimicrobials that might otherwise not be available in Sweden due to low sales

6 World Economic Forum. "This is how to fight antibiotic-resistant superbugs with a simple subscription payment model." Available on https://www.weforum.org/agenda/2022/02/antibiotic-resistance-amr-subscription-payment-model-superbugs/ visited on March 10, 2023.

volumes. Under this model, Swedish county councils and regions continue to pay for their usage of antibiotics. If the drug provider's revenue from county council and region purchases is lower than the guaranteed revenue, the national government pays the difference at the end of the year. This way, Sweden will offer to pay up to a guaranteed revenue per year in exchange for access to a predefined quantity of an antibiotic within a specified delivery time frame.[7] If more units are needed, the company's income goes up proportionally.

In June 2020, the United Kingdom's National Health Service (NHS) launched a fully delinked subscription scheme. The aim is to give companies a better incentive to develop new antibiotics. NHS will pay a fixed fee of £10 million a year for each antibiotic with no additional payments based on sales volumes. The contract value should provide drug providers with a sufficient incentive to invest in antibiotic research and development if other countries pay proportionate sums scaled by the national gross domestic product (GDP) in relation to the world GDP. The selected antibiotics (made by Pfizer and Shionogi) passed a value-for-money evaluation by the National Institute for Health and Care Excellence adapted to antimicrobials.[8]

The United States is discussing the Pioneering Antimicrobial Subscriptions to End Up surging Resistance (PASTEUR) Act. The PASTEUR Act proposes another innovative purchasing and reimbursement approach that seeks to encourage innovative drug development, improve the appropriate use of antibiotics, and ensure domestic availability of critical-need antimicrobial medicines. The bill would set up a subscription model, where the federal government would pay drug providers contractually agreed-upon amounts annually, for a duration ranging from five years up to the antimicrobial's patent life. The subscription contract eligibility and value would be based on the clinical need and novelty of the drug. In case the drug fails or becomes a blockbuster, the subscriptions cease.[9] The PASTEUR Act would also increase resources for antibiotic stewardship programs. Research published by CGD has estimated that domestic return on investment from the PASTEUR act would be 28-fold, and there would be a 125-fold return on investment for the world. Similar returns have been calculated for other high-income countries (Towse and Bonnifield 2022).

2.2. Price caps could limit incentives for companies to introduce new antibiotics to the Brazilian market

Price caps are another characteristic of Brazil's health system that sparks intense debate between regulators and the industry. All medicines in Brazil have a ceiling price, or price cap, set by the Drug Market Regulation Chamber (CMED). These price caps are set for each drug and company pair. Under Resolution 02–2004, the price cap depends on an internal reference price (IRP) or an external

7 Available on https://amr.solutions/2020/03/16/sweden-to-test-an-access-focused-model-for-new-antibiotics-contracting-for-availability/ visited on March 10, 2023.

8 Available on https://www.ft.com/content/c7cbebe4-8597-4340-8c55-56c4b423c1d1 visited on March 10, 2023.

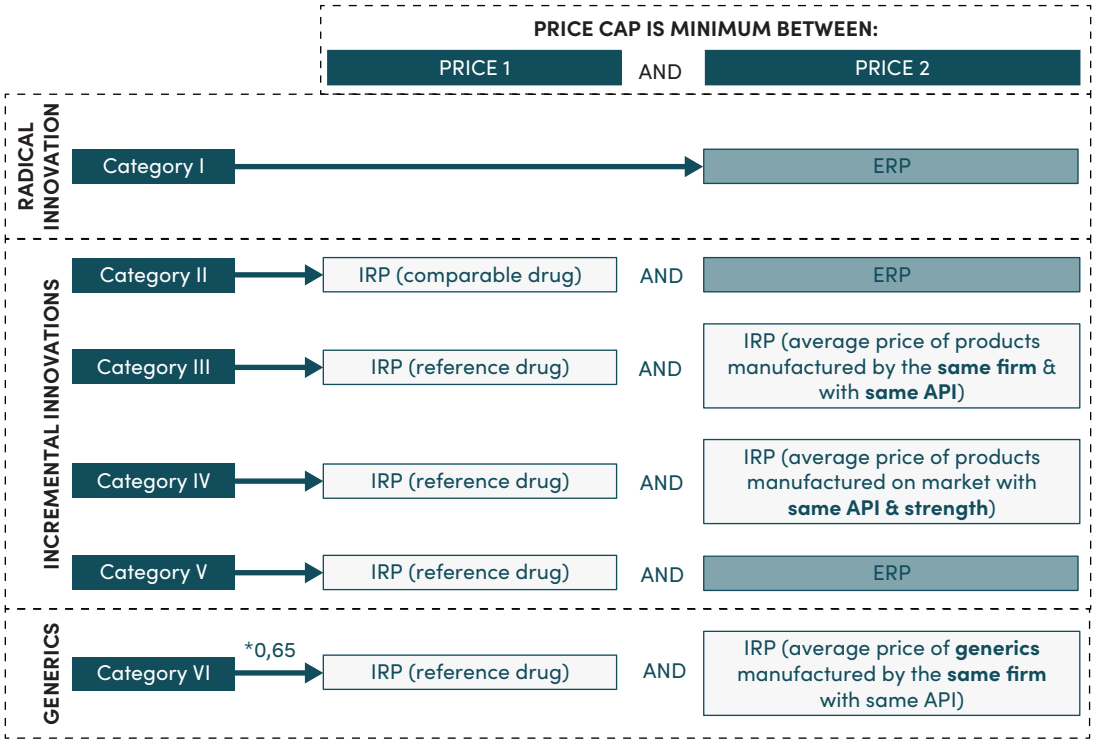
9 Available on https://workingtofightamr.org/wp-content/uploads/2022/03/Antimicrobial-Resistance-What-You-Need-to-Know.pdf and https://www.fightinfectiousdisease.org/_files/ugd/b11210_2973807233214df5a2ae65aafc6b5950.pdf?index=true visited on March 10, 2023.

reference price (ERP). ERP is the lowest price of the same drug in Australia, Canada, France, Greece, Italy, Portugal, New Zealand, the United States, and Spain. IRPs can be the average cost of treatment with the reference drug, the average cost of other similar drugs in the national market, or the company's own average price, depending on the category of the medicine.

These are the price caps (see Figure 2):

- The ERP for "radical innovations"—new molecules not previously available in Brazil that have added therapeutic benefits in relation to the local reference drug (category 1).
- The minimum between the ERP and the IRP for:
    - New molecules not previously available in Brazil but with no added therapeutic benefits or non-patented new molecules (category 2).
    - New combination of APIs previously available in Brazil (category 5)
    - New form in Brazil (e.g., from a capsule to a soft gel; category 5)
- The IRP for drugs entering in the portfolio of a company but already marketed in the country (category 4) or new presentations of drugs already marketed by the same company (category 3).
- 65 percent of the IRP in the case of generics (category 6).

FIGURE 2. Price caps in Brazil, by drug category



Notes: IRP is the internal reference price, and ERP is the external reference price. The definition of IRP depends on the category, as shown in the figure. ERP is the average cost of the reference drug in Australia, Canada, France, Greece, Italy, Portugal, New Zealand, the United States, and Spain. The price cap is the minimum between the price boxes.
Source: Authors'elaboration based on Resolution CMED N°2/2004.

Price caps, together with the current health technology assessment process, generate three main challenges that can affect the drug provider's incentives to introduce new antibiotics in Brazil.

First, it is structurally hard for new antibiotics to show clinical superiority and be classified by CMED into category 1. This is a structural issue because new antibiotics normally go through noninferiority trials (i.e., showing that a new treatment is statistically not worse than a reference treatment by more than an acceptable amount).[10] In this sense, it is hard for manufacturers to have the data to demonstrate "radical innovations" required for category 1 in the price cap system. This means that CMED would classify new antibiotics into category 2 and the innovators will not get the price based on ERP but on IRP. Thus, price caps do not provide sufficient incentives for companies to introduce new antibiotics to the Brazilian market. Experts interviewed agreed that CMED should have a different health technology evaluation process for antibiotics that takes into consideration elements like the evolution of antimicrobial resistance. For example, new antibiotic molecules could be classified as radical innovations when they present lower antimicrobial resistance compared to locally available molecules.

Second, price caps are not adjusted to short-run fluctuations in the cost of raw materials, which decreases the return on investment of selling innovative antimicrobials. The price caps are adjusted annually in response to inflation, a productivity factor, relative prices across sectors, and a relative intra-sector price variation. This process could generate short-run shortages when the cost of raw materials increases substantially more than the authorized price increase. Even though the government has liberalized the price caps of certain antibiotics as an emergency mechanism to cope with shortages, the dependence on imported API and the lack of industrial policies to oversee over pharmaceutical inputs can contribute to shortages.[11]

Third, the same characteristic of CMED's annual adjustments of the price caps, lead price caps today to be much higher than market prices. While market competition between antibiotics providers pushes the market price down over time, CMED reviews price caps annually with inflation. The price caps model in Brazil has been used for almost 20 years without realigning price caps to market values. The result is a detachment of price caps from market value. A recent article mentioned that "The longevity of the [price cap] model, without regular realignment of the ceiling to actual market prices, as recommended in specialized literature, generates price ceilings detached from reality, which deepen information asymmetries and may support abusive price increases in the future" (Dias, Santos, and Pinto 2019, pg. 1). Another study compared the market price of 68 drugs (including seven antibiotics) with their price caps in 2019. The study found that in all cases, the market price was significantly lower than the price cap (40 percent below, on average) (Souza, Paranhos, and

10 Noninferiority is of interest on the premise that the new treatment has some other advantage with respect to the reference treatment (e.g., greater availability, reduced cost, less invasiveness, fewer adverse effects (harms), or greater ease of administration) (Piaggio et al. 2012, pgs. 2594–2595).

11 The following has the list of medicines with risk shortages https://www.gov.br/anvisa/pt-br/assuntos/medicamentos/cmed/risco-de-desabastecimento/medicamentos-com-risco-de-desabastecimento visited on April 20, 2023.

Hasenclever 2021). This situation is fueled by the existence of low-cost and highly efficient antibiotic molecules that were launched many decades ago, and while they continue to be the benchmark for new therapies, their prices have decreased throughout the years.

In sum, price caps might limit the incentives for manufacturers of new antibiotics to enter Brazil when their benefits do not get categorized appropriately. However, under certain circumstances, price caps can be higher than market prices.

Price caps and PDPs. The fact that price caps can be higher than market prices provides space for a PDP where the official laboratory proposes to the MoH a unit price that covers the marginal cost of production plus a profit margin and the technology transfer cost. While the agreements between official laboratories and drug providers are confidential, unit prices must cover the three elements: the technology transfer, the marginal cost of production, and the profit margin. Current PDP regulation does not require distinguishing each of these elements within the proposed PDP unit price.

The outside option of purchasing an antibiotic through the traditional auction mechanism poses a major challenge to the political viability of PDPs. In PDPs without market exclusivity, it is fairly easy to compare the price paid by the MoH for products purchased under a PDP to the price paid for alternative products purchased through a conventional bidding process. This was the case with trastuzumab, whose PDP was not under market exclusivity. In 2018, the Brazilian federal accountability office (*Tribunal de Contas da União*, TCU), which supervises the bidding processes in Brazil, suggested that the government suspend the trastuzumab PDP because the MoH, at one point, was paying almost 38 percent more per unit through the PDP than through the traditional auction mechanism. This presents a dilemma because the price paid by the MoH, through the PDP, should be sufficient to cover the technology transfer, which pushes the price up compared to the market price. The question is, how great a difference is needed between the PDP unit price and the bidding unit price to make the technology transfer economically attractive and still allow for the PDP price to be competitive?

Another challenge that PDPs face is the technological horizon. The PDPs should complete the technology transfer within 10 years. During this time frame, the MoH must pay the official laboratory the price agreed upon and set at the beginning of the PDP (with annual discounts). But 10 years may be enough time for competing drug providers to enter the market or for the marginal costs of production to fall. The result is a competition that makes the PDP price appear substantially higher. An interviewee suggested that future antibiotics' PDPs should be for less than 10 years and include a constant monitoring of the technological horizon. For example, when will the patent expire? Are the barriers to entry low enough for other competitors to enter the market with a substitute molecule?

2.3. Inefficiencies in review processes influence companies' incentives to bring and register antimicrobials to market in Brazil

While the price caps limit the incentives to introduce incremental innovations, the registration process can limit the incentive to bring new antibiotics into Brazil. Registering a new antibiotic is a costly process in any country, especially for those with a demanding formal process. Lengthy registration processes decrease the return on investment for registering new antibiotic molecules and could represent an important barrier to access. In Brazil, the registration process includes presenting the results from clinical trials that require recruiting patients with very particular infections.

In Brazil, ANVISA is the national health regulatory agency responsible for supervising health-related products and services along their life cycle. ANVISA also authorizes clinical trials and marketing approvals for new drugs.

To decrease that registration cost, ANVISA is committed to facilitating regulatory pathways that speed the review process for certain products. These include *priority review*, which decreases normative review times by half among products recognized as of "public health importance"; *harmonization* of its regulatory procedures with international standards; and *reliance* on the decisions of a group of international health regulatory agencies. Our research shows that ANVISA has a clear institutional commitment towards *harmonization*, as demonstrated by its participation in internationally renowned initiatives that promote regulatory harmonization and harmonized regulatory inspections. ANVISA is also moving towards *reliance*, including a fast registration revision for drugs already approved by international agencies. One would expect harmonization and reliance mechanisms to substantially decrease the approval times of new drugs. However, changing these processes requires strong institutional will.

Nevertheless, while ANVISA has used the available mechanisms for fast drug approvals, we did not find evidence of the use of a priority review or reliance pathway for the approval of a new antibiotic.

2.4. Existing initiatives lay the groundwork for stewardship efforts, but still need to be further developed and used

Several initiatives promote antimicrobial stewardship in Brazil. They can be divided into two categories: first, a set of national plans promoted by ANVISA aiming to guide and promote stewardship efforts; and second, the collection of data on AMR.

Brazil's surveillance efforts are aligned with international initiatives. The first major effort is the construction of the first local surveillance network, financed by the US Centers for Disease Control and Prevention, as part of a broader effort to establish two new global networks for containing the resistance of antimicrobials. The second major effort is BR-GLASS, the local chapter of WHO's Global Antimicrobial Resistance and Use Surveillance System (GLASS). GLASS is the first global collaborative

effort to standardize AMR surveillance. While the data produced by BR-GLASS is not representative at the national level, it is the best data available in Brazil about AMR. BR-GLASS has not yet reached small municipalities and private hospitals, and we could not find a date when that will happen.

We see opportunities for improvement in four areas:

Governance mechanisms. While Brazil has national plans, challenges remain to translate them into concrete actions, highlighting the need for increased monitoring of such plans. We were generally unable to identify evaluations of the main national plans. At the regional level, except for the Health Secretaries of the States of Paraná, Rondônia, and Santa Catarina, the States' Health Plans 2020–2023 did not mention the words "bacteria," "antimicrobial," "antibiotic," or similar; in contrast, "diabetes" and "cardiovascular" could be found in most or all state-level plans. One interviewee reported that "the subject of tackling AMR does not extend to the priority, centrality, nor strategic level of the municipal or state healthcare management, or of the MoH itself. It is a very technical subject that is more restricted with hospitals' epidemiology and technical commissions for infection prevention and control."

Decision-making. The Ministry of Health annually responds to the Tripartite AMR Country Self-Assessment Survey (TrACSS) designed by the WHO to monitor the country's progress in the implementation of the goals of the National Action Plan. According to TrACSS, while Brazil has successfully developed a national action plan on AMR, it has failed to use relevant AMR data to amend national strategy and/or inform decision-making. Our interviews and desk review suggest that the AMR data collected and published is not raising needed awareness among policymakers. We could not find evidence of how the surveillance data on AMR is influencing decision-making in general.

One specific area of decision-making is antibiotic procurement. We were unable to identify evidence on how the Department of Pharmaceutical Assistance (DAF) from the MoH is using local AMR data to guide its purchases of antibiotics. The problem also extends to the states and municipalities. We were also unable to identify evidence of how BR-GLASS data is influencing local governments when procuring antibiotics. Local governments are also not using the data to modify the local lists of essential medicines (REMAME).

Prescription and testing. Another challenge is that prescriptions by local physicians are not tied to data from BR-GLASS. Instead, the SMART-CDSS app is a decision support tool for antimicrobial prescription. It combines patient data, local epidemiological information from BR-GLASS data, and machine learning to identify the most effective antibiotic to treat an infection. Local physicians may prescribe whatever antibiotic is available in the local clinic—although the 2022 RENAME incorporated the AWaRe classification tool to support prescribing practices.[12]

12 The AWaRe Classification of antibiotics was developed in 2017 by the WHO as a tool to support antibiotic stewardship efforts. AWaRe classifies antibiotics into three groups, Access, Watch, and Reserve, considering the impact of the use of antibiotics on antimicrobial resistance, to emphasize the importance of their appropriate use.

There are also challenges in providing timely results for any type of test (e.g., pathogen identification, drug sensitivity testing) to inform antibiotic prescribing. Information provided during our interviews highlighted logistical challenges in rural communities of Brazil that delay delivery of samples to the laboratory for up to 10 days; there are also frequent processing delays, sometimes taking a week or longer.

Training. Most stewardship efforts take place at the hospital level, but challenges remain in promoting stewardship among primary care facilities and within healthcare worker training. One interviewee mentioned that "AMR is perceived as an elite problem of the Academy, of well-placed professionals. AMR is not perceived as a problem by professionals who are in small communities, small clinics, and even small laboratories." In this sense, most stewardship efforts are restricted to hospitals (i.e., high-complexity healthcare institutions). The only effort aimed at targeting both hospitals and primary care clinics is Projeto Stewardship Brazil, by ANVISA. Nevertheless, an evaluation of this project found that only 44 percent of the primary care clinics that responded to the self-administered questionnaire had a protocol for the diagnosis and treatment of the main healthcare-associated infections.

2.5. The decentralized and fragmented nature of procurement in the Brazilian Unified Health System is not properly addressing antibiotic access, innovation, and stewardship

The Brazilian health system has three main players: the federal government, the state government, and the municipalities. The degree of participation of each of these players in the provision of health services, and their respective financial contributions, varies by state. The National Council of Health Secretariats (CONASS) includes Health Secretariats of the 27 states of Brazil.

The normative system that regulates the health sector is extremely fragmented, which sometimes hinders the implementation of public policy. For instance, national organizations define a list of drugs that can be used in Brazil, but states and municipalities can add additional medications to that list and purchase them for their populations. In addition, private hospitals that sell services to states or municipalities may use different protocols or medications than their public counterparts. Thus, the public procurement system in Brazil is very complex and, in terms of medications, many purchases are decentralized at the state, municipal, and hospital levels. The health system does define some medications that are bought in a more centralized manner, achieving economies of scale. In the case of antibiotics, modification to the public procurement system in Brazil at the federal level would require congressional approval.

Despite the organizational hurdles, some antibiotics are procured centrally through traditional auction mechanisms. We were unable to find an estimate of the relative importance of central procurement compared to decentralized procurement.

3. Recommendations for antimicrobial purchasing systems in Brazil

Traditional PDPs are a good starting point to promote antibiotic access, innovation, and stewardship, but they have not been used for antimicrobials as much as for antiretrovirals, anticancer, and immunosuppressant medicines. We believe there is a missed opportunity to use traditional PDPs for some antibiotics, specifically, single source antibiotics (i.e., monopolies) or high-cost antibiotics.

Traditional PDPs could directly promote access, innovation, and stewardship of antimicrobials. Regarding *access*, PDPs allow millions of Brazilians to gain access to strategic products of high cost and greater technological complexity. This is done by allowing drug providers to indirectly supply a new market, SUS, that otherwise might be difficult to enter.[13] PDPs also increase access by reducing the cost of acquiring highly complex health technologies. At the end of the PDP, the official laboratory becomes the owner of the health technology and would hold the needed knowledge and infrastructure to participate in bidding processes through which it can supply SUS. Since most of the official laboratories are deliberately not-for-profit organizations (Alfob/CFF 2019), the Brazilian health system would also gain access to health technologies at a lower cost at the end of the PDP, compared to procurement through the traditional auction mechanism. A study calculated the savings of all PDPs to be almost $500 million between 2011 and 2018 (on average, $62.5 million annually), mostly due to a decline in acquisition costs of over 50 percent compared to the traditional auction mechanism (CGU 2019, pg. 91).

Regarding *innovation*, official laboratories like Bio-Manguinhos, Farmanguinhos, and Butantan also perform research and development activities. Gaining the know-how of newly discovered API through PDP-supported technology transfer can also help develop new antimicrobials in the future.

Finally, regarding *stewardship*, there is better control over sales because the official lab is not-for-profit, hence, it is likely to have fewer incentives to increase the volume of sales by overselling or promoting prescriptions.

Key considerations about the proposed benefits and operationalization of the annual fee PDP model are discussed in Section 3.1. A number of smaller changes that could also help address AMR and create a more enabling environment for the antimicrobial procurement system are outlined in 3.2.

3.1. Key considerations for our proposed model: The annual fee PDP

Our proposed model, the annual fee PDP, builds on the traditional PDPs model. It consists of an annual fee model, moderated by the traditional PDP model, which puts a Brazilian laboratory as the intermediate seller. The annual fee PDP would give the MoH the option to pay an annual fixed payment to the official lab. Like in an annual fee model, this annual payment would be *independent*

13 For example, listing in the RENAME involves the approval by CONITEC commission.

of the number of units consumed. The annual payment could decrease over time, as unit prices typically do under the traditional PDP.

In an annual fee PDP, the official laboratory, the MoH, and the drug provider would need to negotiate the annual fixed payment that secures its main objective, i.e., access to the new antibiotic. Brazil might consider benchmarking the fixed payment amount to the NHS annual fee model, scaled by Brazil's GDP in proportion to the UK's GDP. Since Brazil's GDP is about half of the UK's, we estimate that the annual fee would be around R$30.5 million (US$6 million). In this sense, price caps are less relevant for an annual fee PDP. On the contrary, in a traditional PDP, CMED's price cap plays a role during the negotiation of the unit price between the official lab, the MoH, and the drug provider, regarding the cost of purchasing each unit.

The organizations best placed to support an annual fee PDP would be the official laboratories with the most experience in PDP contracts, like Bio-Manguinhos, Farmanguinhos, Butantan, and Lafepe, which together hold 50 percent of the current PDPs.

Benefits of the annual fee PDP. The annual fee PDP provides benefits in addition to the traditional PDP benefits mentioned in Section 2.1. The main objective of an annual fee PDP is to secure access to a new antibiotic. It further improves SUS's *access* to new high-cost antibiotics that might otherwise not be economically attractive to bring to Brazil because of low sales volumes or low price caps per unit. Like subscription models, the annual fee PDP decreases incentives to oversell, thereby fostering *stewardship*. While in a subscription model, the companies earn money, in the case of an annual fee PDP, official labs can use the extra earnings to strengthen stewardship programs, and capabilities, and invest in innovation.

Recommendations on the scope of the annual fee PDP. We propose that the annual fee PDP model be initially applied to recently developed synthetic antibiotics that are available abroad but not in Brazil. These antibiotics would have gone through clinical trials and would have marketing approval abroad by international reference regulatory agencies. This would ease ANVISA's internal review process, based on reliance. We also recommend the annual fee PDP model for single source antibiotics (i.e., monopolies) and/or high-cost antibiotics.

The annual fee PDP would be more politically feasible and economically attractive under market exclusivity for at least two reasons. First, given the low volume of sales of new antibiotics, it makes sense to increase the usage of the annual fee mechanism. Second, PDPs do not necessarily have to cover 100 percent of SUS demand for the health product; most do not. If there is no market exclusivity, then the MoH combines purchases through PDPs with the conventional auction

mechanism. In these cases, as with the case of trastuzumab,[14] the Brazilian federal accountability office (*Tribunal de Contas da União*, TCU), which supervises the PDP and the MoH bidding processes, can compare the price paid by the MoH for products purchased under a PDP to the price paid for substitutive products purchased through a conventional bidding process. However, before the end of the PDP, the price of PDP products should be higher than the price of products procured through the conventional bidding process, because the official lab is purchasing the health technology transfer and this cost needs to be transferred to the MoH.

Finally, we also suggest the MoH should develop strict guidelines for prescription and usage of antibiotics under an annual fee PDP. These protocols can be transferred to local clinics from small states and municipalities that do not have the technical capacity to define the protocols themselves.

Implementation roadmap. The first step to implement an annual fee PDP would be to convince the MoH to enlist new antibiotics available abroad, but not in Brazil, as "strategic products." This is important because PDPs apply only to products declared by the MoH as "strategic products" for SUS—a list of products defined by the MoH, usually of high cost for SUS, highly dependent on imports, of high technological complexity, or at risk of shortage (Gadelha and Braga 2016; Gadelha and Temporão 2018). Fortunately, some antibiotics are already listed as strategic products of SUS. The 2017 list included the rifampin antibiotic and, more recently, there has been a discussion flagging several antibiotics (like amoxicillin) to be at risk of shortage, which would allow the MoH to declare them as strategic products of SUS.[15] The worldwide trend to recognize AMR as the next pandemic would also allow the Brazilian government to recognize the public health importance of both old and recently developed antimicrobials not yet available in the national market. Finally, COVID-19 also set a precedent with the government including vaccines that were not yet approved as strategic products to be used in Brazil, demonstrating that it is possible to approve required legislative changes during crisis conditions. As the annual fee contracting approach has not yet been applied in Brazil, legislative changes to the current procurement regulations are likely required.

Political palatability. The PDP model is already well known among health sector stakeholders in Brazil. Thus, modifying the PDP model via the legislative process may be more politically feasible than introducing an entirely new procurement model for antibiotics. Legislators could build from previous PDP experiences and knowledge on what works and what needs to be improved for these arrangements to work effectively. In addition, the annual fee PDP is most appropriate when there is a single or only a few potential suppliers, as it allows for a negotiation of the annual fee between an official laboratory and the technology holder.

14 Available on https://www.jota.info/tributos-e-empresas/saude/tcu-manda-governo-suspender-pdp-de-remedio-para-cancer-de-mama-04102018 or https://reporterbrasil.org.br/2019/08/investigacao-sobre-setor-farmaceutico-revela-rombo-de-r-170-mi-e-pacientes-com-cancer-ficam-sem-tratamento/ visited on March 10, 2023.

15 Available on https://www.gov.br/anvisa/pt-br/assuntos/medicamentos/cmed/risco-de-desabastecimento/Atada11aReunioExtraordinria_CTECMED_assinada_consolidada.pdf visited on March 10, 2023.

3.2. Broader recommendations to support implementation of the annual fee PDP and the AMR response in Brazil

A series of smaller, cross-cutting changes can help address the above-mentioned challenges in Brazil's antimicrobial market and AMR response while also creating an enabling environment for implementation of the annual fee PDP.

1. **Modify pricing policies to increase incentives for innovation.** Further work is needed to propose and facilitate uptake of adjustments to current pricing policies, especially as CMED discussions around fairer pricing for incremental innovations have stalled. But changing the current rules for price determination, including the price cap, requires passing legislation, which is not easy.
2. **Scale-up processes for priority regulatory review.** ANVISA can reinforce regulatory mechanisms used for health products to speed access to critical antimicrobials. For example, ANVISA can use *reliance* on the decisions of a group of international health regulatory agencies to more rapidly assess new review requests for antibiotics already approved elsewhere but not in Brazil. Additionally, the Brazilian government could distinguish AMR as having "public health importance," which would allow a priority review for new antibiotics.
3. **Expand Brazil's AMR stewardship policies.** Mechanisms and arrangements to monitor and evaluate progress on national stewardship efforts are needed in Brazil's existing AMR policies. Policies to address stewardship should also be established within municipalities to build on Brazil's national initiatives and trickle prioritization and action down to the local level. These policies could be integrated into national action plans or could stand separately. Brazil could set up a list of essential antibiotics that could guide physicians in small states and municipalities.

   As part of this, health systems should increase access to diagnostics for antibiotic-resistant bacterial infections. Making low-cost, reliable rapid tests more available to detect specific strains of bacteria can help prescribers identify appropriate treatments for patients who need them.
4. **Leverage available AMR data to inform decision-making in policy and health care.** For example:

   - ANVISA could use local AMR data to carry out post-approval reviews of the effectiveness of antibiotics.
   - CMED could use such data to re-evaluate antibiotics' effectiveness and modify price caps.
   - The National Committee for Technology Incorporation (CONITEC) could use AMR data to evaluate the inclusion of an antibiotic in the RENAME.
   - The Department of Pharmaceutical Assistance (DAF) from the MoH could use local AMR data to guide its purchases of antibiotics.

- States and municipalities could use local data for evidence-based procurement of antibiotics and adjust the REMAME accordingly.
- Existing AMR data and relevant findings can be disseminated to health professionals and doctors, including those working outside hospital settings in outpatient clinics and small towns, to strengthen knowledge and training among prescribers.

5. **Increase access to diagnostics for antibiotic-resistant bacterial infections.** Making low-cost, reliable rapid tests more available to detect specific strains of bacteria can help prescribers identify appropriate treatments for patients who need them.

4. Conclusions

In this paper, we analyzed how Brazil's policies and current purchasing systems are locally affecting antibiotic access, innovation, and stewardship; and highlighted policy areas that need special attention. These topics are important if we want to secure access to new antibiotics in Brazil in response to increased AMR rates and the low number of new antibiotics in the current pipeline.

We found that the decentralized and fragmented nature of SUS procurement is not properly addressing antibiotic access, innovation, and stewardship. Price caps are limiting the incentives to introduce new antibiotics into Brazil, especially incremental innovations, and review process influence companies' incentives to bring and register antimicrobials to market in Brazil. In addition, drug providers are paid by unit sold, so their revenues depend on sales volume. Hence, the current system for purchasing antibiotics under-incentivizes innovation, motivates overuse, and promotes treating infections with cheap generic drugs that are easily accessible but which may be inappropriate or ineffective when used against resistant infections.

Existing initiatives lay the groundwork for stewardship efforts but need to be further developed and used. While Brazil has national plans to address antimicrobial overuse and track AMR rates, challenges remain to use relevant AMR data to inform decision-making and translate national plans into concrete actions at both the national and regional levels. There is a need for better prescribing and testing practices, and better training of Brazilian healthcare workers around AMR.

Yet, Brazil's pharmaceutical sector has the potential to grow further via a well-established purchasing policy aimed at promoting innovation and transferring new health technologies to official laboratories. The PDPs are an innovative purchasing system that use MoH's central procurement system and SUS purchasing power to bring new drugs to Brazil, stimulate local production, and decrease the cost to SUS of accessing certain treatments. It has been a relatively successful model that is well known locally. But PDPs have not been used around new antibiotics and they have mostly been used on a traditional pay-per-unit scheme.

Brazilian policymakers should enable the MoH to pay a fixed annual payment to the official laboratory, hence the name "annual fee PDP." Like a subscription model, this annual payment would be independent of the number of units consumed. The annual fee PDP would provide *access* to new high-cost antibiotics that might otherwise not be economically attractive to bring to Brazil because of low sales volumes or low price caps per unit. Like subscription models, the annual fee PDP decreases incentives to oversell, fostering *stewardship*. While in an annual fee model the companies earn money, in the case of an annual fee PDP, official labs can use the extra earnings to strengthen stewardship programs and capabilities, and to invest in innovation.

Solutions to AMR that modify current incentives are likely to find resistance among different stakeholders. This is particularly true in the case of low- and middle-income countries, where governments have limited health budgets and scandals about unethical behavior have strengthened mistrust. Even a strong and technically sound proposal must be carefully introduced to attract public and political support, including effective communication about the level of urgency about AMR in Brazil; coalition-building of relevant local partners; and sensitive strategic dialogue.

References

Alfob/CFF. 2019. "Laboratórios Farmacêuticos Oficiais Do Brasil." Associação dos Laboratórios Farmacêuticos Oficiais do Brasil.

CGU. 2019. "Relatório de Avaliação. Secretaria de Ciência, Tecnologia e Insumos Estratégicos." Controladoria-Geral da União.

Dias, Leticia Lucia dos Santos, Maria Angelica Borges dos Santos, and Cláudia Du Bocage Santos Pinto. 2019. "Regulação Contemporânea de Preços de Medicamentos No Brasil—Uma Análise Crítica." *Saúde Em Debate* 43 (121): 543–558. https://doi.org/10.1590/0103-1104201912120.

Gadelha, Carlos Augusto Grabois, and Patrícia Seixas da Costa Braga. 2016. "Health and Innovation: Economic Dynamics and Welfare State in Brazil." *Cadernos de Saúde Pública* 32 (suppl 2). https://doi.org/10.1590/0102-311X00150115.

Gadelha, Carlos Augusto Grabois, and José Gomes Temporão. 2018. "Desenvolvimento, Inovação e Saúde: A Perspectiva Teórica e Política Do Complexo Econômico-Industrial Da Saúde." *Ciência & Saúde Coletiva* 23 (6): 1891–1902. https://doi.org/10.1590/1413-81232018236.06482018.

IDSA. 2021. "2021 AMR Preparedness Index." Infectious Diseases Society of America.

IQVIA. 2022. "The Global Use of Medicines 2022. Outlook to 2026." IQVIA Institute for Human Data Science. https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/the-global-use-of-medicines-2022/global-use-of-medicines-2022-outlook-to-2026-12-21-forweb.pdf.

Nunn, Amy S, Elize M Fonseca, Francisco I Bastos, Sofia Gruskin, and Joshua A Salomon. 2007. "Evolution of Antiretroviral Drug Costs in Brazil in the Context of Free and Universal Access to AIDS Treatment." Edited by Mauro Schechter. *PLoS Medicine* 4 (11): e305. https://doi.org/10.1371/journal.pmed.0040305.

Piaggio, Gilda, Diana R. Elbourne, Stuart J. Pocock, Stephen J. W. Evans, Douglas G. Altman, and for the CONSORT Group. 2012. "Reporting of Noninferiority and Equivalence Randomized Trials: Extension of the CONSORT 2010 Statement." *JAMA* 308 (24): 2594. https://doi.org/10.1001/jama.2012.87802.

Rodrigues, William C. V., and Orenzio Soler. 2009. "Licença compulsória do efavirenz no Brasil em 2007: contextualização." *Revista Panamericana de Salud Pública* 26 (6). https://doi.org/10.1590/S1020-49892009001200012.

Souza, Caroline Miranda Alves de, Julia Paranhos, and Lia Hasenclever. 2021. "Comparativo Entre Preço Máximo Ao Consumidor de Medicamentos e Preços Praticados Na Internet No Brasil: Desalinhamentos e Distorções Regulatórias." *Ciência & Saúde Coletiva* 26 (11): 5463–5480. https://doi.org/10.1590/1413-812320212611.44082020.

Towse, Adrian, and Rachel Silverman Bonnifield. 2022. "An Ambitious USG Advanced Commitment for Subscription-Based Purchasing of Novel Antimicrobials and Its Expected Return on Investment." Center for Global Development. cgdev.org/sites/default/files/ambitious-usg-advanced-commitment-subscription-based-purchasing-novel-antimicrobials.pdf.

Trusheim, Mark R., William M. Cassidy, and Peter B. Bach. 2018. "Alternative State-Level Financing for Hepatitis C Treatment—The 'Netflix Model.'" *JAMA* 320 (19): 1977. https://doi.org/10.1001/jama.2018.15782.

Varrichio, Pollyana de Carvalho. 2017. "As Parcerias para o desenvolvimento produtivo da saúde." In *Políticas de inovação pelo lado da demanda no Brasil*. Brasília: Instituto de Pesquisa Economica Aplicada (Ipea).

WHO. 2018. *WHO Report on Surveillance of Antibiotic Consumption: 2016–2018 Early Implementation*. Geneva: World Health Organization. https://apps.who.int/iris/handle/10665/277359.