IFPMA

Sustainable access to effective antibiotics

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Introduction

It is estimated that each year, 7.7 million people globally die due to an infection associated with 33 bacterial pathogens[1], of which approximately 5 million deaths are associated with resistant pathogens, and 1.3 million directly attributable to a resistant infection[2]. The UN High-Level Meeting (HLM) on Antimicrobial Resistance (AMR) in September 2024 will draw much-needed global attention to this pressing global health threat, offering an opportunity for meaningful progress at all levels. To achieve this, leaders need to agree to an ambitious and impactful set of commitments against AMR, consider how best to address evidence gaps, and build structures to track progress. In this context, ensuring access to effective antibiotics is a key public health priority – now and in the future. Tackling the different barriers so patients everywhere can access both new and existing[3] antibiotics will require a tailored package of policy reforms. Also recognizing the importance of infection prevention and control in reducing the burden of infectious disease is critical, through improving water, sanitation and hygiene (WASH) infrastructure, better leveraging vaccines, and other measures.

Key challenges

Poor and uneven access to antibiotics contributes significantly to the global infectious disease burden, unnecessary mortality and morbidity, inappropriate use, and the development and spread of AMR. The vast majority of antibiotics in use today have been around for many years, even decades, yet sustainable and equitable access is hindered by a complex set of interconnected challenges. Due to these, patients face shortages, high out-of-pocket costs and substandard antibiotics in many places. At the same time, a rise in resistance rates and untreatable infections necessitates continued development and availability of new antibiotics. Of the few antibiotics approved in recent years, often used to treat resistant infections in hospitals, many are not available widely in high-income countries (HICs), and even less in low- and middle-income countries (LMICs) which often face the highest rates of AMR. Unique market challenges for new antibiotics and the resulting weak antibiotic pipeline means that the world may soon run out of effective treatments to address resistant infections. These challenges are closely linked and will require a series of complementary measures.

Policy reforms are urgently needed to support equitable and sustainable access to effective antibiotics, and to ensure a robust antibiotic pipeline that can deliver these.

Challenges in ensuring access to safe and quality-assured antibiotics – both existing and new – include:

- Weak health systems and challenges in implementing comprehensive Universal Health Coverage (UHC), leading to limited healthcare infrastructure to appropriately diagnose infections, dispense appropriately, and deliver antibiotics efficiently to patients.
- Inefficient regulatory procedures and differing requirements between countries, with weak regulatory capacity and supply chain surveillance, resulting in delays in regulatory approval and the circulation of substandard and falsified medicines.
- Insufficient disease surveillance and demand forecasting/planning over a longer term, contributing to inappropriate use and preventing timely and robust demand signaling to suppliers.
- The lack of public reimbursement lists or donor-funded procurement for essential antibiotics, and procurement policies that do not appropriately recognize the value of antibiotics to the healthcare system and to societies.
- A weak clinical development pipeline due to slow progress on new financial incentives at a national and/or regional level that would address the market challenges for new antibiotics by rewarding innovation, thus encouraging greater investment to build a resilient and sustainable pipeline and base of R&D expertise.

Call to action

Enacting a coherent set of policy changes that will both be able to sufficiently incentivize action and address the multiple barriers to antibiotic access will require a coordinated approach from all stakeholders in the ecosystem. We believe the following actions should be prioritized across the different countries globally:

1

Improving sustainable access to antibiotics, which will require a broad set of measures, tailored to individual context – both in terms of products and geographies:

- Leveraging principles of regulatory harmonization and reliance in order to facilitate product approval and introduction.
- Improved surveillance and forecasting to better inform antibiotic demand.
- Reimbursement reform that recognizes the broad value of antibiotics which can include access-supporting subscription models that countries beyond G7 (including G20) could be well positioned to explore.
- Sustainable tendering policies for off-patent antibiotics that involve multiple suppliers in the procurement process.
- Procurement mechanisms that pool demand could support access in lower income settings, as could new partnership agreements between developers, global health agencies and/or appropriate commercial partners[4].

2

Implementing effective pull incentives in G7 and the EU and an overall sustainable market that supports antibiotic launches, which will not only revitalize private investment in R&D but are necessary reforms to safeguard current and future global public health.

- Global dynamics and sources of AMR burden need to be considered as an important factor in the R&D of new antibiotics. Globally relevant R&D targets jointly determined by all stakeholders involved in AMR, including the industry, can in turn support incentive implementation efforts in a way that considers the needs of all countries.

Improving access to existing antibiotics

A significant part of the infectious disease burden could be addressed with reliable access to existing antibiotics – in addition to strengthening measures for infection prevention and control, such as WASH infrastructure, and improved access to vaccination.

In 2017, the WHO created the first Access/Watch/Reserve (AWaRe) classification framework to guide the prescribing of antibiotics (43 of which are on the 23rd WHO Essential Medicines List[5]) and aiming to preserve the effectiveness of last line, "Reserve" antibiotics. Most existing antibiotics in use today are off-patent and classified as "Access" or "Watch," which means they should be widely available, and used more frequently than Reserve antibiotics. The WHO recommends at least 60% of national antibiotic use should be from the Access group[6] and recent guidance suggests 90% of all common infections seen in primary health care should be treated with Access antibiotics as a first choice[7]. Across AWaRe categories, diverse characteristics of the different antibiotics need to be taken into account. For example, some are used in high volumes with many millions of doses in many countries, while others are used in hundreds or thousands of doses only. In addition, some antibiotics are relatively more straightforward to manufacture, while others require specialist facilities, equipment and expertise.

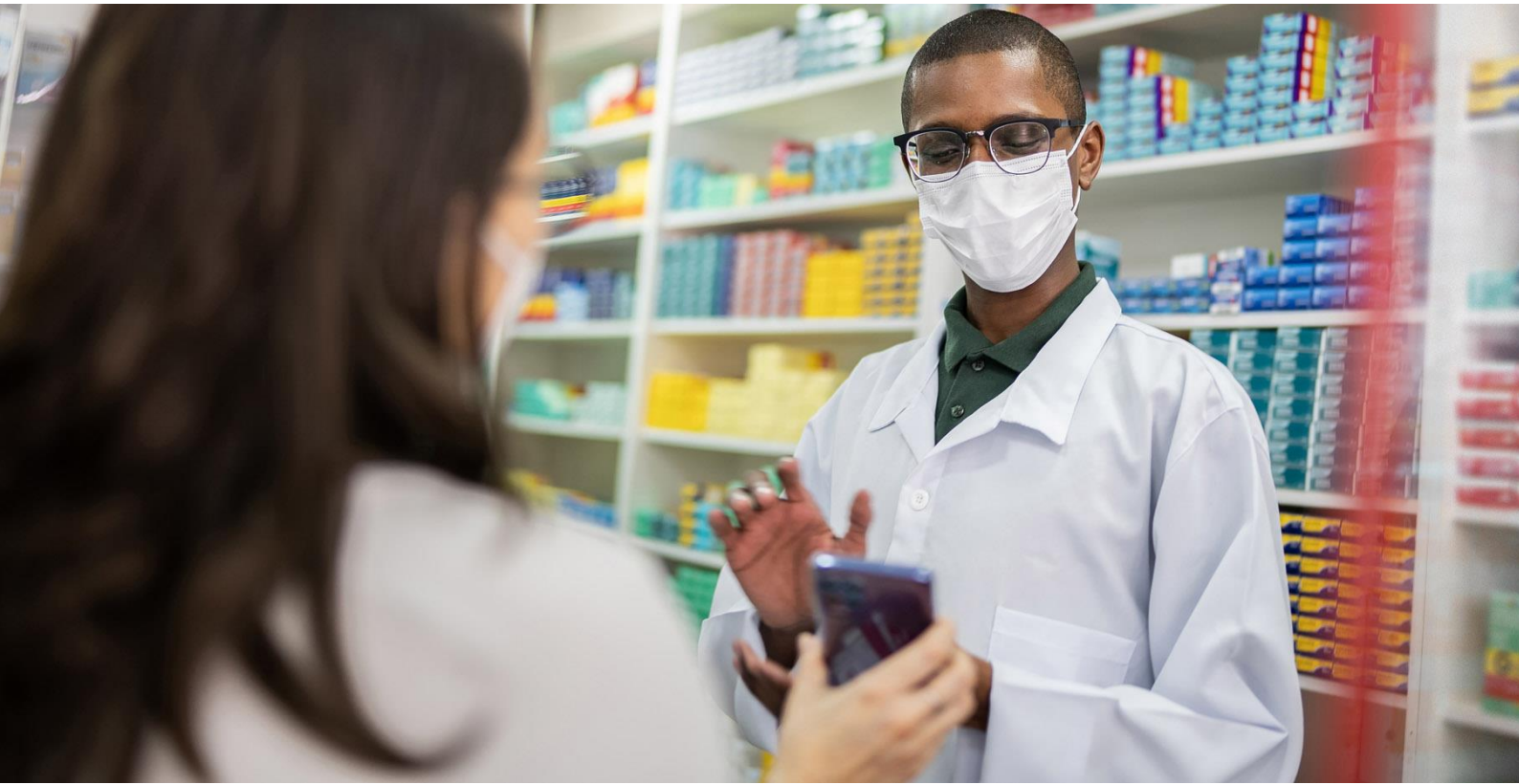
Many Access and Watch antibiotics have been generic for decades, and any manufacturer with the appropriate facilities and fulfilling Good Manufacturing Practices (GMP) criteria can register and market them. For most types of medicine, market forces result in a healthy supply chain and reliable and high-quality product availability. However, for many antibiotics, the supply chain lacks resilience leading to shortages, product withdrawals, lack of registrations and substandard and falsified products. For many important antibiotics, supply is highly consolidated at both finished products and active principal ingredients level. Few global manufacturers remain active, and/or are limited to a handful of geographies[8], resulting in a fragile supply that cannot accommodate changes in demand. At the same time, as antibiotic manufacturing can be a contributing factor to the environmental development of AMR, manufacturers are investing to implement responsible manufacturing standards and independent certification has been introduced[9,10].

Multiple factors are causing these supply challenges, including unpredictable or unclear demand, fragmented and low-volume purchases, unsustainable tendering practices focused solely on price, inefficient distribution and lack of robust regulatory oversight. It is not economically sound for a supplier to invest in registering a product in

many countries if the volume of use and the revenue will not cover its costs. Despite generally low prices and low margins for manufacturers of these antibiotics, out-of-pocket costs for patients can be high, especially in countries with weaker health systems, usually due to the lack of public reimbursement lists and multiple price mark-ups along the distribution and retail chain.

A package of measures is needed to address both the demand and the supply for these markets, and we welcome early efforts such as the SECURE initiative that are working with all relevant stakeholders to build a comprehensive approach to improve the supply of antibiotics. At national level, improved demand planning and signaling would make a significant difference to product availability. Better recognition of antibiotic value, more efficient distribution (coupled with measures to ensure appropriate use and remove substandard products) and inclusion of essential antibiotics on reimbursement lists would also attract the necessary registration and supply improvements.

In addition, we note that there are currently no major donor-funded procurement mechanisms to support antibiotic access in LMICs. On the other hand, bilateral programs like PEPFAR and multilateral initiatives like the Global Fund to Fight AIDS, TB, and Malaria have enabled significant improvements in global access to treatments for other infectious diseases. For example, 76% of HIV patients globally were receiving treatment at the end of 2022, compared to 24% in 2010[11]. Despite the diversity of antibiotic treatments in use, similar models for antibiotic access in lower income settings could be explored via entities with expertise in procurement at scale. Leveraging additional expertise with programmatic support, health system strengthening and capacity building, could also facilitate the development of appropriate treatment portfolios that are aligned with public health need in specific contexts. This could significantly improve demand planning and support alignment with the supply side, facilitating greater access.



Improving access to new antibiotics

Most new antibiotics, once approved and incorporated into treatment guidelines, are classified as Reserve, meaning they are intended for last line use. They are therefore used in low volumes to slow the development of resistance and to safeguard antibiotic effectiveness. However, the value assigned to them is often also low, which creates a significant disconnect between the investment required to develop and bring a new antibiotic to market and the potential returns developers can achieve. Even without considering the significant cost and risk of developing these new antibiotics, this revenue is insufficient to support broad launches in multiple markets, sustainable supply, and fulfilment of post-approval commitments including surveillance.

Consequently, investment in antibiotic R&D has been drying up, with very few antibiotics currently in late-stage development and a persistent downward trend. Between 2017 and 2023, only 10 small molecule direct acting antibiotics were approved and recent modelling suggests we may only see 8 new ones in the decade to 2033 unless changes are made[12].

> **In addition to sustainable access to existing antibiotics, there is an urgent need to develop new antibiotics to treat resistant infections for all patients globally.**

Most new antibiotics have limited registrations and launches, even in HICs[13], as it is not economically sustainable to launch them. Many of the recently developed antibiotics were driven by smaller companies which faced significant financial struggles despite their success, leading to bankruptcies, distressed sales, and/or winding down of operations[12]. Economic failures and the unattractiveness of antibiotic R&D have also led to a continued drain of R&D expertise[14], which will be difficult to retain or resurrect under current circumstances. This vicious circle will likely lead to a further decline in development and potential future antibiotic approvals.

Another significant barrier to utilization of new antibiotics is the requirement of robust infrastructure to ensure appropriate use. This challenge includes not only hospital infrastructure, but also lack of surveillance and resistance data, inconsistent use of diagnostics and resistance testing, slow updates of clinical use guidelines to include new antibiotics, and reimbursement systems that incentivize the use of older antibiotics even when they may not be the most appropriate choice. Additionally, current value frameworks do not reflect and reward the full clinical, health system, and economical value as well as the societal value of new antibiotics.

Solutions in the form of new pull incentives that could bring back private R&D investment, reinvigorate the pipeline, and support sustainable access, are well known, as is the scale of the global challenge[15]. It is generally agreed that pull incentive implementation will need to be led by G7 countries and the EU, and each should contribute to the global total based on their relative GDP.

To date, push incentives have helped maintain a rich and diverse preclinical pipeline. For example, CARB-X announced in March 2024 its 100th investment[16], and

the industry-led USD 1 billion AMR Action Fund has so far made investments in eight companies as of June 2024, with one portfolio company receiving FDA approval in April 2024[17]. However, while support for push incentives must continue, they must be paired with pull incentives that reward successful antibiotic R&D separately from volume of sales, at a level that enables further R&D investment. Without pull incentives to create a sustainable market and bring new antibiotics to patients, the push incentive investments in early- and late-stage research will have been wasted.

There is also a role for countries beyond G7, such as G20 and other HICs and MICs to take action that both contributes to a sustainable antibiotics market and ensures that new product launches can be pursued sustainably and globally.

For countries in lower income settings, novel mechanisms that support sustainable access to new antibiotics are needed. The volume of use of most new antibiotics will be comparatively low, and all countries need to establish robust stewardship measures to ensure appropriate use. Therefore, models that can improve demand visibility while providing a level of oversight are likely to be preferred by all stakeholders. Initiatives like SECURE and other global health partnerships[18] could play a meaningful role in supporting procurement and appropriate use of new antibiotics in lower income settings. Additionally, companies may sign a voluntary licensing and collaboration partnership to increase access to their products such as that between Shionogi, GARDP, and CHAI for cefiderocol[4], a new antibiotic first approved in 2019.

Conclusion

While there are specific access challenges for both existing and new antibiotics, they have a common characteristic which is that their contribution to societies and health and economic security is not sufficiently recognized. Improving access to all antibiotics globally will require all countries that have the ability to do so to implement appropriate policy reforms and frameworks that meaningfully reflect and reward this value. At the same time, we need to progress mechanisms that can bridge gaps in global access to both existing and new antibiotics, especially in lower income settings which also tend to have the highest infectious disease burden. It is important that these models are tailored to individual products and geographical context and that use is aligned firmly with public health need, to preserve antibiotic effectiveness.

The pharmaceutical industry is committed to playing its part in increasing access to antibiotics by working with relevant partners and stakeholders to make feasible and economically sustainable changes to ensure that all patients can access the essential antibiotics they need, including broad and timely access to new antibiotics around the world.

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