Technical Brief
February 2024

The PASTEUR Act is Not the Way for the US Government to Address Antimicrobial Resistance

Executive summary

The problem of antimicrobial resistance (AMR)

- Antimicrobials are medicines, such as antibiotics, that are used to treat and prevent infections caused by microorganisms including bacteria, viruses, and fungi. When these microorganisms evolve to survive antimicrobial treatment, it is called antimicrobial resistance (AMR).
- AMR is one of the leading health threats confronting humanity, with the potential to undermine many of the medicines that make up the foundation of modern healthcare, take millions of lives, and cause massive economic harm.
- AMR is already taking a huge toll on people's wellbeing, particularly in low- and middle-income countries (LMICs) around the world, but is also a major concern in the US.

Prospective policy approaches for addressing AMR

- To address AMR in the US and globally, increased investment in research and development (R&D) for new antimicrobial drugs is important but should not be prioritized above R&D for diagnostic tests and vaccines or improving public health systems' capacity for infection prevention and control (IPC), laboratory-based diagnosis, and antimicrobial stewardship (the judicious use of antimicrobial treatments). These activities, which are also within the US National Action Plan on Combating Antibiotic-Resistant Bacteria, should be robustly resourced and expanded, including those that focus on international support and collaboration.
- The US government should nonetheless prudently expand its role in encouraging antimicrobial R&D because new drugs are and will continue to be needed and this type of innovation is currently neglected. Inappropriate use of antimicrobials is a major driver of resistance, so these drugs need to be used judiciously – which makes antimicrobial R&D unattractive to pharmaceutical corporations who do not see an opportunity to reap large profits from blockbuster sales.
- Neglect of antimicrobial R&D has prompted the US government to experiment with "pull" incentive interventions to try to entice corporations to invest in this space, such as reimbursement reforms to support higher drug prices, extended monopolies, and other market-entry rewards and guarantees, including the proposed Pioneering Antimicrobial Subscriptions to End Upsurging Resistance (PASTEUR) Act.

Why the PASTEUR Act is not the right way to spur antimicrobial innovation

- The Act would offer pharmaceutical corporations an upfront payment in exchange for access to new antimicrobials they develop, awarding contracts valued between $750 million and $3 billion each to be paid out over 5-10 years. The contracts would secure an agreed-upon amount of each new product for people in federal health programs or plans and the Act would establish a Committee on Critical Need Antimicrobials to determine which products merit a contract and how they would be valued. The latest slimmed-down version of the bill would commit a total of $6 billion over five years.
- MSF USA is concerned that the Act would: 1) drive up prices of PASTEUR-supported novel antimicrobials in all markets besides federal procurement, negatively impacting access to the new products for people who need them – outside the public system in the US and elsewhere in the world; 2) compromise stewardship of resulting antimicrobials; and 3) be an inefficient means of incentivizing meaningful antimicrobial innovation.

- Both antimicrobial stewardship and access are essential for countering AMR. To both encourage antimicrobial stewardship and facilitate access to new treatments for people in need, R&D incentives should be "delinked" from sales volumes and prices of resulting products. But the Act's contract payments do not delink its R&D incentive sufficiently from sales volumes or at all from prices, allowing corporations to engage in sales to private and global healthcare markets under "normal" conditions. This preserves incentives for increasing sales volumes in the most lucrative locations rather than where need is greatest and setting prices at what the market will bear. This is likely to make the price of resulting drugs an obstacle for people outside of federal healthcare programs/plans in the US and in lower-resource settings globally while concentrating sales in locations that can pay the highest prices.
- The Act would impose a soft "cap" on sales by ceasing to pay the annual subscription allotment if revenues earned for the antimicrobial outside of US federal procurement "exceed 5 times the average annual amount" of the contract. While this would presumably encourage a measure of restraint in sales volumes, it would do so through a crude mechanism that fails to rationalize the location of those sales in any way according to public health need. Neither this cap nor high drug prices would serve the objective of antimicrobial stewardship and both could, in different ways, impede equitable access.

Other means of fostering antimicrobial R&D would be a more effective, judicious, and impactful use of public funds than the PASTEUR Act

- The Department of Health and Human Services (HHS) could expand its own intramural research program to directly conduct more late-stage research.
- HHS could also: offer discrete monetary prizes as an alternative to a monopoly to reward successful innovations; contract with R&D institutions, including not-for-profit ones, to develop antimicrobials but retain intellectual property (IP) rights over resulting products; or purchase IP rights from a pre-existing patent holder.
- These approaches would retain federal authority in the production and distribution of resulting products, better ensuring stewardship, equitable access, innovation of public health significance, and the kind of open science and collaboration that are badly needed to advance antimicrobial R&D.
- Investment in public or nonprofit antimicrobial R&D and production is also estimated to cost dramatically less than the Act.

Is the PASTEUR Act salvageable, considering its negative repercussions for access and stewardship?

- Unlike the alternative approaches mentioned above, the Act's essential structure works against equitable access and adequate stewardship – so it does NOT seem possible to graft provisions onto it to mitigate its harms. Any effort to do so would need to include, at a minimum:
    - Preferentially awarding contracts to non-profit drug developers; and
    - Requiring PASTEUR contract recipients to:
        - disclose R&D costs and drug prices;
        - register products in low- and middle-income countries (LMICs);
        - make products affordable beyond federal programs/plans; promote diversified manufacturing sources including in LMICs through non-exclusive licensing and other means;
        - engage with non-profit and multilateral initiatives focused on facilitating access for LMICs;
        - establish and participate in large global clinical trial networks with sites in LMICs;
        - generate and follow detailed plans for promoting stewardship;
        - support development of and access to companion diagnostic tools; and
        - conduct phase 3 or post-approval studies specifically on resistant pathogens and in highly impacted patient groups.

Background: antimicrobial resistance and priorities for addressing it

Antimicrobials are medicines, such as antibiotics, that are used to treat and prevent infections caused by microorganisms including bacteria, viruses, and fungi. When these microorganisms evolve to survive antimicrobial treatment, it is called antimicrobial resistance (AMR). Antimicrobial-resistant infections are more difficult to treat and therefore more likely to spread and cause severe illness or death. AMR is one of the leading health threats confronting humanity, with the potential to undermine many of the medications that make up the foundation of modern healthcare, take millions of lives, and cause massive economic harm.[1,2,3,4] AMR is already taking a huge toll on people's wellbeing, particularly in low-resource settings where MSF carries out medical humanitarian operations and where many of the multiple drivers of drug-resistant infection are most prevalent – including lack of access to clean water, sanitation, and quality health care.[5] AMR is, however, a major concern in the US as well, and – as the COVID-19 pandemic demonstrated – infectious threats do not respect national boundaries.[6]

To address AMR in the US and globally, both increased investment in public health systems and research and development (R&D) for new antimicrobials, diagnostic tests, and vaccines is needed. Although these priorities are all reflected in the US National Action Plan on Combating Antibiotic-Resistant Bacteria (NAP CARB), the plan's authors qualify its implementation as dependent upon "the availability of resources and capacity" and cite "limited resources" as a key challenge.[6] The US Centers for Disease Control and Prevention (CDC), for example, expanded much-needed AMR-related activities with pandemic-related supplemental funding, but those gains are fragile and have been affected by recission, with international activities being the most vulnerable to cuts.[i] Given resource constraints, prioritization within the US government's approach to countering AMR – both domestically and globally – is inevitable.

US policy discussions about how to step up efforts against AMR to date have focused disproportionately on R&D for new antimicrobials, rather than other critical areas such as the need for developing new diagnostics and vaccines, strengthening capacity for infection prevention and control (IPC), diagnosis, and the appropriate and judicious use of antimicrobials, known as antimicrobial stewardship.[7,ii] IPC is a key element for slowing the emergence and proliferation of AMR because it prevents infectious spread and reduces the number of patients in need of antibiotics. Good quality laboratory-based diagnosis is needed for individual patient care, preventing and managing outbreaks, and guiding population-level policymaking. Stewardship is essential to improve patient outcomes and help minimize inappropriate antimicrobial use, which is a major driver of resistance. Measures to strengthen laboratory capacity and train healthcare workforces in IPC and stewardship – both domestically and abroad – will be an indispensable bulwark against the rising tide of AMR and cannot be overlooked in the allocation of US resources or sacrificed in exchange for antimicrobial R&D. [3,4]

MSF USA nonetheless also recognizes the significant need for R&D for new antimicrobials that can treat drug-resistant pathogens of global public health importance and for public actors to take action to support drug development.[7]

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[i] Most of CDC's global AMR-related work is funded though the "Antibiotic Resistance Solutions Initiative" annual appropriation and 90% of these funds go to domestic rather than global activities. Recission of supplemental pandemic-related funding resulted in a 65% reduction of the AMR-related extramural funding activities of the agency's international infection control branch. See: https://www.hhs.gov/ash/advisory-committees/paccarb/meetings/upcoming-meetings/december-20-2023-public-meeting/index.html and https://www.youtube.com/playlist?list=PLrl7E8KABz1HnWhPMHKxSqPUjh3V4VK0Q

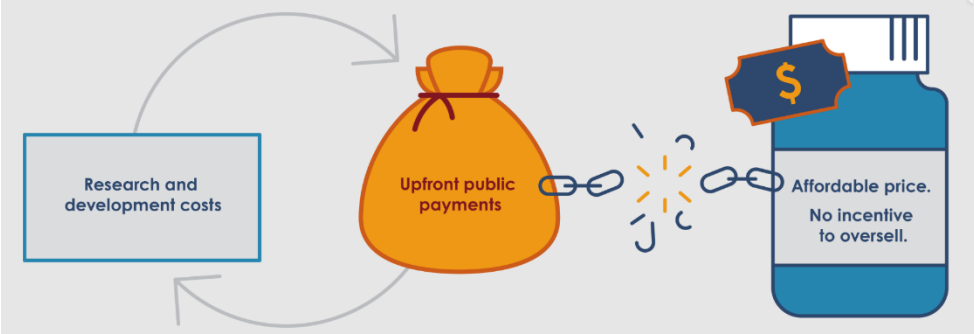
[ii] On the importance of developing new diagnostic tools, see: https://www.nationalacademies.org/our-work/accelerating-the-development-of-rapid-diagnostics-to-address-antibiotic-resistance-a-workshop

Encouraging antimicrobial R&D

There has been a serious dearth of novel antimicrobials entering the market in recent decades. According to the World Health Organization's (WHO) 2021 analysis, of 45 antibiotics in the current clinical pipeline, only 27 are active against WHO priority pathogens, only six fulfil more than one of the WHO's innovation criteria, and only two are active against multi-drug resistant Gram-negative bacteria, which pose a profound threat within MSF operations and beyond.[iii] In comparison, the Biotechnology Innovation Organization found that there are 160 clinical stage drug products for breast cancer alone.[8] The weak pipeline for new antimicrobials is due to many factors including significant scientific challenges and lack of private sector interest in engaging in R&D for agents that are perceived as unlikely to yield major profits.[9]

Public and philanthropic actors have traditionally played a leading role in providing "push" financing for early-stage R&D, often seen as too risky for private sector actors. In the last decade such funding for antimicrobial R&D has increased in recognition of the threat AMR poses and the weak pipeline – most notably in the founding of the non-profit partnership Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) in 2016 with significant US government backing, alongside grants through NIH and BARDA.[10] The private sector is generally perceived as the dominant player in financing late-stage development of new medical tools and technologies, though the public also plays a major and often underappreciated role in funding late-stage development – through direct funding of late-stage research, through spin-off companies created from public sector research institutions, and by paying high prices for resulting products.[11,12,13,14] Larger, multinational pharmaceutical corporations have mostly withdrawn from developing new antimicrobials, though, perceiving markets for new antimicrobials as unlucrative – in part because of the need for restraint in antimicrobial usage. Smaller- to medium-sized corporations, which have developed the majority of antimicrobials approved in recent years, have also struggled to successfully commercialize products.[15] The failure of the usual incentive of high-volume sales to draw major private sector actors into late-stage antimicrobial development has prompted governments to begin devising and experimenting with additional "pull" interventions to entice corporations to invest in this space, such as reimbursement reforms to support higher drug prices, extended monopolies, and other market-entry rewards and guarantees.[16]

Given the fact that novel antimicrobials are essential tools for countering AMR but inappropriate use of antimicrobials is a major driver of resistance, in the last decade consensus has grown that policies delinking R&D incentives from both sales volumes and prices of resulting antimicrobial products are necessary to successfully encourage antimicrobial stewardship and access alongside innovation. This position was explicitly articulated in the 2016 political declaration of the high-level meeting of the UN General Assembly on antimicrobial resistance.[17]



Infograph: Zellout, courtesy of ReAct

The pharmaceutical industry, however, advocates for government interventions that delink R&D incentives at least partially from volumes but not from prices – committing public funds for the advanced purchase of novel

[iii] The WHO's innovation criteria are: new chemical class, new target, new mode of action, or absence of known cross-resistance. See: https://www.who.int/publications-detail-redirect/9789240047655

antimicrobials at prices that they claim will be motivating to developers, boosting reimbursement for antimicrobials through federal programs, and doing little to constrain prices corporations might charge for novel antimicrobials.[18] As an organization that has long witnessed the ways in which prices of drugs and other lifesaving medical tools bar access for people all around the world, however, MSF takes the view that incentives for antimicrobial R&D must be delinked from both volumes and prices.

High prices that impede access for people (or countries) with fewer resources should not be encouraged or enabled by the US government – either as a method of incentivizing R&D or under the guise of encouraging antimicrobial stewardship. Access and stewardship are equally important in the global struggle against AMR, and neither the appropriate use of antimicrobials nor the best health outcomes can be achieved by simply limiting access to those who are able to pay for costly treatments. MSF's position aligns with that of other civil society voices who argue that impediments to new antimicrobial development are more complex than just an insufficient return on investment – including significant scientific challenges requiring extensive "push" financing and collaborative approaches to research. More transformative end-to-end interventions across the entire course of the innovation process are needed to overcome these barriers successfully and sustainably, and to ensure that resulting products will be accessible to all who need them and yet still be used judiciously.[9,19] This document will apply this perspective in analyzing the Pioneering Antimicrobial Subscriptions to End Upsurging Resistance (PASTEUR) Act – the world's most ambitious pull incentive proposal, currently under consideration by the US Congress – and proposing alternative approaches for incentivizing antimicrobial R&D.

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The Pioneering Antimicrobial Subscriptions to End Upsurging Resistance (PASTEUR) Act

The US has implemented or considered several pull-incentive interventions in the last decade to coax private sector actors back into antimicrobial R&D. These include the Generating Antibiotic Incentives Now (GAIN) Act of 2012, which rewarded new antimicrobials with five additional years of extended market exclusivity, and a revision of the Inpatient Prospective Payment System (IPPS) rule operative since 2020, which aimed to facilitate both the uptake and development of new antimicrobials by boosting reimbursement.[20] Still other such incentives to further increase federal reimbursement for antimicrobials have been under consideration in recent years, but by far the most ambitious pull incentive proposal to date is the PASTEUR Act, introduced most recently in April 2023 by a bipartisan group of legislators in both House and Senate.[21,22,23]

The Act would establish what its proponents call a "subscription-style model" that would depart from the current federal procurement model in which "contracts between the government and drug makers base payment on volume" and would instead "offer… developers an upfront payment in exchange for access to their antibiotics" by creating a new stream of federal funding to award contracts (valued between $750 million and $3

billion each, awarded over 5-10 years) to pharmaceutical corporations that have developed new antimicrobials.[24] The contracts would secure a certain pre-agreed-upon amount of each new product for federal health programs or plans, and the Act would establish a Committee on Critical Need Antimicrobials to determine which products merit a contract and how they would be valued. Earlier iterations of the bill committed $11 billion for the program over 10 years, while the most recent slimmed-down version committed $6 billion over five (though subscriptions would still run up to 10 years, so presumably additional funds would be required at that point).

The interventions enacted or contemplated for spurring antimicrobial innovation in the US, including the PASTEUR Act, hew closely to those proposed by industry voices. The industry-driven AMR Action Fund, for example, calls for pull incentives, including "reimbursement reform" and subscription models to further reward antimicrobial R&D.[18] In MSF USA's view, however, the US is paying insufficient attention to the effects its approach to incentivizing R&D will have on access to and stewardship of novel antimicrobials outside of federal health plans and – most pertinently for MSF USA – globally. The logic of "value-based pricing" that underpins "reimbursement reform" has been used to justify extremely high medicine prices and the World Health Organization (WHO) does not recommend they be used in the absence of other affordability measures.[25,26] The PASTEUR Act raises similar concerns. Sponsors of the Act say its objectives are "to encourage innovative drug development targeting the most threatening infections, improve the appropriate use of antibiotics, and ensure domestic availability of antibiotics when needed."[24] MSF USA is concerned, however, that the Act would:

1) drive up prices of PASTEUR-supported novel antimicrobials in all markets besides US federal procurement and negatively impact access to the new products for people who need them – outside the public system in the US and around the world;

2) compromise stewardship of resulting antimicrobials; and

3) be an inefficient means of incentivizing meaningful antimicrobial innovation.

The remaining sections of this document will further detail MSF USA's concerns; propose alternative means of spurring antimicrobial R&D that we see as superior to the PASTEUR Act; and outline suggested revisions to the Act to mitigate some of its negative impacts should Congress nonetheless continue to advance the bill toward passage.

MSF USA's concerns about the PASTEUR Act

The PASTEUR Act's contract payments do not delink its R&D incentive sufficiently from sales volumes or at all from prices, allowing corporations to engage in sales to private and global healthcare markets under "normal" conditions. This model would maintain incentives for increasing sales volumes in the most lucrative locations rather than where need is greatest and setting prices at what the market will bear rather than what people most in need can afford. In this way, the Act would pit its stated function as a reward for bringing new products to market against its purported goals of promoting access and antimicrobial stewardship.

The Act would impose a soft "cap" on sales in that corporations would cease to receive their annual subscription payment if revenues earned for the antimicrobial outside of US federal procurement were to "exceed 5 times the average annual amount" of the PASTEUR subscription contract. While this cap would presumably encourage a measure of restraint in sales volumes outside of federal programs/plans, it would do so through a crude mechanism that fails to rationalize the geographic distribution of those sales according to public health need. Moreover, the Act's preservation of corporations' incentive to sell products at the highest price outside of the federal procurement system further jeopardizes such distribution – particularly given the very high prices of novel antimicrobials developed in recent years. The Act threatens to concentrate the sales it permits outside of federal programs in markets that will bear the highest prices (rather than wherever use is most needed and appropriate). If/when drugs become available in lower-income contexts under a tiered pricing arrangement like those commonly

used by corporations to segment markets, the relatively lower prices charged in these contexts will also be higher – driven up by the steeper gradient established by high prices in countries like the US. The structure of the Act would therefore have negative repercussions both for equitable access, particularly for those in the US with private insurance or no insurance and people in LMICs, and stewardship.

1. Impact on access and affordability

Lack of access to novel antimicrobials is a major issue for MSF and the low-resource contexts in which we work. When new antimicrobials promising to address drug-resistant infections are introduced, there is often a significant delay in access for low- and middle-income countries (LMICs) due to a range of factors.[27] Many countries are simply excluded as markets for new antimicrobials on the basis of their being economically unattractive.[28] Scaling up access to novel antimicrobials meant to be reserved for last-line use is particularly challenging. New drugs tend to have very high prices that are prohibitive in many countries, as well as intellectual property (IP) protections that delay the introduction of generics for a significant amount of time. In the case of cefiderocol, which costs $1,434.00 per day of therapy in the US, concerns about constrained and delayed access for LMICs led the non-profit Global Antibiotic Research & Development Partnership (GARDP) to broker an arrangement whereby "GARDP will manufacture and commercialize cefiderocol through sub-licensees in a large range of countries that have delayed access (if any) to newer antibiotics."[29,30] More comprehensive solutions are needed, however, as price and access are an issue with all newly developed and approved antimicrobials. The budget of even a well-resourced humanitarian organization such as MSF stands to be significantly impacted by extensive need for any costly new drug, as antibiotics already account for 20-24% of our annual international drug supply expenditure.

The PASTEUR Act's architects have been almost entirely inattentive to the impact that the Act will have on access to novel antimicrobials outside of federal programs, including internationally. The Act does include a requirement that drug sponsors "submit a plan for registering the antimicrobial drug in additional countries where an unmet medical need exists, which such plan may be consistent with the Stewardship and Access Plan (SAP) Development Guide (2021)," a document generated by the Wellcome Trust, CARB-X, and other stakeholders to guide pharmaceutical corporations in articulating stewardship and access plans for the products they develop.[31] However, the vague and equivocal language used to frame this requirement in the bill ("submit a plan" that "may be consistent with") is insufficient to guarantee that sponsors' plans for registering antimicrobials in other countries will be substantive and achieve their intended ends. Moreover – as is acknowledged in the SAP Development Guide – registration in countries with need is by no means the only measure needed to ensure meaningful access. Products need to actually reach those markets and be available at affordable prices. The Act fails to include provisions conducive to global access, for example, on pricing, removal of IP-based and technological barriers to competition, and transparency of prices, IP, and R&D costs.

The Act's proponents call it a "subscription-style" model, though it differs in meaningful ways from other analogous initiatives trialed thus far – including in its consequences for access and stewardship. The initiative most similar to PASTEUR has been the pilot program begun by England's National Health Service (NHS) and National Institute for Health and Care Excellence (NICE) in 2019, now in the process of being institutionalized and expanded UK-wide.[32,33] The NHS/NICE program is the only other subscription-like initiative for antimicrobials undertaken with the express goal of spurring R&D alongside access for a given population. The English pilot, though, was launched in the context of a national healthcare system that provides healthcare to the population as a whole, which holds out the possibility of rational, comprehensive, and equitable domestic distribution according to health needs rather than market imperatives – a context that sets it apart from the PASTEUR Act.

The Act is also distinct from subscription initiatives launched in recent years to secure access to drugs that have been inaccessible due to high prices (e.g. programs for direct-acting antivirals for hepatitis C in Australia, Washington state, and Louisiana) or might otherwise be unavailable due to the small size of a given market (e.g. the program for antimicrobials in Sweden)[34,35,36,37,38] Whereas these programs provide up-front or ongoing

payments in exchange for unlimited supply of a given product and are expressly focused on securing access, the PASTEUR Act procures a predetermined volume of product and aims to incentivize R&D. Unlike the hepatitis C programs, in the case of the PASTEUR Act, increased utilization would not result in a better value for the federal government. Only if a subscribed-for antimicrobial sells in blockbuster volumes outside of both federal markets and other subscription-like arrangements would the government cease subscription payments and possibly see a reduction in its procurement costs – an outcome that would also likely raise stewardship concerns. In these ways, the Act more closely resembles an "advance market commitment" (AMC) – an incentive structure that has so far mostly been implemented for vaccines in which governments or other sponsors commit to purchase an agreed-upon amount of medical product at an agreed-upon price as a pull incentive.[39]

From MSF's perspective, the failures of the AMC model in promoting optimal R&D and equitable access to people in LMICs thus far, especially with respect to pneumococcal conjugate and COVID-19 vaccines, are well documented.[40,41] Given past experiences with their access-related failures, MSF has advised that future AMCs be structured to safeguard against overpricing, demand cost transparency from drug producers, facilitate access for all countries with need, and encourage competition. Were the PASTEUR Act to advance toward passage, MSF USA would recommend – at a minimum – that similar safeguards be built into the legislation (see the last section of this document, below).

While proponents of the PASTEUR Act call it a "subscription-style" model, it differs significantly from certain subscription initiatives for access to medicines launched in recent years. Whereas other programs provide up-front or ongoing payments in exchange for unlimited supply of a given product and are expressly focused on securing access, the PASTEUR Act procures a predetermined volume of product and aims to incentivize R&D. It more closely resembles an "advance market commitment" (AMC) an incentive structure whose failures in promoting optimal R&D and access for people in LMICs are well documented.

In a limited gesture toward the importance of competition, the Act does specify that the HHS "Director may award a subscription contract… to a manufacturer of a generic or biosimilar version of an antimicrobial drug for which a subscription contract has been awarded," which could ultimately encourage the sale of more affordable versions of brand-name drugs beyond the confines of the PASTEUR program. This would depend, however, upon a generic manufacturer's independently overcoming regulatory challenges and IP barriers to market entry and seeking a PASTEUR contract. Indeed, the same obstacles would hinder corporations trying to secure any kind of federal contract or purchase agreement for a generic version a patent-protected, PASTEUR-supported product. It is hard to understand or justify the US government's taking this costly, passive, and unreliable approach to encouraging competition and affordability. The US could, instead, retain for itself IP rights to products its R&D dollars help bring into being and directly facilitate both stewardship and access, including through encouraging public, non-profit, or generic production. The preservation of drug developers' control over a product's manufacturing, pricing, and distribution – as a way of incentivizing R&D investment – is both intrinsic to the Act's structure and fundamentally in tension with its stated goals of facilitating access and stewardship.

2. Impact on antimicrobial stewardship

While the PASTEUR Act contains elements to monitor resistance and requires some actions of manufacturers to limit environmental exposure and guide, monitor, and assess the use of antimicrobials supported through the program, its preservation of the incentive to increase sales volumes outside of federal procurement is problematic from the standpoint of stewardship. The Act's allowance for sales in private and global markets amounting to revenue up to five times the amount of an annual subscription payment, alongside the existence of other volume-based incentives such as the US Centers for Medicare & Medicaid Services's technology add-on payment (in the domestic context), may in fact drive some inappropriate use of subscribed-for antimicrobials.[42] While the cap on revenues outside of the Act might deter sales beyond a certain volume and encourage conservation of novel antimicrobials in absolute terms, this method of constraining volumes – like high drug prices – is a crude one that does nothing to encourage distribution according to public health need, which goes hand in hand with appropriate use.

Beyond this fundamental question of how the Act's structure would impact responsible distribution, the bill does not extract strong commitments from contract recipients to encourage antimicrobial stewardship throughout the life cycle/value chain of a given antimicrobial, such as: appropriate promotion and sales strategies, post-approval surveillance and data-sharing, and facilitating development and availability of relevant diagnostics.

The Act does require manufacturers who receive a designation of a critical need antimicrobial to: submit a plan for the appropriate use of their antimicrobial; submit "an appropriate use assessment" to HHS/FDA/CDC every two years regarding use of the drug including its marketing; track and publicly report resistance data; develop and implement education and communication strategies about appropriate use of the drug; and ensure manufacturing practices that control/minimize discharge of antimicrobial agents. The 2021 SAP Development Guide discussed above contains helpful specific suggestions for what further action could be taken, however it is only mentioned once in the Act: with reference to the specific issue of registering products in countries of unmet need rather than as a resource for developing a robust and comprehensive plan for encouraging stewardship. Moreover, it is not clear whether drug sponsors' "appropriate use" plans must be published for public scrutiny – in contrast to the CARB-X stewardship and access plans based on the SAP Development Guide – or that sponsors would be bound to adhere to them.

The Act does specify that for each antimicrobial receiving the designation, HHS – in consultation with professional societies and experts - will publish clinical guidelines specific to the antimicrobial. Such guidelines are not mandatory, however, and from the Act it is unclear how adherence to them will be monitored in the fragmented, and largely private, US healthcare context. It also specifies that sponsors of antimicrobial drugs that receive the critical need antimicrobial designation submit a plan for appropriate use of diagnostics within 90 days, for HHS to use in developing clinical guidelines, which includes "appropriate use of diagnostic tools, where available, or a plan to coordinate development of diagnostic tools as necessary." The concept that sponsors should actively support development of companion diagnostics where appropriate is a key one and should be framed more strongly – as a requirement for receipt of a contract.

The Act's other elements aimed at "encouraging appropriate use of antimicrobials and combating resistance," including support for surveillance and reporting of antimicrobial use and resistance and the establishment of a health facility grant program, are welcome but do not directly address stewardship of the specific products supported by the subscription program – and are also assured to be limited in scope by the provision that "the Secretary may use not more than 5 percent of the amounts appropriated… to carry out this section."

3. High costs and a failure to foster more transparency and collaboration in antimicrobial R&D

As mentioned above, the nature of the UK's health system, which enables the NHS/NICE program to be "fully delinked" from volumes, gives the program advantages over the PASTEUR Act with regards to domestic access and stewardship. Critics of the program, however, have still raised key questions regarding the ability of

the NHS/NICE pilot to adequately spur innovative R&D and the judiciousness and sustainability of the investment it entails.[43,44] Indeed, as the UK subscription model moves toward permanence following its pilot phase, the cap on annual payments per drug has risen from £10 million ($12.4 million) to £20 million ($24.8) per year.[33] These considerations should likewise be paramount for lawmakers considering passage of the PASTEUR Act in the US. In fact, by offering contracts of up to $3 billion for each new antimicrobial, the Act would constitute a much larger investment than the NHS/NICE program and likely require a new infusion of public funds after five years. The size and nature of investment make the Act's global impacts all the more significant and worrying: by electing to invest so heavily in antimicrobial R&D rather than other public health infrastructure and in a manner that not only fails to facilitate but undermines equitable, needs-driven access, Congress risks misallocating limited resources and moving the world further away from, rather than toward, an approach toward antimicrobials as a global public good.

This concern about the PASTEUR Act's global repercussions is compounded by the fact that it explicitly promotes replication of its own model in other locales – in many of which the Act's features may be an even less suitable intervention for addressing the acute and complex challenge that AMR represents. The provision in the Act that encourages other countries to create their own subscription-style models similar to the Act is vague and presumes without justification that market entry rewards would be the best use of resources to address the dearth of novel antimicrobials in all contexts. Low-resource settings like those in which MSF carries out medical humanitarian operations often have fragmented and underfunded healthcare systems. In these settings, other interventions to address antimicrobial resistance – such as increased access to quality healthcare, vaccination, water, and sanitation – are top priorities that must be pursued in tandem with increased access to existing and novel antimicrobials. In contexts like these, other approaches to facilitating access to novel antimicrobials are more relevant and promising than an arrangement in PASTEUR's mold, such as those being advanced by GARDP and the SECURE Antibiotic Facility – with their focus on gauging local need, forecasting, creation of a context-specific "market introduction roadmap," pooled procurement, stewardship, capacity-building, and evidence generation.

Recent influential estimates of the public investment required to spur antibacterial R&D found that while the investment needed to bring a product to market under the PASTEUR Act is within the range of an effective pull incentive, it would be significantly lower if directed to non-profit or public R&D entities rather than private sector enterprises, due to the latter's profit-making imperatives.[4546] This raises the question of whether a much smaller investment of US public funds, spent differently, might yield greater benefits for public health in the US and around the world – and preserve resources for other crucial public health measures to counter AMR. The Organization of Economic Cooperation and Development (OECD), for example, has proposed intervention packages to address AMR focused on public health measures such as IPC, stewardship, and testing and posits that an investment of just $2 per capita per year would avert 47,000 deaths per year in OECD countries, pay for itself in one year, and save $4.8 billion.[4] The World Bank found that an annual investment of $9 billion globally – half to support public health and veterinary systems in 139 LMICs – would avert trillions of dollars in economic losses.[3]

The Act contains some provisions to protect, review, and learn from its initial investments of public resources in the development of antimicrobials in order to evaluate and optimize the subscription program. Specifically, there are provisions that empower the Secretary of HHS to terminate subscription payments if certain conditions are not met, and that mandate a study within six years of PASTEUR's impact on the development of priority antimicrobials. There are, however, no transparency provisions included at all, such as a requirement that payment recipients share detailed R&D cost data (including clinical trial costs) that would facilitate public scrutiny of the valuation and pricing of supported antimicrobials and better inform other R&D initiatives (including public and not-for-profit ones) aiming to bring important new antimicrobials to market.

In determining which drugs to prioritize for subscriptions, the Act indicates that it will identify "infections for which new antimicrobial drug development is needed, taking into account organisms, sites of infection, and type of infections for which there is an unmet medical need, findings from the most recent report entitled 'Antibiotic Resistance Threats in the United States' issued by the Centers for Disease Control and Prevention, or

an anticipated unmet medical need, including a potential global health security threat." The proposed list of infections contained in latest CDC report titled "Antibiotic Resistance Threats in the United States" that will be the starting place for prioritization of products is sufficiently broad to contain infections of greatest concern to MSF. However, with the "favored characteristics" and their monetary value yet to be determined, there is not yet enough information to assess the selection and valuation criteria for antimicrobials included in the subscription payment. If the more clinically significant drugs garner the greatest subscription payment as anticipated, though, they will be subject to a steeper price gradient in markets outside PASTEUR's remit.

Also, as pointed out by GARDP, the favoring of drugs "containing no active moiety…that has been approved" already by the FDA would not encourage investigation or development of combination treatments. We share GARDP's concern, given the importance of novel combination drugs in countering drug-resistant infections, and support their call "for specific legislative provisions to incentivize accelerated development of new antibiotics that address the needs of children."

Finally, the PASTEUR Act does nothing to foster the more open, collaborative innovation ecosystem that – along with economic incentives – is badly needed to overcome scientific bottlenecks in antimicrobial R&D, encourage clinically significant innovation, and facilitate both access and stewardship. Through PASTEUR or other means of incentivizing antimicrobial R&D, HHS could, for example, encourage exploration of open-source compound libraries that accelerate non-duplicative drug discovery research and/or the establishment of sizable global clinical trial networks, including sites in LMICs (with appropriate technical and financial support), that continuously enrol patients in concomitant parallel trial protocols.[iv,v] Participation in multiple concomitant protocols helps efficiency and early achievement of sufficient sample sizes and is essential for difficult-to-enrol trials, more challenging patient groups, or difficult-to-measure clinical outcomes or strategies.

The PASTEUR Act does nothing to foster the more open, collaborative innovation ecosystem that – along with economic incentives – is badly needed to overcome scientific bottlenecks in antimicrobial R&D, encourage clinically significant innovation, and facilitate both access and stewardship.

The US should use different means than the PASTEUR Act to incentivize R&D

In MSF USA's view, given all of the concerns articulated above, legislators should be looking at alternative methods of spurring antimicrobial R&D that would constitute a more effective, impactful, and judicious use of public funds than the PASTEUR Act. If the US government is to significantly augment its role in antimicrobial R&D, as it should, legislators must make sure those investments are prudent and structured in ways that center global public health needs. Moreover, legislators must recognize that the obstacles to antimicrobial R&D are not only financial, but scientific and logistical, and the manner in which governments incentivize R&D must not undermine collaboration between developers and should instead, foster it.

[iv] One example to build on is the joint natural product library effort being carried out by the National Cancer Institute and the National Institute of Allergy and Infectious Diseases. See: http://dx.doi.org/10.1021/acsinfecdis.3c00067

[v] Examples of such globally coordinated trials include: the WHO-coordinated Solidarity trial and the UK RECOVERY trial for COVID treatments and the SNAP collaboration focused on Staphylococcus aureus.

The Department of Health and Human Services could expand its own intramural research program to directly conduct more late-stage research. The agency could also offer discrete monetary prizes to reward successful innovations instead of market exclusivity; contract with R&D institutions, including not-for-profit ones, to develop antimicrobials but retain IP rights over resulting products; or purchase IP rights from a pre-existing patent holder. All of these approaches could not only ensure that public investment is strategically deployed to meet global public health needs but also retain federal authority in distribution of resulting products. This would better ensure both stewardship and equitable access and could facilitate diversified production – including public sector or non-profit production – and lower-cost drugs.[47,48,49] Non-profit initiatives such as Civica Rx in the US, GARDP, and the SECURE Antibiotic Facility, among others, are all well-positioned to be significant players in late-stage drug development, manufacturing, and supply. The state of California, for example, has contracted with Civica Rx to produce insulin as part of the state's CalRx initiative to produce its own generic drugs – and Civica Rx has already begun producing generic antibiotics for its member health systems.[50,51] Investing public funds in public or non-profit development is more likely to be cost-effective (costing significantly less than what the PASTEUR Act would, according to Outterson's recent analysis) and ensure resulting products are affordable and accessible. [45,52,53]

That approaches like these are more compatible with an open science framework is extremely significant in the context of antimicrobial R&D. In making research outputs freely and immediately available to all, open science encourages collaboration and accelerates innovation – which is particularly important in instances where scientific obstacles are significant and incentives for profit-driven R&D are weak. Long-standing challenges in antimicrobial development, including penetration issues, efflux, and toxicity will continue to affect efforts at drug discovery, as will difficulties in structuring and conducting clinical trials, e.g. enrolling sufficient numbers of trial participants infected with a given specific resistant pathogen, gaining participation from hard-to-enroll patient groups (e.g. children, pregnant women, those with hard-to-treat infections like sepsis), and negotiating difficult-to-measure clinical outcomes or strategies.[9] To overcome such barriers, and take full advantage of the potential of approaches like drug repurposing, antimicrobial R&D should be maximally open and collaborative.[54] MSF can attest to the importance of engaging more LMICs in generating data about treating resistant infections and indications outside of those explored to support initial market approval – and has itself developed laboratory innovations that have and/or could continue to benefit from open science frameworks.[55,56,57]

Policies establishing subscription models may have a place in safeguarding access to certain drugs and have been used to interesting effect in securing access to antimicrobials in Sweden, for example, and expensive newer hepatitis C treatments in Australia, Washington state, and Louisiana.[34-38] However, as mentioned above, these differ from the PASTEUR Act in numerous significant ways, including that they do not aim to also function as an R&D incentive. Analysts examining the preliminary results of some of these recently implemented subscription programs have pointed out that the viability of subscription models as a cost-saving and access-assuring mechanism for governments is indication-, drug-, and context-specific – and some have in fact proposed structural elements to mitigate undesirable impacts that certain subscription arrangements might otherwise have, such as keeping prices high and reducing competition.[35,36]

Is PASTEUR salvageable, considering its negative repercussions for access and stewardship?

The PASTEUR Act's current structure largely works against ensuring equitable access and adequate stewardship. As a result, it does not seem possible to graft provisions onto it in order to mitigate its harms. Any effort to do so, however, should include the following provisions at a minimum:

- Preferentially award contracts to non-profit drug developers.
- Require that manufacturers publicly disclose:
  - the prices of subscribed-for drugs; and

    - R&D costs incurred in their product's development – particularly the costs for clinical trials, in disaggregated detail – and the proportion of private vs. public funding for R&D.
  - Require that manufacturers:
    - register their products in LMICs within a short, fixed timeframe that will quickly facilitate access in those countries;
    - set prices according to a reasonable, pre-agreed margin based on auditable costs of goods;
    - engage in non-exclusive licensing to promote diversification of manufacturing sources, including through LMIC-based production that could facilitate more responsive and resilient supply chains, and increase sustainable access; and
    - engage with non-profit and multilateral initiatives focused on facilitating access for LMICs, such as GARDP and the WHO SECURE Antibiotic Facility.
- Remove "containing no active moiety…that has been approved" already by the FDA as a "favored characteristic."
- Include specific provisions to incentivize accelerated development of new antimicrobials for infants and children.
- Require sponsors to help establish and participate in large global clinical trial networks, including sites in LMICs (with appropriate technical and financial support) that continuously enroll patients in concomitant parallel trial protocols.
- Require that sponsors generate, disclose publicly, and adhere to a detailed plan for promoting stewardship of subscribed-for drugs.
- Require that sponsors support development of diagnostic capacity for subscribed-for antimicrobials where appropriate.
- Require manufacturers to sponsor phase 3 or post-approval studies specifically on resistant pathogens.
- Refrain from promoting the use of "subscription-style" R&D incentive models in contexts beyond the US. If the Act does address this topic, however, it should: – acknowledge that subscription models are not appropriate in all contexts, that there is a need for international coordination to both encourage R&D and ensure sustainable access to and stewardship of novel antimicrobials, and that in LMICs, in particular: 1) other approaches may be more suitable, such as those that the SECURE Antibiotic Facility is currently exploring; and 2) such efforts must be accompanied by measures and resources to bolster access to laboratories, infrastructure for infection prevention and control, and development of trained human resources.

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