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The Broken Wheel of Access for Antimicrobials

Barriers to Rolling out Antimicrobials in Low- and Middle-Income Countries

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Introduction

Access to effective antimicrobials is crucial to any healthcare system, but in many countries, necessary antimicrobials are not available to patients because they have not been registered and/ or introduced (Frost et al., 2019). This introduction barrier is particularly prevalent in low- and middle-income countries (LMICs). Not only does this directly cause mortality and morbidity, but, by leaving infections to spread unchecked, it can also lead to increased rates of resistance.

Through interviews with experts, we sought to learn why LMICs see fewer antimicrobial registrations and product introductions than other countries—what we refer to as the "rollout problem." We wanted to understand why large pharmaceutical companies may not register and introduce antimicrobial products in LMICs and to identify potential solutions to overcome these barriers. This was not intended as an exhaustive analysis of the problem, but carried out as part of CGD's Working Group on antimicrobial resistance (AMR) to understand if this is an issue which should be addressed in future research and agreements on AMR. While we focused on registration and introduction, it is important to note that this is not the only barrier to access: for example, if a country cannot afford the price of a new drug, there is no use in pushing for registration. Additionally, while our research focused on the rollout problem for novel antimicrobials, a complete understanding of access problems also requires consideration of issues around generics and other older anti-infectives, some of which are coming back into use.

The problem

When patients cannot access antibiotics, infections may remain untreated, causing direct mortality and indirect mortality as infections continue to spread; 33 bacterial pathogens are estimated to cause 7.7 million annual deaths, globally (Ikuta et al., 2022). Lack of access to antibiotics may also fuel the use of inappropriate antibiotics, which can increase resistance as less effective antibiotics do not completely treat infections and allow partially resistant bacteria to propagate (Rafiqi et al., 2022). Additionally, use of inappropriate antibiotics can include using important later-line antibiotics which, when possible, should be kept in reserve. Ensuring access to necessary antibiotics is, therefore, one of three key pillars (along with stewardship of antimicrobials and innovation of new products) of a sustainable solution to antimicrobial resistance (AMR) (McDonnell et al., 2022). Indeed, in scoping interviews with 28 AMR experts as part of the Center for Global Development's (CGD) overarching antimicrobial resistance project, 50 percent of interviewees mentioned ensuring access as a key policy priority. Perhaps unsurprisingly, experts who highlighted access as a priority disproportionately represent LMICs.

In many LMICs, the lack of access stems from a lack of introduction of key antibiotics in the country (the "rollout problem"). Previous research demonstrates the scale of this problem: of 25 new antibiotics approved between 1999 and 2014, only 12 had registered sales in more than 10 countries, and availability in multiple regions and country classes was "rarely seen within a few years of market authorisation" (Kållberg et al., 2018). The AMR Benchmark, produced by the Access to Medicines Foundation, demonstrates how the rollout problem primarily impacts LMICs[1] (Rafiqi et al., 2021). Pharmaceutical companies generally first register their products in higher-income countries with larger markets. In 2021, of 17 on-patent medicines, only six were filed for registration in ten or more of the 102 LMICs in scope; only seven were covered by an access strategy. While this is an improvement from 2020, when only four products were filed in ten or more countries, the numbers are still too low. Pfizer and Viatris each expanded registration of specific on-patent medicines in more than 15 LMICs since the last benchmark, but they were the only companies to do so. It is clear that there is still a large problem: there were 14 LMICs where no antimicrobial products were registered.

Even within the LMIC category, there is a stark difference: the five LMICs with the most registrations are all larger, middle-income countries: South Africa, the Philippines, India, Brazil, and Thailand. Only three patented products (developed by Johnson & Johnson, Pfizer, and Viatris) have been registered in any low-income country (LIC). While the overall number of products covered by access strategies may have increased, there is a widening access gap due to exclusion of LICs: in LICs, 65 percent of products assessed did not have an on-the-ground access strategy, compared to only 19 percent of products in upper-middle income countries.

1 While this problem is particularly concerning for LMICs, it is not unique to these countries: as interviews demonstrated, even in small high-income counties with insufficient market sizes, there can be rollout delays.

Methodology

Many experts and policymakers noted access as an issue of concern, and there is a vast extant literature on wider access issues for LMICs (Ozawa et al., 2019; World Health Organization & Health Action International, 2008). Still, there is a lack of research on the specific rollout issue for antimicrobials. We posited that rollout might be a particular issue for antimicrobials given their unique property that use in one patient decreases efficacy in another. We hypothesized that this might make pharmaceutical companies reluctant to register products in countries where both revenue is likely low, and use may be inappropriate – leading to resistance increases which could harm sales in more profitable countries.

Therefore, we conducted five in-depth, semi-structured interviews with experts representing three pharmaceutical companies conducting AMR research, one access-focused NGO, and one country regulator. We also re-reviewed notes from the 28 scoping interviews conducted by CGD and collaborated with the Access to Medicines Foundation to re-review notes from six interviews they conducted with pharmaceutical companies and academics.

The causes

Interview findings suggest three reasons for the lack of registration of on-patent medicines in LMICs: lack of a market in many LMICs, complexities with introducing drugs into these markets, and fears that resistance might develop, which could harm the market in high-income countries (HICs). While each of these problems, in isolation, may be solvable, the difficulty arises from their combination.

Lack of market for novel antimicrobials

There is only a limited market for novel antimicrobials in most LMICs, and even in some smaller HICs. This means there is insufficient return on investment (RoI) to motivate companies to overcome the difficulties associated with providing access for these markets. For example, one interviewee stated that it takes at least 10 years from launching novel anti-infectives in sub-Saharan Africa to recover the costs. Another pharmaceutical representative stated that even in HICs, it is a question of if, not when, to launch novel antimicrobials. When a drug is launched, it is only viable within the private sector—and even there it is only a marginal financial case.

In terms of volume, the market is small both because of low intrinsic demand and because external factors inhibit demand from being realised. On the intrinsic side, on-patent antimicrobials are typically indicated for only very specific cases, leading to low sales volumes. Most newly developed antibiotics go into the Reserve category of the WHO's AWaRe categorisation, meaning they should "only be used as a last resort when all other antibiotics have failed" (World Health Organization, 2019). This small market size is further restricted by extrinsic factors. For example, the healthcare systems in some countries are not strong enough to efficiently diagnose patients as requiring Reserve

antibiotics. Many LMICs suffer from a lack of demand generation. Patient advocacy for antiretrovirals (ARVs) played a large role in ensuring access to these drugs, but there is not the same awareness of novel antimicrobials, and so not the same assured demand.

Due to a lack of data, companies may also struggle to estimate the number of patients in LMICs who could benefit from the medication, impacting the business case assessment of the balance of commercial returns against ensuring patients have access to necessary medications. Relatedly, demand assessment is complicated by forecasting issues. Levine et al., 2008, highlight the difficulties of demand forecasting for all medical technologies—but antimicrobials, more than other drugs, are subject to massive swings in demand as outbreaks can quickly lead to a surge in demand. Thus, antibiotics are 42 percent more likely to be in shortage than other drug types (Raghavendran & Christian, 2022). For example, in late 2022 and early 2023, many countries faced shortages of amoxicillin after a surge in respiratory infections led to increased demand, with demand in the US in October 2022 345 percent higher than in October 2019 (Blank, 2022). These swings are problematic both when demand surges, straining supply chains, and when demand is less than predicted, frustrating manufacturers who were pushed to register their drugs.

As well as selling at low volumes, novel antimicrobials are often priced too low to generate sufficient RoI. This is due to issues with the current reimbursement systems in many countries, which do not adequately capture the value of antimicrobials. For example, many Health Technology Assessments (HTAs) do not consider the societal value of antimicrobials when setting the price of the product (Colson et al., 2021). It is also difficult to estimate the ability of new drugs to reduce resistance. Given that HTAs are usually conservative when counting benefits, this leads to systematic undervaluing of such drugs. Indeed, representatives from several pharmaceutical companies mentioned the HTA system as a barrier. Even where HTAs have been updated to better reflect the specifics of antimicrobials, such as in the new NICE model in England (Schurer et al., 2023), interviewees noted that some pharmaceutical companies still find the system is too challenging and there is insufficient data to meet the standards. One interviewee stated that countries often replicate industry-produced data, leading to inefficiencies. Additionally, interviewees reported that the pricing systems are unclear in LICs, with one stating "we prefer to launch in developed markets where the pricing reimbursement is clear." Even in HICs, price negotiation is a difficult and time-consuming process.

Complex product introduction processes

Compounding the issue of low RoI is the burdensome process for product introduction in many regions, and the fact that processes may differ among countries due to differences in local health systems and epidemiology. One interviewee described the process as so convoluted that the pharmaceutical company (s)he represents was still launching drugs in new countries nine years after the initial country launch.

Data and infrastructure requirements

Ahead of introducing a drug in a new country, companies need to conduct surveillance about which infections are dominant; determine what clinical trial data is required for approval; and consider the medical situation in each country, including what drugs are currently used and how appropriately, whether guidelines for appropriate use are in place, and usage rates of diagnostics. Additionally, after introduction, further post-marketing surveillance is required. Combined, this data collection and surveying are hugely burdensome for companies—and each additional country considered entails additional effort. Data collection can be especially burdensome in convoluted or fragmented, regionalised markets such as in India, or in markets with little transparency, and often requires pharmaceutical companies to partner with an organisation on the ground. While many of these steps are universal for the rollout of all medicines, it is especially challenging for antimicrobials due to the additional lift of understanding resistance rates; the difficulties in generating clinical trial data for antimicrobials (Stafford et al., 2014); and the particular importance of understanding antimicrobial usage due to the negative externalities of use.

The introduction of antimicrobials also requires more infrastructure than is needed for other drugs, due to the extra importance of ensuring appropriate use. There should be suitable healthcare infrastructure for stewardship measures, for example accurate and up-to-date treatment protocols, effective diagnostics, and good provider understanding of resistance. In many LMICs, however, there is insufficient public infrastructure to manage the rollout of drugs. Companies and countries can become stuck in a loop where "pharma [only] goes where infrastructure allows," but governments have little incentive to build infrastructure for a drug that does not exist in their country – and the cost to the company of developing infrastructure would not make sense given the RoI. Where there is political momentum and interest in AMR, resources instead flow to research and development or surveillance. However, one pharmaceutical representative told us of seeing an encouraging shift towards a "build while we go" approach, rather than being paralysed by a lack of infrastructure.

Similarly, finding manufacturing facilities which appropriately control discharge of active ingredients is a particularly acute concern for antimicrobials given the interlinkage of resistance in the environment and in humans and animals (UN Environment Programme, 2017). Innovative pharmaceutical companies are often uninterested in low-margin antimicrobial manufacturing for LMICs, meaning technology transfers are required. However, these take time, especially when working with major manufacturers which lack local country presence, and it can be challenging to find manufacturers with the technical equipment and knowledge for the complex manufacturing processes required for certain novel antimicrobials. For example, one interviewee reported that appropriate manufacturing is a bottleneck in the rollout of cefiderocol due to the specific "non-standard" manufacturing processes required (European Medicines Agency, 2020a). There can also be bottlenecks in the availability of materials: one pharmaceutical company reported that they rely on only a few countries for Active Pharmaceutical Ingredients.

Registration requirements

Another hurdle for companies is the registration process, and the fact that registration is required in each additional country but often via a different process requiring different data or materials. This imposes delays as companies compile the relevant dossiers, translate documents, and adapt to different requirements, for example to manufacture in-country. One interviewee described the documentation requirements for all 52 African countries—and the lack of synergy between them—as a "headache." Furthermore, even after a product has been registered for one indication, gaining approval for other indications entails significant effort, often requiring further trials. Approval of amendments to dossiers can interrupt supply chains and impose delays.

While the complexities of registration can be a barrier for all classes of drugs, the difficulty of recruiting patients and running clinical trials for antibiotics can make it especially challenging for pharmaceutical companies to compile the necessary trial data to meet the requirements of different countries (Miseta, 2020). Increasingly, countries such as the US are exploring and using innovative new trial designs (for example: FDA, 2024), but smaller and/or poorer countries may not have sufficient expertise to assess such submissions. In addition, high registration fees combined with the low RoI for antibiotics can prove a prohibitive barrier. Indeed, this was even seen in the European Union, the world's second largest pharmaceutical market (European Federation of Pharmaceutical Industries and Associations, 2024): Cipla withdrew their marketing authorisation application to the European Medicines Agency for the antibiotic Zemdri, citing the "cost expected to be required for approval and post-approval" – and this antibiotic is included on the WHO's Essential Medicines List (European Medicines Agency, 2020b; World Health Organization, 2023a).

While companies may commit to filing for registration in countries where clinical trials were conducted, there is often no such commitment for other places. Therefore, while registration might be guaranteed in (the predominantly upper-middle income) countries such as South Africa, China, and Brazil where trials are often run, smaller, low-income countries are often excluded.[2]

Resistance fears

Finally, while the combination of low RoI and burdensome processes means companies have little incentive to rollout antimicrobials, they may also have disincentives to ensure access to these products in LMICs. This is due to fears that the development of resistance in these countries could harm their (profitable) markets elsewhere. This fear is unique to antimicrobials since they differ from other drugs, where use in one person does not impact efficacy in another. Antimicrobials are also much more prone to misuse due to wide-spread misunderstandings about their efficacy (with many people believing they can treat viruses such as the flu (World Health Organization, 2015)), and oral antimicrobials being easy for patients to use.

2 In 2021, 21,974 clinical trials were conducted in upper-middle-income countries, and only 440 in low-income countries (World Health Organization, 2023b).

We know that inappropriate overuse of antimicrobials leads to increasing resistance, and that resistance does not respect borders (Barlam & Gupta, 2015). Therefore, companies want to be confident that their drug will be used appropriately and thus will maintain efficacy. One pharmaceutical company told us that they check hospital protocols to ensure their product will be used appropriately and will not register in places with insufficient infrastructure to support conditions for good stewardship. While WHO experts agreed that this is a "valid" concern, it can nonetheless cause difficulties for LMICs which do not have strong stewardship records. For example, some LMICs do not have sufficient capacity to properly enforce prescription rules (Auta et al., 2019; Jacobs et al., 2019), nor to ensure reliable adherence to prescriptions, as this requires strong healthcare systems.

However, while all five interviewees mentioned stewardship concerns, two interviewees (who did not represent pharmaceutical companies) expressed scepticism that this truly impacted the failure to rollout antibiotics, believing instead that resistance fears could be an "excuse" for companies to hide behind.

Possible solutions

While there is no "one-size-fits-all-products" approach, there are many tools and approaches which can motivate and support companies to rollout antimicrobials in LMICs. It is encouraging to see a range of innovative new models being piloted to resolve this problem.

Improving the market

There are several levers through which the lack of RoI for antimicrobials can be addressed. Firstly, the value assessment system can be improved so as to more accurately reflect the societal value of antimicrobials and so increase revenue for developers. This could entail carving antibiotics out of traditional reimbursement systems (as in Germany and France (Gotham et al., 2021)), or updating HTA systems to consider the broader "STEDI" aspects of value (Outterson & Rex, 2020)[3] (as in the UK (Leonard et al., 2023)). However, more work is needed to determine the best methodology to assess value in LMIC scenarios, since different attributes may be valuable in these contexts. In general, tendering systems need to consider other aspects of value, including valuing durability in supply, valuing appropriate manufacturing practices (which minimise effluence and discharge), and valuing a split market that is more robust against economic difficulties.

3 STEDI stands for Spectrum (the value of narrower spectrum drugs because of their lower impact on the microbiome), Transmission (the value in reducing infection spread), Enablement (the value of enabling procedures through prophylaxis), Diversity (the value of a range of treatment options to reduce selection pressure) and Insurance (the value of being prepared for future infections).

Secondly, the market can be improved by ensuring adequate and predictable demand. As one interviewee stated, we need to fix both the supply and demand sides, because without demand there is no access. Even if drugs are added to the WHO's Essential Medicines List, pharmacists and/or regulators may not check this. Therefore, demand generation—including working with countries to change guidelines and engaging with clinicians and prescribers to update their practices—is key. Similarly, end-user engagement—such as educating patients—could help improve access: HIV patients played an important role in advocating to secure access to anti-retrovirals (Sunguya et al., 2016). Companies could also improve their market intelligence to better understand where there is demand for specific products.

Alternatively, rather than directly improving the RoI, interviewees suggested on drawing on ideas of corporate social responsibility, given the pandemic risk of AMR. Companies could approach LMIC markets with a "not profit/not loss" model; they could use non-exclusive voluntary licensing agreements to ensure sustainable supply. Indeed, we are seeing some encouraging signs from industry. On advice from the Access to Medicines Foundation, Pfizer and Shionogi are both now disclosing surveillance data. Pfizer recently launched the philanthropic Accord for a Healthier World (Pfizer Inc., 2022), and one pharmaceutical representative stated that their "first objective is to expand access to everyone who needs novel anti-infectives." Most interviewees seemed to accept that industry should not expect to make large profits on antimicrobials in LMIC markets—and that any mechanism which could provide a cost neutral way of reaching smaller LMIC markets would be beneficial compared to the status quo.

Ensuring appropriate stewardship

Ensuring stewardship is crucial, both because access without stewardship is unsustainable, and to allay industry fears which may inhibit rollout. Countries need to be supported to introduce antimicrobial stewardship programs, including education programs for both physicians and patients, and diagnostic training. Additionally, usage and resistance rates should be tracked. One interviewee noted that, to ensure appropriate use, we should be prioritising access to easy-to-use diagnostics, which can be used without infectious disease experts.[4]

Partnerships

There was universal agreement among interviewees on the power of partnerships for ensuring access. Partnerships also increase trust in industry, which can facilitate data sharing and so remove inefficiencies. Interviewees cited examples where big vertical programs comprised of governments, donors, local NGOs, and companies have successfully worked together on issues of supply chains, infrastructure, guidelines, tendering and procurement. Partnerships can span multiple stakeholders: pharmaceutical companies, NGOs, governments, or supranational organisations.

4 While this note focuses on novel antibiotics, it is crucial that we continue to emphasize the importance of point-of-care diagnostics for all antimicrobials to ensure we preserve their efficacy and thus minimise the need for novel antimicrobial rollouts.

At the international level, countries should work together, with HICs enacting push and pull incentives to increase antimicrobial development and supporting LMICs to strengthen their healthcare systems to develop financially viable and sustainable markets. This could be facilitated by advocacy messaging explaining to HICs the potential global harms from increasing resistance. At the country level, pharmaceutical companies can benefit from local partners who can speak to local laws and norms and advise on the most effective ways to change local practice to ensure stewardship. Where companies do not have capacity to manufacture for smaller markets, technology transfer to local manufacturers is crucial, although one interviewee stressed the importance of product developers remaining involved given their knowledge of the product. Local manufacturing partnerships also reduce underserved regions' dependency on fragile supply chains.

For example, Shionogi partnered with GARDP and CHAI to rollout cefiderocol (Global Antibiotic Research & Development Partnership, 2022), and are additionally looking for strong country partners and infectious disease networks to ensure stewardship. Pfizer are working with groups such as the British Society for Antimicrobial Chemotherapy to promote good stewardship (British Society for Antimicrobial Chemotherapy, 2022).

Registration reform

Proposals to improve registration can be categorised into several buckets. Several interviewees discussed the possibility of pooled registration, possibly at the regional level. Such a system would reduce the workload both for pharmaceutical companies (in terms of fewer dossiers required) and for national regulators, who could coordinate to share the workload and prevent duplication of effort. For example, the European medicines regulatory system pools expertise from a network of around 50 regulatory authorities from the 30 European Economic Area countries, the European Commission, and the European Medicines Agency (European Medicines Agency, 2023). Products need only one application, one assessment, and one market authorisation for the whole of the EU. The success of such a model depends on harmonised requirements across countries and adequate legal provisions so that national regulatory agencies do not need to repeat the submission/revision process at the country level after the regional review is conducted.

A related approach is to harmonize registration requirements, or to allow leveraging of submissions from other countries while leaving registration as a national right. The Southern African Development Community has endorsed the ZaZiBoNa collaborative medicines initiative, where different country regulators each take part of the dossier and share the reports (Sithole et al., 2022). Each country regulator then makes an individual decision, allowing governments to receive the registration fees, which can be an important source of income. This model can help companies launch in multiple markets simultaneously. However, while most interviewees stated that regulatory harmonization could be beneficial, one warned that harmonisation needs to be carefully implemented to ensure it cannot be used as a cover to remove pressure on individual national regulators to approve drugs.

Interviewees also discussed additional ways to improve the efficiency of registration, including companies proactively communicating with regulators; an international system to aid with translation of dossiers for different countries; working with in-country partners to generate dossiers with the necessary data for each country; and a focus on education and knowledge transfer to ensure sufficient expertise in countries to assess dossiers. The rollout of HIV medications was aided by the WHO pre-qualification system, which allowed smaller countries to fast-track the registration process ('t Hoen et al., 2014); experts believed that a similar fast-tracking or prioritisation system could be used for antimicrobials. There could even be a process of requesting waivers for bypassing registration in certain situations, such as compassionate use in a small number of patients in designated hospitals. Data requirements could also be adjusted—for example, allowing data from adaptive randomised control trials which allow for more flexibility and incorporate changes as the study proceeds (Lanini et al., 2019). One company proposed increasing flexibility for different indications.

Finally, systems could be enacted to motivate companies to register their drugs more broadly. For example, one interviewee explained that the Global Fund uses both a "carrot and stick approach" to ensure registration in smaller countries, including penalising firms for registering only in large countries. The UNITAID-funded CHAI Innovation in Paediatric Market Access scheme updated their tender from price-based only to include points for number of country registrations (Cambridge Economic Policy Associates Ltd., 2018), resulting in 223 new registration dossiers submitted in project countries, including low-volume countries.

Conclusions and recommendations

Based on the stakeholder interviews described in this note, and on wider discussions of the CGD Working Group on a New Grand Bargain for Antimicrobial Resistance (McDonnell et al., 2023), we make the following three recommendations:

First, there should be greater utilisation of partnerships, both among companies and organisations (for example following the Shionogi-GARDP-CHAI model) and among countries (i.e., governments supporting each other to build from collective expertise). HICs can play an important role in enacting push and pull incentives to generate necessary innovation, and in supporting LMIC access to the fruits of such research. In the spirit of such collaboration, we were pleased to see the UK's recent pledge of £85 million to support the international community in tackling AMR and the £45 million pledge by GSK to develop a global network of experts and institutions to understand the drivers of, and propose interventions to tackle, AMR (Dall, 2024). Additionally, companies, countries, and multilateral organisations should work together to share disease burden and resistance data. This will help ensure drugs can be targeted to regions of greater need.

Second, countries should expedite and/or harmonize regulation requirements. Work by the One Health Trust found that addressing regulatory hurdles is critical to improve access to antimicrobials (Kalanxhi et al., 2022). For example, while national regulators in Brazil, South Africa, and India allow expedited registration of medicines targeting unmet public health needs, this category does not include antimicrobials. A specific category within regulatory frameworks should be created for antimicrobials targeting serious infections. Countries should work together to harmonize requirements or leverage information from other submissions. Essential antibiotics could be used as pilots for expanding joint reviews at the regional level. Alongside this, pharmaceutical companies should commit to global registration as a condition of receiving grant money.

Finally, a Sustainable Access Hub, as laid out in the final report of the Working Group (McDonnell et al., 2023) could play a critical role in improving access to antimicrobials. This Hub (acting either as a single global organizing entity, or as several regional hubs; and ideally acting through an existing organisation) would provide a backstop to ensure access where the market fails to do so. It would register and distribute products in LMICs where pharmaceutical companies do not have capacity to do so; procure a complete package of essential antimicrobials and diagnostics so as not to promote unnecessary use of later line drugs; stockpile antimicrobials to ensure supply; and provide technical or financial assistance. We applaud access initiatives such as SECURE (which seeks to use coordinated pooled procurement, stockpiling and forecasting to expand access to a portfolio of essential antibiotics (SECURE, 2023)) and USAID's Antimicrobial Resistance Access and Stewardship Initiative (which is working on country-level interventions to improve the availability of diagnostic tools and the appropriate use of antimicrobials in LMICs (CHAI, 2024)). We encourage the scale-up of such initiatives to cover all the Sustainable Access Hub functions laid out above.

Bibliography

Auta, A., Hadi, M. A., Oga, E., Adewuyi, E. O., Abdu-Aguye, S. N., Adeloye, D., Strickland-Hodge, B., & Morgan, D. J. (2019). Global access to antibiotics without prescription in community pharmacies: A systematic review and meta-analysis. *Journal of Infection*, 78(1), 8–18. https://doi.org/10.1016/j.jinf.2018.07.001

Barlam, T. F., & Gupta, K. (2015). Antibiotic Resistance Spreads Internationally Across Borders. *The Journal of Law, Medicine & Ethics: A Journal of the American Society of Law, Medicine & Ethics*, 43 Suppl 3, 12–16. https://doi.org/10.1111/jlme.12268

Blank, C. (2022, November 10). *Hospital Demand for Amoxicillin Increases While Shortage Continues*. Managed Healthcare. https://www.managedhealthcareexecutive.com/view/hospital-demand-for-amoxicillin-increases-while-shortage-continues

British Society for Antimicrobial Chemotherapy. (2022). *Addressing access disparities: BSAC and Pfizer announce successful Antimicrobial Stewardship proposals*. https://bsac.org.uk/addressing-access-disparities-bsac-and-pfizer-announce-successful-antimicrobial-stewardship-proposals/

Cambridge Economic Policy Associates Ltd. (2018). *UNITAID End of Project Evaluation of the CHAI Paediatric HIV/AIDS and Innovation in Paediatric Market Access (IPMA) Projects* (Issue November).

CHAI. (2024, January 12). *USAID taps CHAI, GETF to launch coalition that will test innovative approaches to address antimicrobial resistance in low- and middle-income countries.* Clinton Health Access Initiative. https://www.clintonhealthaccess.org/news/usaid-taps-chai-getf-to-launch-coalition-that-will-test-innovative-approaches-to-address-antimicrobial-resistance-in-low-and-middle-income-countries/

Colson, A. R., Morton, A., Årdal, C., Chalkidou, K., Davies, S. C., Garrison, L. P., Jit, M., Laxminarayan, R., Megiddo, I., Morel, C., Nonvignon, J., Outterson, K., Rex, J. H., Sarker, A. R., Sculpher, M., Woods, B., & Xiao, Y. (2021). Antimicrobial Resistance: Is Health Technology Assessment Part of the Solution or Part of the Problem? *Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research*, 24(12), 1828–1834. https://doi.org/10.1016/j.jval.2021.06.002

Dall, C. (2024, May 16). *UK announces funding to boost global fight against antimicrobial resistance*. CIDRAP. https://www.cidrap.umn.edu/antimicrobial-stewardship/uk-announces-funding-boost-global-fight-against-antimicrobial-resistance

European Federation of Pharmaceutical Industries and Associations. (2024). *Trade*. https://www.efpia.eu/about-medicines/development-of-medicines/trade/

European Medicines Agency. (2020a). *Fetcroja assessment report*. https://www.ema.europa.eu/en/documents/assessment-report/fetcroja-epar-public-assessment-report_en.pdf

European Medicines Agency. (2020b). *Withdrawal of application for the marketing authorisation of Zemdri (plazomicin)*. https://www.ema.europa.eu/en/documents/medicine-qa/questions-and-answers-withdrawal-application-marketing-authorisation-zemdri-plazomicin_en.pdf

European Medicines Agency. (2023). The European Regulatory System for Medicines. https://www.ema.europa.eu/en/documents/leaflet/european-regulatory-system-medicines_en.pdf

FDA. (2024, May 7). *Complex Innovative Trial Design Meeting Program*. FDA; FDA. https://www.fda.gov/drugs/development-resources/complex-innovative-trial-design-meeting-program

Frost, I., Craig, J., Joshi, J., Faure, K., & Laxminarayan, R. (2019). *Access Barriers to Antibiotics*. Center for Disease Dynamics, Economics & Policy. https://onehealthtrust.org/wp-content/uploads/2019/04/AccessBarrierstoAntibiotics_CDDEP_FINAL.pdf

Global Antibiotic Research & Development Partnership. (2022). *Shionogi, GARDP and CHAI announce landmark license and collaboration agreements to treat bacterial infections by expanding access to cefiderocol in 135 countries*. https://gardp.org/shionogi-gardp-and-chai-announce-landmark-license-and-collaboration-agreements-to-treat-bacterial-infections-by-expanding-access-to-cefiderocol-in-135-countries/

Gotham, D., Moja, L., Heijden, M. van der, Paulin, S., Smith, I., & Beyer, P. (2021). Reimbursement models to tackle market failures for antimicrobials: Approaches taken in France, Germany, Sweden, the United Kingdom, and the United States. *Health Policy*, 125(3), 296–306. https://doi.org/10.1016/j.healthpol.2020.11.015

Ikuta, K. S., Swetschinski, L. R., Robles Aguilar, G., Sharara, F., Mestrovic, T., Gray, A. P., Davis Weaver, N., Wool, E. E., Han, C., Gershberg Hayoon, A., Aali, A., Abate, S. M., Abbasi-Kangevari, M., Abbasi-Kangevari, Z., Abd-Elsalam, S., Abebe, G., Abedi, A., Abhari, A. P., Abidi, H., … Naghavi, M. (2022). Global mortality associated with 33 bacterial pathogens in 2019: A systematic analysis for the Global Burden of Disease Study 2019. *The Lancet*, 400(10369), 2221–2248. https://doi.org/10.1016/S0140-6736(22)02185-7

Jacobs, T. G., Robertson, J., van den Ham, H. A., Iwamoto, K., Bak Pedersen, H., & Mantel-Teeuwisse, A. K. (2019). Assessing the impact of law enforcement to reduce over-the-counter (OTC) sales of antibiotics in low- and middle-income countries; a systematic literature review. *BMC Health Services Research*, 19(1), 536. https://doi.org/10.1186/s12913-019-4359-8

Kalanxhi, E., Gopal Parameswaran, G., Van Wijk, M., Kapoor, R., Osena, G., Joshi, J., & Laxminarayan, R. (2022). *Drug Regulatory Approvals and Opportunities for Antimicrobial Innovation—Perspectives from Brazil, India and South Africa*. One Health Trust. https://onehealthtrust.org/wp-content/uploads/2022/06/Drug-Regulatory-Approvals-and-Opportunities-for-Antimicrobial-Innovation_July-2022.pdf

Kållberg, C., Årdal, C., Salvesen Blix, H., Klein, E., M. Martinez, E., Lindbæk, M., Outterson, K., Røttingen, J.-A., & Laxminarayan, R. (2018). Introduction and geographic availability of new antibiotics approved between 1999 and 2014. *PLOS ONE*, 13(10), e0205166. https://doi.org/10.1371/journal.pone.0205166

Lanini, S., Ioannidis, J. P. A., Vairo, F., Pletschette, M., Portella, G., Bari, V. D., Mammone, A., Pisapia, R., Merler, S., Nguhuni, B., Langer, M., Caro, A. D., Edwards, S. J. L., Petrosillo, N., Zumla, A., & Ippolito, G. (2019). Non-inferiority versus superiority trial design for new antibiotics in an era of high antimicrobial resistance: The case for post-marketing, adaptive randomised controlled trials. *The Lancet Infectious Diseases*, 19(12), e444–e451. https://doi.org/10.1016/S1473-3099(19)30284-1

Leonard, C., Crabb, N., Glover, D., Cooper, S., Bouvy, J., Wobbe, M., & Perkins, M. (2023). Can the UK 'Netflix' Payment Model Boost the *Antibacterial Pipeline? Applied Health Economics and Health Policy*, 21(3), 365–372. https://doi.org/10.1007/s40258-022-00786-1

Levine, R., Pickett, J., Sekhri, N., & Yadav, P. (2008). Demand forecasting for essential medical technologies. *American Journal of Law & Medicine*, 34(2–3), 225–255. https://doi.org/10.1177/009885880803400206

McDonnell, A., Klemperer, K., Pincombe, M., & Guzman, J. (2022). *Leveraging Purchasing Systems to Ensure Access, Stewardship, and Innovation: A Landscape Review of Current and Potential Market Structures for Antimicrobials*. Center for Global Development. https://www.cgdev.org/publication/leveraging-purchasing-systems-ensure-access-stewardship-and-innovation-landscape-review

McDonnell, A., Klemperer, K., Pincombe, M., Silverman Bonnifield, R., Yadav, P., & Guzman, J. (2023). *A New Grand Bargain to Improve the Antimicrobial Market for Human Health*. Center for Global Development. https://www.cgdev.org/sites/default/files/new-grand-bargain-improve-antimicrobial-market-human-health.pdf

Miseta, E. (2020, May 7). *The (Almost) Insurmountable Recruitment Challenges of Antibiotic Clinical Trials*. Clinical Leader. https://www.clinicalleader.com/doc/the-almost-insurmountable-recruitment-challenges-of-antibiotic-clinical-trials-0001

Outterson, K., & Rex, J. H. (2020). Evaluating for-profit public benefit corporations as an additional structure for antibiotic development and commercialization. *Translational Research : The Journal of Laboratory and Clinical Medicine*, 220, 182–190. https://doi.org/10.1016/j.trsl.2020.02.006

Ozawa, S., Shankar, R., Leopold, C., & Orubu, S. (2019). Access to medicines through health systems in low- and middle-income countries. *Health Policy and Planning*, 34(Supplement_3), iii1–iii3. https://doi.org/10.1093/heapol/czz119

Pfizer Inc. (2022). *An Accord for a Healthier World | Pfizer*. https://www.pfizer.com/about/responsibility/global-impact/accord

Rafiqi, F., Cesari, E., Dinar-Farjon, D., van Gerven, M., Hellamand, M., & Pascua, T. S. (2021). *Antimicrobial Resistance Benchmark 2021. Access to Medicines Foundation*. https://accesstomedicinefoundation.org/medialibrary/antimicrobial-resistance-benchmark-report-2021-1692626276.pdf

Rafiqi, F., Hellamand, M., & van Gerven, M. (2022, October 17). Lack of access to generic antibiotics and antifungals is an overlooked issue in AMR. *REVIVE*. https://revive.gardp.org/lack-of-access-to-generic-antibiotics-and-antifungals-is-an-overlooked-issue-in-amr/

Raghavendran, V., & Christian, M. (2022, May 24). Supply chain vulnerabilities exist for antimicrobial medicines: USP Medicine Supply Map analysis. *U.S. Pharmacopeia Blog*. https://qualitymatters.usp.org/supply-chain-vulnerabilities-for-antimicrobial-medicines

Schurer, M., Patel, R., van Keep, M., Horgan, J., Matthijsse, S., & Madin-Warburton, M. (2023). Recent advances in addressing the market failure of new antimicrobials: Learnings from NICE's subscription-style payment model. *Frontiers in Medical Technology*, 5, 1010247. https://doi.org/10.3389/fmedt.2023.1010247

SECURE. (2023). *SECURE's Economic & Procurement Tools to Address Access Challenges for Antibiotics*. https://static1.squarespace.com/static/6322df0faf9d110638ea0974/t/6536849fdd213b67adbdf9dd/1698071712838/SECURE+Development+phase+Economic+Model+version_17+Oct+2023.+FINAL.pdf

Sithole, T., Mahlangu, G., Walker, S., & Salek, S. (2022). Regulatory Authority Evaluation of the Effectiveness and Efficiency of the ZaZiBoNa Collaborative Medicines Registration Initiative: The Way Forward. *Frontiers in Medicine*, 9, 898743. https://doi.org/10.3389/fmed.2022.898743

Stafford, K. A., Boutin, M., Evans, S. R., & Harris, A. D. (2014). Difficulties in demonstrating superiority of an antibiotic for multidrug-resistant bacteria in nonrandomized studies. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America*, 59(8), 1142–1147. https://doi.org/10.1093/cid/ciu486

Sunguya, B. F., Munisamy, M., Pongpanich, S., Yasuoka, J., & Jimba, M. (2016). Ability of HIV Advocacy to Modify Behavioral Norms and Treatment Impact: A Systematic Review. *American Journal of Public Health*, 106(8), e1–e8. https://doi.org/10.2105/AJPH.2016.303179

't Hoen, E. F. M., Hogerzeil, H. V., Quick, J. D., & Sillo, H. B. (2014). A quiet revolution in global public health: The World Health Organization's Prequalification of Medicines Programme. *Journal of Public Health Policy*, 35(2), 137–161. https://doi.org/10.1057/jphp.2013.53

UN Environment Programme. (2017). *Antimicrobial resistance from environmental pollution among biggest emerging health threats, says UN Environment*. https://www.unep.org/news-and-stories/press-release/antimicrobial-resistance-environmental-pollution-among-biggest

World Health Organization. (2015, November 16). *WHO multi-country survey reveals widespread public misunderstanding about antibiotic resistance*. https://www.who.int/news/item/16-11-2015-who-multi-country-survey-reveals-widespread-public-misunderstanding-about-antibiotic-resistance

World Health Organization. (2019). *Adopt AWaRe: Handle antibiotics with care*. https://adoptaware.org/

World Health Organization. (2023a). *World Health Organization Model List of Essential Medicines – 23rd List, 2023*. https://iris.who.int/bitstream/handle/10665/371090/WHO-MHP-HPS-EML-2023.02-eng.pdf?sequence=1

World Health Organization. (2023b, February). *Number of clinical trials by year, country, region and income group*. https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/number-of-clinical-trials-by-year-country-who-region-and-income-group

World Health Organization & Health Action International. (2008). *Measuring medicine prices, availability, affordability and price components. 2nd Edition*. https://iris.who.int/bitstream/handle/10665/70013/WHO_PSM_PAR_2008.3_eng.pdf?sequence=1

Appendix: Interview Guide

1. What do you think drives decisions on where/ when to rollout antimicrobials?

2. Do you believe there is a particular problem with the timely rollout of antimicrobials into low- and middle-income countries? Is this problem worse than for the rollout of other medicines into LMICs?

   If yes:

   - Is this for all antimicrobials, or only certain classes/ indications?
     - If only for certain drugs – what is different about these?
   - What do you think is the cause of the delay?
   - Do you have any suggestions as to how we might overcome this issue? What policy levers could we use to make a more enticing rollout environment?

If no:

   - What features of the current system prevent there being such an issue?

3. Might this ever become an issue as new drugs are rolled out?

4. What models might be most effective for ensuring successful rollout in LMICs?

5. Anyone else should we speak to?

6. Any other comments?

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