ANTIMICROBIAL RESISTANCE (AMR) PROGRAMME

How can pharma get the few promising drugs in development to patients battling superbugs?

MAY 2024

In the race to create replacement antibiotics and antifungals to combat superbugs, we are falling dangerously short, putting people all over the world at risk. But with a fundamental shift in research and development (R&D), including investment in access and stewardship, there is an opportunity to stop drug resistance in its tracks. This report shows how this can be achieved by examining key antimicrobials in late-stage R&D that target some of the most severe drug-resistant pathogens. If patients globally were able to access these promising antibiotics and antifungals, at least 160,000 lives could be saved from drug-resistant infections each year. By highlighting what can be done with what is currently in the pipeline, this report sets out ways in which companies can develop sustainable solutions amid the seemingly losing battle against this global health threat.

access to medicine FOUNDATION

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The Access to Medicine Foundation is an independent non-profit organisation that seeks to transform the healthcare ecosystem by motivating and mobilising companies to expand access to their essential healthcare products in low- and middle-income countries.

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About this paper

This report is part of the Access to Medicine Foundation's Antimicrobial Resistance (AMR) Programme, which works to mobilise pharmaceutical companies in responding to the growing challenge of drug-resistant infections. The AMR Programme's publications – including both the AMR Benchmark (published in 2018, 2020 and 2021) and targeted thematic reports such as this – focus on how pharmaceutical companies perform in terms of acting on identified priorities to address AMR.

HOW THIS REPORT WAS DEVELOPED

The case studies, discussion and recommendations in this report have been drawn from companies' pipeline verification process for the upcoming 2024 Access to Medicine Index, research published in the 2021 AMR Benchmark, as well as from recent interviews with selected companies. Consultations were also held with relevant expert stakeholders, including funder and partner organisations working to support antimicrobial R&D. The report was further informed by sources available in the public domain, including peer-reviewed literature, company and global health reports, policy literature and government documents. The information collected from the sources was cross-checked to ensure accuracy, including directly with companies and other stakeholders, as appropriate and relevant.

SCOPE OF THE RESEARCH

Companies

In identifying a combination of large and small companies, as well as late-stage (Phase II and onward) antibacterial and antifungal projects, two (2) large research-based pharmaceutical companies (GSK and Pfizer) and three (3) small- and medium-sized enterprises (SMEs*: F2G, Innoviva Speciality Therapeutics and Venatorx Pharmaceuticals) were selected for case studies. In addition, 25 other companies are specifically mentioned in this report. This includes Basilea, Menarini Group, Shionogi and Wockhardt.

R&D Projects

This study includes five (5) case studies on the most promising projects currently in the pipeline that, taken together, can save at least 160,000 lives from deadly, resistant bacterial and fungal infections each year. The selected projects include: aztreonam-avibactam, cefepime-taniborbactam, gepotidacin, olorofim and zoliflodacin. Note that after project selection, aztreonam-avibactam was approved by the European Commission on 22 April 2024. Four projects are in late-stage development (Phase II and onward) as this is when companies are expected to start planning for access and stewardship. The selection was based on unmet medical need, AMR burden, the World Health Organization's Priority Pathogen Lists for bacteria and fungi (excluding *Mycobacterium tuberculosis*, due to different access and stewardship challenges, and national and supranational initiatives), and the projects' innovativeness** and capacity to overcome resistant pathogens.

Countries

The report's geographical scope is global. However, for access planning, the report focuses on 113 low- and middle-income countries (LMICs) where greater access to medicine is needed, as defined in the geographic scope of the 2024 Access to Medicine Index Methodology.[1]

*Innoviva Speciality Therapeutics and Venatorx Pharmaceuticals are referred to as Innoviva and Venatorx respectively in the rest of this report.

**As assessed by the four innovation criteria of the World Health Organization: new chemical class, new target, new mode of action, and absence of known cross-resistance.

Executive summary

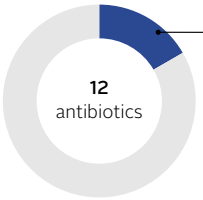
The development of replacement antibiotics that can treat rising drug-resistant infections has fallen dangerously short. With a vast majority of large research-based pharmaceutical companies no longer active in antimicrobial research and development (R&D) due to a lack of commercial viability, few new treatments that target priority pathogens are making it to market – leaving people across the globe at risk.

Despite this reality, there are a handful of projects in late-stage clinical development that could help patients overcome some of the most severe drug-resistant infections they are currently facing. The Access to Medicine Foundation has tracked four such innovative, late-stage R&D projects across the pipelines of GSK, F2G, Innoviva and Venatorx (gepotidacin, olorofim, zoliflodacin, and cefepime-taniborbactam, respectively) as well as Pfizer's recently approved aztreonam-avibactam (Emblaveo®).

Collectively, these projects could save at least 160,000 lives each year by providing much-needed medicines to treat drug-resistant gonorrhoea, urinary tract infections (UTIs), intra-abdominal infections (IAIs), respiratory infections and invasive fungal infections. While these diseases and syndromes affect a wide range of patients globally, women and children – especially those living in low- and middle-income countries (LMICs) – are disproportionately affected.

To save as many lives as possible, it is vital to ensure these much-needed medicines reach the patients who need them most, particularly in countries that face the highest burden of drug resistance. To achieve this, companies need to develop comprehensive access and stewardship plans during clinical development to make sure these drugs are made available and stay effective for as long as possible once they make it to market.

World Health Organization pipeline analysis reveals how underprepared the pipeline is



Only 12 antibiotics gained market approval between 2017 and 2021. Of these, only 2 represent a new chemical class.

5 projects analysed in this report could save at least **160,000 lives annually** by providing medicines to treat drug-resistant gonorrhoea, urinary tract infections, intra-abdominal infections, respiratory infections and invasive fungal infections.

What does this report find?

The five case studies reveal that companies are employing a diverse range of strategies within their access and stewardship plans, but structured advance planning has not yet become standard, risking patient care globally. While all the companies are conducting clinical trials in LMICs and have indicated some level of post-trial access commitments, these are not always detailed and clear. When it comes to stewardship planning, aside from some surveillance and data sharing strategies, overall stewardship strategies are lacking across the board. Four key findings gleaned from the analysis highlight where efforts need to be scaled and how shortcomings can be addressed.

1. **Concrete plans for registration are lacking for almost all LMICs**
   For all five projects combined, concrete commitments for registration were identified for five LMICs – China, India, Mexico, South Africa and Thailand. However, for 108 of 113 LMICs in scope, where people also face high burdens of the diseases and syndromes targeted by these projects, it is currently unclear whether any of them will be made available upon initial approval. Yet, to avoid lengthy registration procedures, the Global Antibiotic Research & Development Partnership (GARDP) plans to provide access to cefepime-taniborbactam (Venatorx) in 64 LMICs through export waivers and an international procurement agency.

2. **Affordability and stewardship in LMICs are largely overlooked during planning**
   Some of the companies assessed in this report are addressing affordability and stewardship. For example, Pfizer applies specific pricing strategies for aztreonam-avibactam – and offers products in its portfolio at a not-for-profit basis through its 'Accord for a Healthier World' initiative. However, no robust plans for making new products affordable to patients in any LMIC could be identified in

the other four case studies in this report. In addition, besides large companies, like GSK and Pfizer who have comprehensive surveillance programmes in place, other strategies to ensure appropriate use – for example, by responsible promotion and ensuring companion diagnostics – were lacking across the board.

3. **Paediatric trials prior to market approval are a hopeful sign for children**
   Encouragingly, four of the five companies analysed – GSK, Pfizer, Innoviva and Venatorx – are running or initiating clinical trials involving children. The efforts from these four companies to prioritise children early on during clinical development are positive steps in moving towards closing the gap between adult and paediatric access and set an example of what can be done by other developers.

4. **Partnerships help scale efforts, but other tools to broaden access and stewardship plans are underutilised**
   Small- and medium-sized enterprises (SMEs) rely heavily on partners to help commercialise products and drive global access. As demonstrated in this report, partnering and collaborating with the publicly funded GARDP has enabled SMEs to pursue access on a wider scale through licencing agreements that cover many countries, including LMICs that face the highest burden of drug resistance. Aside from collaborations with GARDP, SMEs actively seek partnerships directly with large research-based pharmaceutical companies.

   Over and above these vital partnerships and licensing agreements, companies – SMEs and large pharmaceutical companies alike – have opportunities to utilise even more tools and strategies to advance their access and stewardship plans more broadly. For example, to support companies in planning ahead for access and stewardship, the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) – in collaboration with key partners, including the Wellcome Trust and the Access to Medicine Foundation – published the Stewardship and Access Plan (SAP) Development Guide in 2021. However, the report finds that the companies in scope are underutilising the recommendations in this Guide.

What's next?

Both large research-based pharmaceutical companies and SMEs active in the antimicrobial R&D space need to pursue access and stewardship planning for all late-stage clinical projects for antibiotics and antifungals, both innovative and adaptive. For sustainable solutions to take hold, it is vital that comprehensive and detailed access and stewardship plans are embedded in companies' antimicrobial innovation, ahead of a product's market approval. This includes, for example, targeting countries with particularly high burdens of disease and disproportionately affected populations, such as children, women and immuno-suppressed patients. To strengthen their efforts and increase their reach, companies can seek out partnerships for co-development, as well as licencing agreements to ensure newly developed drugs are made available to those who need them most.

With the SAP Guide being fit for purpose and signed off by multiple key stakeholders in the AMR space, companies have an opportunity to utilise it to help plan effectively for access and stewardship – particularly by implementing its recommendations earlier in the development phase – without jeopardising the progress towards market approval. At the same time, funders can also utilise the SAP Guide to set contractual provisions on access and stewardship and hold companies accountable. In doing this, they can help ensure qualitative access and stewardship planning will be implemented effectively throughout clinical development – while making sure their vast financial support translates into sustainable progress and improved global health. (For a comprehensive list of recommendations, see p.34 -35 of this report.)

It is critical to act now and make sure the few antimicrobials are made available to patients on the frontlines of drug resistance.

INTRODUCTION

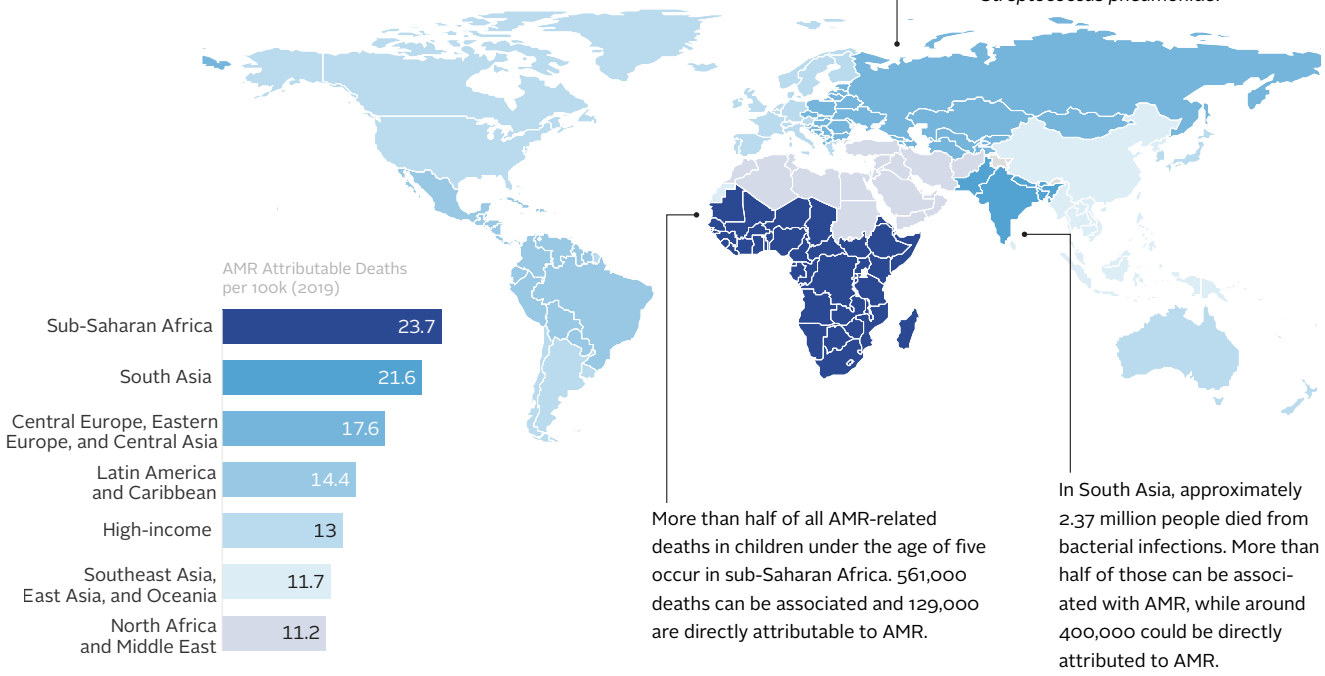
When the drugs don't work

Antimicrobial resistance (AMR) is not a looming threat. Its unprecedented rise is edging the world closer to a reality where the medicines that revolutionised modern medicine will no longer work. Today, drug-resistant pathogens, or 'superbugs', are spreading faster than predicted and patients across the world are battling drug-resistant infections that cannot be treated with existing medicines. At the same time, the development of new and innovative antibiotics and antifungals that target some of the world's deadliest superbugs is failing to keep pace.

These drug-resistant bacteria and fungi can lead to a wide range of diseases and infections and affect people across the globe in different ways. As illustrated in the accompanying map, drug-resistant infections already claim the lives of people the world over, but people living in sub-Saharan Africa (SSA) are hardest hit. For people living in this region, which is home to many low- and middle-income countries (LMICs), new and innovative treatments are critical. Without access to the right antibiotics and antifungals, drug resistance will only develop further, spread wider and cost more lives.

FIGURE 1 **Drug resistance affects people globally**

Drug-resistant pathogens know no borders and threaten the lives of people the world over. However, antimicrobial resistance (AMR) disproportionately affects people in certain regions. Specifically in sub-Saharan Africa and Asia, both regions that include many low- and middle-income countries (LMICs).



Source: IHME MICROBE database; data in the map is based on estimates from 2019.

Who is most at risk?

Superbugs know no borders, putting the lives of people in countries across the globe at risk. However, for people living in LMICs, where the burden of infectious diseases is already higher, this risk is an everyday reality. Especially for the most vulnerable, including infants and children, and for those living in countries facing the highest threats of drug resistance. Oftentimes, patients in LMICs don't have access to newer treatments that are effective against drug-resistant pathogens, leaving them vulnerable at best – or proving fatal at worst.

For children living in LMICs, already life-threating infections can prove fatal when existing treatments are not effective or are unavailable.[2] In these countries, for example, bacterial resistance rates to gentamicin which – together with ampicillin – is used to treat neonatal sepsis, is approximately 60%.[3] This puts neonates (infants under a month old) in LMICs, where 99% of global neonatal deaths occur, at even more risk.[3]

Drug resistance can also lead to childhood pneumonia becoming untreatable and can lead to devastating outcomes, such as trouble breathing, bleeding into the lungs and even death from sepsis.[4] Bacterial infections due to *Streptococcus pneumoniae* are the primary cause of pneumonia, although viruses and fungi can also lead to pneumonia. In recent years, *S. pneumoniae*'s rate of resistance to penicillin, which is the recommended first-line treatment in many countries for children diagnosed with severe pneumonia, has increased to over 60%. For example, in Vietnam resistance rates of 99% were found.[5]

These examples are only snapshots of the harsh impact drug-resistant infections have on people living in LMICs. Drug-resistant pathogens affect lives through a far wider range of syndromes and infections as well (also see fact sheet on p.11 of this report). Aside from the fatal drug-resistant infections that are rising, some of the life-changing medical procedures that have been made possible with the availability of effective antibiotics are also under threat. Many of the dangerous pathogens that can cause drug-resistant infections are present in hospital settings, putting already vulnerable patients, and those who need to undergo standard medical procedures at risk.

Oncology treatments, caesarean-sections and hip replacements, for example, are only possible if effective antibiotics are on hand to prevent infection. Cancer patients, who undergo therapies that can be aggressive and compromise their immune systems, are particularly susceptible to contracting bacterial infections. In fact, bacterial infections are the second most prevalent cause of death among cancer patients and result in the hospitalisation of 1 in every 5 patients undergoing treatment.[6] Historically antimicrobials have been effective in supporting patients undergoing oncology treatment. However, clinicians are increasingly observing infections that are resistant to previously effective antibiotics that could treat them and cure the infection.

Neonatal sepsis in LMICs[2,3]

99% of all annual neonatal deaths occur in LMICs

13% of these deaths are attributable to neonatal sepsis

680,000 babies lose their lives to neonatal sepsis

60% rate of resistance to gentamicin, a recommended treatment for neonatal sepsis

Pneumonia disproportionately affects children under five[7,2]

Childhood pneumonia **killed over 740,000 children** in 2019

2 in 3 children with pneumonia do not receive the antibiotics they need

Cancer patients are at high risk[6]

Bacterial infections are the **2nd leading cause of death** amongst cancer patients

1 in 5 patients undergoing treatment will be hospitalised as a result

Only a handful of companies are targeting the deadliest pathogens

In response to the threat posed by some of the most dangerous, drug-resistant superbugs, the World Health Organization (WHO) published its first-ever bacterial Priority Pathogen List in 2017, followed by the second iteration in 2024. Furthermore, the WHO published its fungal Priority Pathogen List in 2022. In a bid to guide and promote R&D of innovative antimicrobials, these lists provide a clear call to action for pharmaceutical companies, indicating where to focus their resources and efforts (also see sidebar on p.9).

What is an innovative antimicrobial?

In 2024, the World Health Organization (WHO) published the second iteration of the WHO bacterial Priority Pathogens List (WHO BPPL), summarising 14 pathogens, in addition to *Mycobacterium tuberculosis,* that have the greatest potential to harm human health.[7] Inspired by the proven value of the WHO BPPL, the WHO published the first WHO fungal Priority Pathogens List (WHO FPPL) in 2022. The WHO FPPL outlines 19 fungi recognised as posing the greatest threat.[8]

The pathogens listed in the WHP BPPL and the WHO FPPL are categorised into three distinct groups, aligning with the urgency for development of new antibiotics and antifungals to address them: critical, high and medium priority.

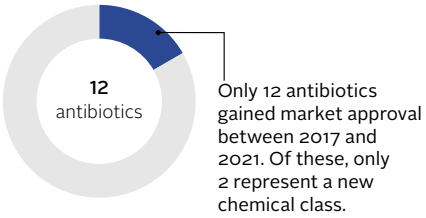
In 2021, the WHO conducted an analysis of all the antibacterial agents in clinical and preclinical development. In addition, the WHO identified whether the agents in development were innovative using the WHO innovation criteria. This report employs the WHO innovation criteria, meaning that for an R&D project to be considered innovative, it must fulfil at least one of the four predefined criteria for innovation, namely: the absence of known cross-resistance, a new target, a new mode of action (MoA), and/or new chemical class. For the fungal projects no assessment is made on their innovativeness as this data is not readily available.

In addition to the WHO BPPL and the WHO FPPL, the WHO Paediatric Drug Optimisation for Antibiotics (WHO PADO) list highlights important products for which optimal formulations for paediatric populations are needed.[9] Without optimal treatments being made available for children, healthcare providers and parents often resort to using or manipulating adult medicine, increasing the risk of inadequate dosing and spurring drug resistance[9] However, it must be noted that developing paediatric formulations is challenging; it requires ensuring maximal efficacy and no toxicity, while simultaneously being easy to administer. Additionally, before recruiting children for clinical trials, there are stricter ethical considerations that need to be addressed.

The clinical pipeline for antimicrobial medicines has struggled to keep pace with rising drug resistance (see figure alongside). In recent years more and more large research-based pharmaceutical companies have abandoned antimicrobial R&D and commercialisation, with recent decisions by AstraZeneca, Bayer, Bristol-Myers Squibb, Eli Lilly, Johnson & Johnson, Novartis and Sanofi to leave, or significantly minimise their presence in this space. Given this reality, the world has come to rely on small- and medium-sized enterprises (SMEs) to plug the gap. However, these 'biotechs' lack the vast financial resources that large pharmaceutical companies have, leading to many going bankrupt.

Of course, several pharmaceutical companies invest in the AMR Action Fund that works to develop new antimicrobials, and R&D funder organisations – public and private – currently invest in or provide grants to companies for the development of new antimicrobials. However, this is not sufficiently addressing the lack of access to antimicrobials, nor is it enough to build up the antimicrobial R&D pipeline.

World Health Organization pipeline analysis reveals how underprepared the pipeline is[73]



Given the current R&D landscape, how can lives be saved today?

People across the world urgently need access to innovative antimicrobials, which is why it is vital to engage in long-term, sustainable efforts to ensure that, at the very least, the few promising drugs in development reach patients that need them most. Specifically, companies need to develop and implement access and stewardship planning as early as possible in the R&D process that is designed to address priority populations' access requirements, regardless of geography.

To date, the Access to Medicine Foundation's AMR Programme has found that access strategies for antimicrobial products already approved, and on the market, have not been implemented at scale. The 2021 AMR Benchmark, for example, found that just one third of antimicrobial products in the portfolios of companies in scope are covered by access strategies in LMICs.[10] This emphasises the need for advance planning of access and stewardship plans for projects that are still in development.

The five case studies in this report zero in on the access and stewardship planning of R&D projects of two large research-based pharmaceutical companies (GSK and Pfizer) and three SMEs (F2G, Innoviva and Venatorx), specifically to determine whether plans are targeting the LMICs that are facing the greatest threats.

Should these projects prove safe and effective and successfully leave the R&D pipeline, the resulting new antimicrobial products will have a significant impact on the lives of patients battling drug-resistant infections. As set out in the accompanying fact sheet on p.11, these projects target a wide range of diseases and syndromes, including drug-resistant gonorrhoea, urinary tract infections (UTIs), intra-abdominal infections (IAIs), respiratory infections and invasive fungal infections. By providing patients with much-needed medicines to treat these diseases and syndromes, the lives of at least 160,000 people could already be saved each year.*

While findings from this report show that advance access and stewardship planning has not become the norm yet, there are clear opportunities for industry to enhance efforts, address gaps and drive stepwise change to ensure patients are reached. Moreover, many of the projects analysed are being developed with the support of partner funding, and these organisations can help ensure companies will develop – and follow up on – access and stewardship plans. By doing this, they can ensure their vast financial support for antimicrobial R&D translates into sustainable progress and improved global health.

*This number is based on the number of deaths per syndrome annually due to the resistant pathogens that are specifically targeted by the projects in scope. The data is derived from the estimated global burden of bacterial antimicrobial resistance in 2019 by the Institute for Health Metrics and Evaluation.[11] Note that the number of deaths due to invasive aspergillosis caused by drug resistant *Aspergillosis* spp. is not estimated and therefore not included.

A CLOSER LOOK

The global impact of the diseases targeted by the projects analysed in this report.

RESPIRATORY INFECTIONS

Most caused by *S. pneumoniae* and *S. aureus*

413,000

estimated deaths in 2019, making lower respiratory infections the leading cause of AMR-related deaths.[11]

Infections acquired in the **hospital** are increasingly associated with multidrug resistance and result in poor clinical outcomes and higher mortality rates.[12]

Without treatment options, **community-acquired** pneumonia is the most common cause of sepsis and a major cause of hospitalisation and death.[13]

IN THE NEWS

CIDRAP

"Undiagnosed pneumonia outbreak in China puts pressure on pediatric hospitals, prompts questions" [14]

URINARY TRACT INFECTIONS (UTIs)

Most caused by *E. coli*

375,000

people died in 2019 globally, as a result of UTIs.[11]

50-60% of women will develop at least one UTI within their adult lives.[15]

>50% of women have **asymptomatic infections**, preventing them from participating in screening procedures and getting the appropriate treatment.

>92% of the bacteria that cause UTIs are resistant to at least one common antibiotic.[16]

If complicated UTIs cannot be treated, they can lead to **sepsis** and even **septic shock**.[15]

IN THE NEWS

The New York Times

"Urinary Tract Infection affect millions. The cures are faltering."[17]

GONORRHOEA

Caused by *N. gonorrhoeae*

Gonorrhoea, a sexually transmitted infection (STI), is a **major public health threat** globally.

82.4 million

estimated new cases worldwide in 2020.[18]

Women are specifically affected with complicated infections and worse outcomes.[19] Gonorrhoea can lead to a **five-fold increased risk of HIV transmission**.[20]

N. gonorrhoeae has **developed resistance to all antibiotics**, including ceftriaxone, the last available recommended treatment option. Cases of such **'Super-Gonorrhoea'** are emerging globally.[20]

If untreated, or when untreatable, gonorrhoea can cause serious, lifelong consequences, such as **infertility** and **arthritis**.[19]

IN THE NEWS

BBC

"Super-gonorrhoea's spread causing huge concern"[21]

ABDOMINAL INFECTIONS

Most caused by *E. coli* and *S. aureus*

1,281,000

deaths globally were caused by complicated intra-abdominal infections (cIAIs) in 2019. **63%** of those were associated with **AMR**.[11]

Inaccessible and ineffective treatment options, due to drug resistance, make IAIs hard to treat in LMICs.

Children in **Western sub-Saharan Africa** face a high prevalence of cIAIs.[22,23] Children under the age of five, and **men**, are specifically affected.

With increasing resistance rates, usually treatable infections are more often turning into deathly cIAIs. If untreated, cIAIs can lead to systematic complications, such as **sepsis**.[24]

IN THE NEWS

CBC news

"How E. coli infections wreak havoc on the body, causing dangerous disease – particularly in kids"[25]

INVASIVE FUNGAL INFECTIONS

For example, caused by *A. fumigatus*

Fungal diseases disproportionately affect immunocompromised and vulnerable patients, such as those in ICUs, **COPD** and cancer patients, and people living with HIV.

Each year[26]

7 million

people are affected by life-threatening fungal diseases.

2.5 million

people die as a direct cause of the fungal disease.

1 million

COPD patients die due to invasive aspergillosis.

Emerging rates of resistance are threatening the effectiveness of **azoles** – the current treatment option for **aspergillosis**. If untreated, death rates for invasive aspergillosis go up to >95%.[26]

>10% azole resistance found in *A. fumigatus* samples globally.[27]

IN THE NEWS

THE CONVERSATION

"Global deaths from fungal disease have doubled in a decade – new study" [28]

AT LEAST 160,000 LIVES

could already be saved from deadly drug-resistant infections each year if patients around the world were able to access the few promising antimicrobials assessed in this report.

ACCESS AND STEWARDSHIP DURING R&D

From pipelines to patients

Using the priority pathogens for R&D of new antibiotics and antifungals listed by the World Health Organization (WHO) (also see p.9), the Foundation has scoped promising late-stage R&D projects that are currently in the pipeline. The WHO updates these priority lists to accurately represent gaps in the pipeline and global unmet needs. Companies can consistently refer to them when making strategic decisions about their antibacterial and antifungal pipelines in the future.

What is currently in development to target superbugs?

Ideally, to be adequately prepared and keep pace with the sheer speed at which drug resistance is developing, there should be an abundance of late-stage R&D projects targeting a wide range of the WHO's listed priority pathogens.

Currently there are only 19 antibacterials in late-stage development targeting 8 priority pathogens (see Figure 2 on p.13). Notably, there is not a single project in the clinical pipeline (early, or late stage) addressing the other 6 of the 14 bacteria designated as priority pathogens by WHO. This leaves infections caused by *Enterococcus faecium*, Group A Streptococci, Group B Streptococci, Non-typhoidal *Salmonella*, *Salmonella* Typhi, and *Shigella* spp. completely unaddressed. Three of which, Non-typhoidal *Salmonella*, *Salmonella* Typhi, and *Shigella* spp., cause diarrhoeal disease, which is the third leading cause of death in children under five years of age.[29] *E. faecium* can cause a variety of infections, including urinary tract infections (UTIs) as well as intra-abdominal infections (IAIs).[30]

Similarly, there are currently only 7 antifungals in late-stage development targeting 18 priority pathogens (see Figure 3 on p.14). Although there are very few antifungals in late-stage development, most of them act against a wide range of pathogens, which leaves only one priority pathogen – *Talaromyces marneffei* – entirely unaddressed. Inhaling *Talaromyces marneffei* spores may lead to the onset of Talaromycosis, an infection primarily observed in immunocompromised people, including cancer patients and people living with HIV.[31]

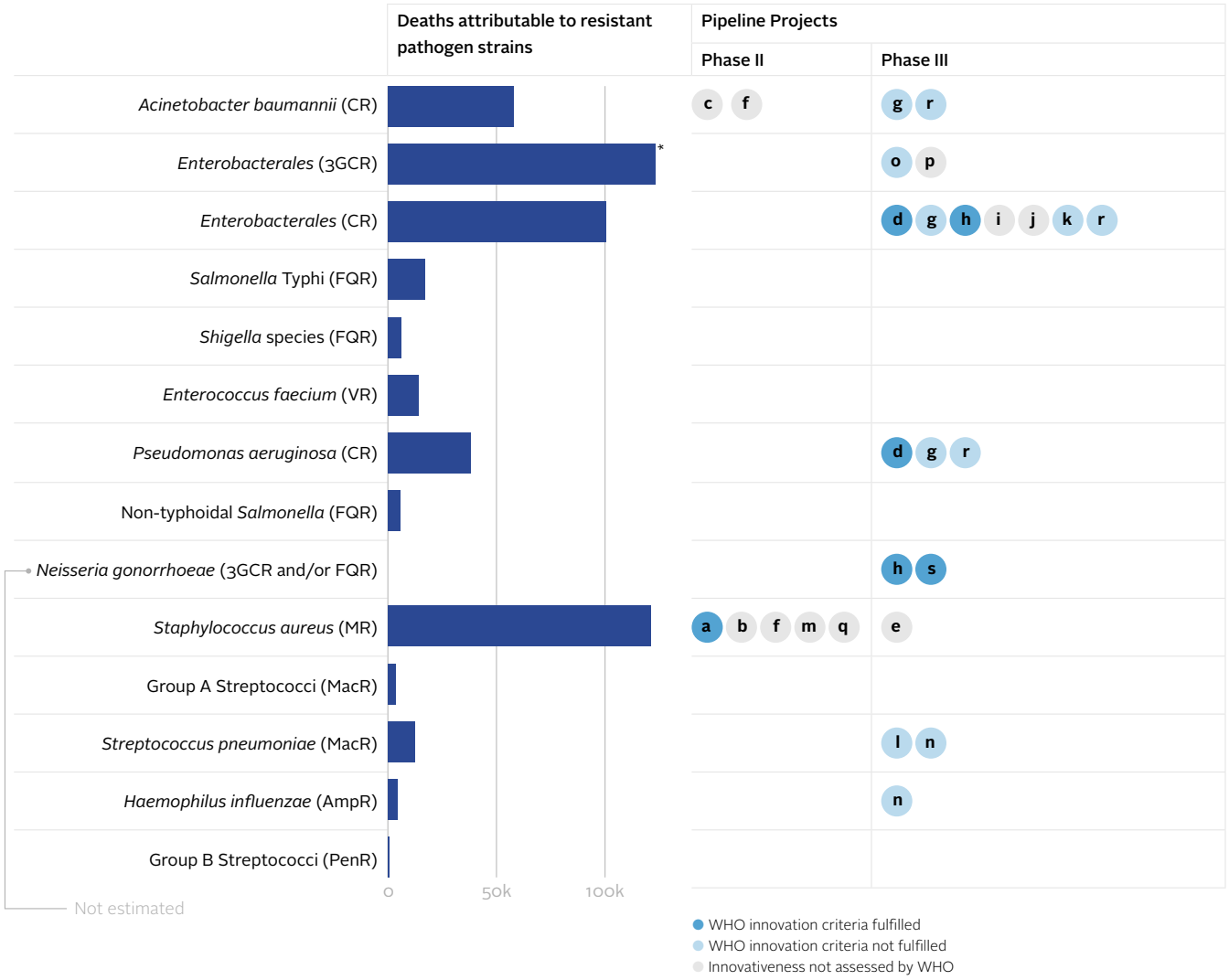
Narrowing in on four bacterial pathogen projects and one fungal pathogen project

Of the limited projects currently in late-stage development across both the antibiotic and antifungal pipelines, this report analyses five promising projects for individual, in-depth case studies. During the period of analysis, one of these projects, aztreonam-avibactam, was approved by the European Commission (22 April 2024). Of the five featured projects, four are antibiotic agents and one is an antifungal agent.

The projects were selected based on WHO innovation criteria, priority pathogens, unmet medical need, and high resistance rates to current treatments. Furthermore, the projects were selected to reflect a balance of large research-based pharmaceutical companies and small- and medium-sized enterprises (SMEs), with more of the featured projects belonging to SMEs, reflective of the current antibacterial and antifungal R&D landscape.

Three of the four selected antibacterial agents also meet at least one of four innovation criteria outlined by WHO. Specifically, cefepime-taniborbactam, gepotidacin and zoliflodacin all fulfil the new chemical class criterion making them potentially very impactful projects. While the fourth remaining antibacterial agent aztreonam-avibactam does not meet any of the WHO innovation criteria, it is highlighted as a noteworthy pipeline agent by the WHO and highlighted in WHO's Paediatric Drug Optimisation for Antibiotics (WHO PADO) list as a compound that may be of

FIGURE 2 **Late-stage R&D projects targeting bacterial pathogens**
This figure shows the 14 priority pathogens recognised by the World Health Organization bacterial Priority Pathogen List (WHO BPPL) 2024 for the urgency in development of new antibiotics.[7] The burden attributable to the resistant strains of bacteria outlined in the WHO BPPL is summarised by the number of deaths per year globally.[11] The right side of the figure details all late-stage R&D projects currently progressing within the pipelines of both large research-based pharmaceutical companies and small- and medium-sized enterprises (SMEs), specifically directed towards combating these priority pathogens.



a. Afabicin (Debiopharm), **b.** Brilacidin (Innovation Pharmaceuticals), **c.** BV100 (BioVersys), **d.** Cefepime + taniborbactam (GARDP and Venatorx Pharmaceuticals), **e.** Cefilavancin (R-Pharm and Theravance Biopharma), **f.** Finafloxacin (MerLion Pharma), **g.** Funobactam + imipenem + cilastatin (Evopoint Bioscience), **h.** Gepotidacin (GSK), **i.** Nacubactam + aztreonam (Meiji Seika), **j.** Nacubactam + cefepime (Meiji Seika), **k.** Nacubactam + meropenem (Meiji Seika), **l.** Nafithromycin (Wockhardt), **m.** Nilofabicin (CrystalGenomics), **n.** Solithromycin (Fujifilm Toyama Chemical), **o.** Sulopenem; sulopenem etzadroxil / probenecid (Iterum Therapeutics), **p.** Tebipenem pivoxil (GSK), **q.** TNP-2092 (TenNor Therapeutics), **r.** Zidebactam + cefepime (Wockhardt), **s.** Zoliflodacin (GARDP and Innoviva)

Note: During the period of this report's analysis, one of the projects in scope, aztreonam + avibactam (AbbVie and Pfizer) was approved by the European Commission (22 April 2024). As such, the project is not reflected in this pipeline figure.

*includes resistance data against fourth-generation cephalosporin for *Enterobacter* spp.

FIGURE 3 **Late-stage R&D projects targeting critical fungal pathogens**

This figure lists the 19 priority pathogens recognised by the World Health Organization fungal Priority Pathogen List (WHO FPPL) 2022, listed by priority for the urgency in development of new antifungals.[8] Unlike in Figure 2, the attributable deaths associated with these priority pathogens have not been illustrated as such data is underreported. In addition, the innovativeness of these R&D projects has not been assessed by WHO. The figure details all late-stage R&D projects currently progressing within the pipelines of both large research-based pharmaceutical companies and small- and medium-sized companies (SMEs), specifically directed towards combating these priority pathogens.

	Pipeline Projects	
	Phase II	**Phase III**
Cryptococcus neoformans		**b** **c**
Aspergillus fumigatus	**a**	**c** **d** **e** **f** **g**
Candida auris		**b** **c** **d** **g**
Candida albicans		**b** **c** **d** **g**
Candida glabrata		**b** **c** **d** **g**
Candida tropicalis		**b** **c** **d** **g**
Candida parapsilosis		**b** **c** **d** **g**
Histoplasma species		**d**
Mucorales		**c**
Eumycetoma causative agents	**e**	**c**
Fusarium species		**c**
Scedosporium species	**e**	**c**
Lomentospora prolificans	**e**	**c**
Coccidioides species	**e**	**c** **d**
Cryptococcus gatti		**b** **c**
Candida krusei		**c** **d** **g**
Talaromyces marneffei		
Pneumocystis jirovecii		**d** **g**
Paracoccioides species		**d**

● Innovativeness not assessed by WHO

a. BAL2062 (Basilea), **b.** Encochleated ampothericin B (Matinas BioPharma Holdings, Inc.), **c.** Fosmanogepix (Basilea), **d.** Ibrexafungerp (Scynexis), **e.** Olorofim (F2G), **f.** Opelconazole (Pulmocide), **g.** Rezafungin (Mundipharma)

How access and stewardship planning can ensure patients are reached

The analysis of case studies that follows determines the depth and breadth of access and stewardship planning that companies are currently implementing. Specifically, having already set out where their products would be needed the most, the analysis identifies whether companies are targeting the low- and middle-income countries (LMICs) that are facing the highest threats. If lives are to be saved, it is crucial that the regions currently disproportionately affected by the targeted pathogens are prioritised to receive appropriate access to newly developed products that may result from the projects in the pipeline.

Companies have diverse tools for ensuring access and stewardship (see box-out alongside), and it is not necessary for every company to apply every available strategy to its access and stewardship plan. Appropriate access and stewardship strategies will also vary, depending on the product at hand, and its specific characteristics.

Taking proactive steps early in the development process

Certain components of access and stewardship plans can already be undertaken earlier in clinical development, while others may take shape later in the development process. However, it is critical for all companies to consider, as early in the development process as possible, which populations could benefit from this project if it eventually reaches the market. By doing so, companies proactively identify target populations and gain a better understanding of the countries with the highest disease burden, as well as the distinct characteristics within the target population – such as whether paediatric populations are disproportionately affected. For example, obtaining market approval for paediatric use typically takes up to ten years longer than adult use.[32] Therefore, having a paediatric formulation under development before market approval of the adult formulation will drive progress towards closing the gap between adult and paediatric access.

Identifying these factors early on allows companies to take them into consideration during the development process. This is crucial because countries may have specific regulatory requirements for approval, that companies may not foresee in a timely manner.

For instance, some countries may require an in-country clinical trial, which, if not planned for, can significantly impact the waiting time for patients to access a product. Therefore, it is encouraging when companies already have a preliminary list of countries where they plan to prioritise filing for registration, particularly when these decisions are informed by data on the burden of disease. This indicates that the company has already considered which populations could benefit from the project.

Using the Stewardship and Access Plan Development Guide

When developing an access and stewardship plan, companies can utilise the Stewardship and Access Plan (SAP) Development Guide, published in 2021 by the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) in collaboration with key partners, including the Wellcome Trust and the Access to Medicine Foundation.[34] The Guide provides practical guidance that companies can use to inform and scale up their access and stewardship plans. It was specifically designed to assist SMEs, particularly CARB-X awardees, in developing appropriate access and stewardship plans while also serving as a template for other product developers in the global health community. While the SAP Guide offers practical steps for companies in access and stewardship planning, its relevance may vary for each company, and some companies report implementing plans independent of the SAP Guide. However, it is critical that the depth and breadth of companies' access and stewardship plans are in line with the recommendations set out in the SAP Guide. In addition, the Access to Medicine Foundation has been assessing pharmaceutical companies approaches to appropriate access and stewardship since the publication of the first AMR Benchmark in 2018, setting clear expectations on how companies can act.

Strategies companies can consider when developing effective access and stewardship plans

▶ Access
- Registration
- Collaborative registration or availability mechanisms (e.g., EU-M4all, special importation waivers, WHO Collaborative Registration Procedure, WHO Prequalification)
- Responsible intellectual property and licensing agreements
- Early access programmes
- Manufacturing and supply
- Equitable pricing
- Clinical trials in LMICs and post-trial access commitments
- Paediatric formulations
- Product donation programmes

▶ Stewardship
- Surveillance and data sharing
- Responsible promotion and sales strategies
- Availability of companion diagnostics

How appropriate and timely access to innovative antibiotics can save people's lives from resistant infections

Early access programmes provide patients with a pathway to access medicines that are yet to be registered in a country and can be particularly impactful for patients who have exhausted all existing treatment options. For example, in August 2022, a 50-year-old woman from Nepal was infected with multidrug-resistant *P. aeruginosa* after undergoing abdominal surgery. The intra-abdominal infection caused by the pathogen induced sepsis, leaving the patient in critical condition. As existing antibiotics (ceftazidime/avibactam, imipenem/relebactam and ceftolozane/tazobactam) could not cure the infection, a Phase III antibiotic (cefepime/zidebactam) developed by Wockhardt was provided under an early access programme. In receiving this innovative antibiotic, the patient was cured from an otherwise untreatable infection, and she left the hospital in a stable condition.[33] While this example illustrates how an early access programme can help provide timely access to innovative medicines that are not yet registered, this strategy is only one of many components that can be utilised by companies as part of developing comprehensive access plans.

*The Guide was developed collaboratively by a working group comprising of CARB-X, several of its funders, which include the United States Department of Health and Human Services' (HHS') Office of Global Affairs (OGA) and Biomedical Advanced Research and Development Authority (BARDA); the Global AMR Innovation Fund (GAMRIF); UK Department of Health and Social Care (DHSC); the Bill & Melinda Gates Foundation and the Wellcome Trust, as well as the Global Antibiotic Research and Development Partnership (GARDP) and the Access to Medicine Foundation, with consultative input from the Biotechnology Innovation Organization (BIO).

ANALYIS: COMPANY CASE STUDIES

Assessing the five selected projects

This report focuses on the five projects from F2G, GSK, Innoviva, Pfizer and Venatorx, highlighting which elements of their current access and stewardship planning are on track – and identifying what needs to be done to ensure they address gaps in these plans. Findings from the case studies can also provide other companies with guidance on what to focus on to ensure they take proactive and pre-emptive action to implement effective access and stewardship planning.

The table below provides an overview of the access and stewardship planning for the projects analysed, with the individual case studies taking an in-depth look at the various strategies that are being employed.

Following the case study analyses, the report also considers how R&D funder organisations – private or public organisations that invest in or provide grants to companies for the development of new antimicrobials – can work with companies to make progress.

Note: Throughout the case studies, several abbreviations are used. Please refer to p.36 -37 in this report for a list of abbreviations for reference.

FIGURE 4 **Companies apply diverse range of strategies within access and stewardship plans**
The table shows to what extent the five companies are incorporating various strategies in their access and stewardship and plans.** The most appropriate strategies depend on the project and company in question – not all strategies are apprioriate for all projects and companies.

○ Strategy not in place or no information available
◐ Strategy partially in place for LMICs
● Strategy in place for LMICs

	GSK	Pfizer	Venatorx	Innoviva	F2G
Product	Gepotidacin	Aztreonam-avibactam	Cefepime-taniborbactam	Zoliflodacin	Olorofim
Target indication	uUTI, gonorrhoea	cIAI, HABP/VABP, cUTI, infections due to aerobic gram-negative organisms	cUTI, HABP/VABP	Gonorrhoea	Invasive fungal infections, including invasive aspergillosis
Access					
Registration	◐	◐	◐	◐	○
Responsible intellectual property and licensing agreements	◐	◐	●	●	●
Early access programmes	○	◐	○	◐	●
Manufacturing and supply	◐	○	○	●	◐
Equitable pricing	◐	●	◐	◐	○
Clinical trials in LMICs and post-trial access commitments	●	◐	◐	●	◐
Paediatric formulations	●	●	◐	●	○
Collaborative registration or availability mechanisms*	○	○	◐	○	○
Product donation programmes	○	○	○	○	○
Stewardship					
Surveillance and data sharing	●	●	◐	○	○
Responsible promotion and sales strategies	◐	◐	○	○	◐
Availability of companion diagnostics	○	○	○	○	○

*These include mechanisms such as EU-M4all, special importation waivers, WHO Collaborative Registration Procedure and WHO Prequalification

**For a strategy to be in place, the company reports a clear, well-described, and detailed plan, either at product level or on a wider scale specifying the geographic reach for the 113 LMICs in scope. A strategy that is partially in place has limited information on how the company's plan addresses access or stewardship for the 113 LMICs in scope.

CASE STUDY 1

Plans for gepotidacin to fulfil global needs of patients yet to mature

Gepotidacin, which belongs to a new chemical class of antibiotics and has a new mode of action, is currently being developed by GSK to treat patients with uncomplicated urinary tract infections (uUTIs) and uncomplicated urogenital gonorrhoea.

Half of all women develop at least one urinary tract infection (UTI) during their adult life, and resistance rates of UTI-causing *Escherichia coli* infections are rising.[16] Similarly, as experts warn that gonorrhoea is increasingly becoming resistant to all available antibiotics, global access to new antibiotics, such as gepotidacin, is crucial to alleviate the burden of gonorrhoea.

Product
Gepotidacin

Target pathogen(s)
- *N. gonorrhoeae* (third-generation cephalosporin-resistant and/or fluoroquinolone-resistant)
- *Enterobacterales* (Carbapenem-resistant *E. coli*); *E. coli* (ESBL producing)

Target indication(s)
uUTI, gonorrhoea

Mode of administration
Oral

Phase
- Adult formulation for uUTIs: Phase III (completed)
- Adult formulation for gonorrhoea: Phase III (completed)
- Paediatric formulation for uUTIs: Phase I (completed)

Clinical trials in LMICs in scope
- uUTIs: Mexico and India
- Gonorrhoea: Mexico

Funding partners

BARDA reports it has provided USD 203.8 million since 2013.[35]	No contractual provisions on access and stewardship planning reported as part of these funding announcements
Defense Threat Reduction Agency[36]	

GSK seeks market approval for two indications

GSK plans to submit a New Drug Application (NDA) for uUTI in the second half of 2024, followed by the submission for gonorrhoea in 2025, both to the US Food and Drug Administration (FDA).[37]

Despite positive Phase III trial results for gepotidacin in treating uUTIs in April 2023, GSK pushed back the deadline to file for registration from June 2023 to the second half of 2024.[38] While the reason for this shift remains unclear, it will inevitably result in a delay in access to gepotidacin globally.[38] In addition, there is currently no early access plan in place for gepotidacin, which would make it available ahead of market approval.

Populations with medical need, including children, prioritised in clinical trials

To address needs in low- and middle-income countries (LMICs) with a high burden of disease, GSK is conducting clinical trials in such countries. For example, its Phase III clinical trial for uUTIs was conducted in India where the most deaths due to carbapenem-resistant *E. coli* occur – with *E. coli* being the single most common causative pathogen for uUTIs.[39]

In addition to the adult formulation for women, there is a paediatric oral formulation of gepotidacin currently under development in Phase I of clinical trials. These trials include paediatric patients aged 2 – 12 and aim to address the unmet medical need of uUTIs in paediatric populations.[40] This could lead to the acceleration of access to gepotidacin for children.

Structured plans to make gepotidacin widely accessible and affordable in LMICs not yet in place

Limited information is available on how gepotidacin will reach patients in LMICs in scope of this report. For example, it is unclear in which LMICs GSK plans to register gepotidacin upon initial approval. However, GSK reports that is seeking to bring gepotidacin to patients globally for the treatment of gonorrhoea and uUTIs, where unmet need exists. In addition, GSK publicly reports it only conducts clinical trials in countries where it also intends to file for registration.[41] Given that GSK is undertaking clinical trials in Mexico and India, filing for registration of gepotidacin can be expected in Mexico for treatment of uUTIs and in India and Mexico for the treatment of gonorrhoea. Furthermore, GSK does not file patents, nor does it enforce historic patents, for its medicines in least-developed countries and low-income countries, which enables generic manufacturers to also supply to these countries.

For gonorrhoea, GSK reports that it will closely monitor the development of Innoviva's zoliflodacin, an alternative second-line treatment for gonorrhoea currently in late-stage development, and assess the potential of these two new antibiotics in the global management of multidrug-resistant gonorrhoea.

Although GSK generally reports employing responsible pricing strategies in LMICs to expand product reach and ensure affordability, it remains unclear which exact pricing strategies will apply to gepotidacin and whether patients' ability to pay will be considered.

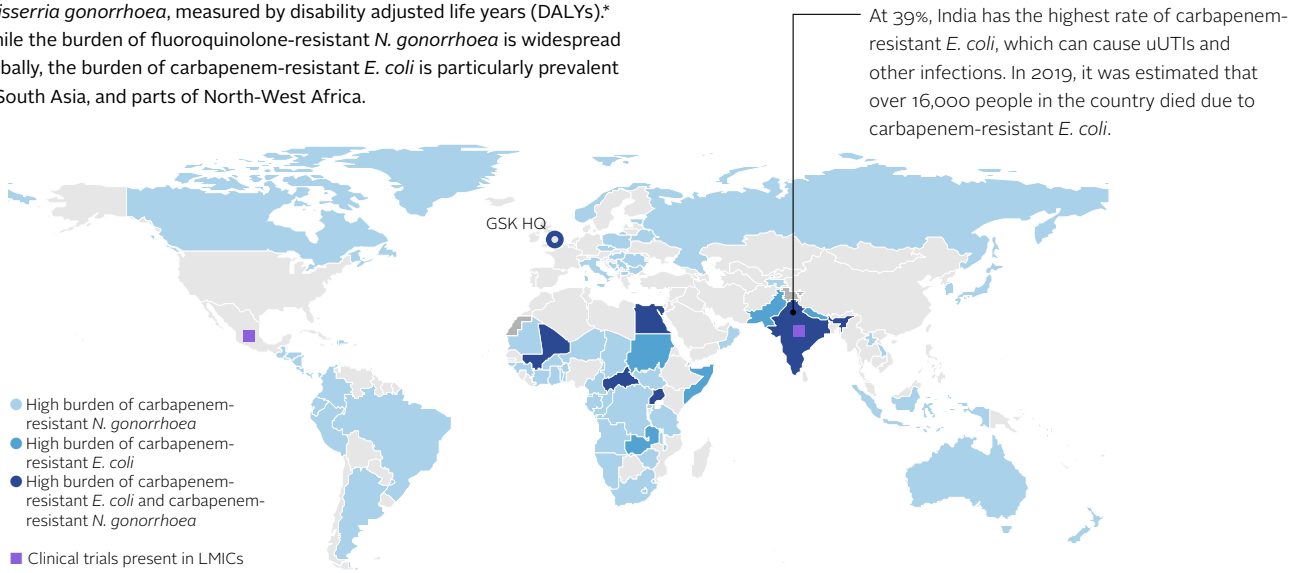
Commitment to surveillance for appropriate use and education support

GSK reports that introduction of gepotidacin in LMICs would be accompanied by educational programmes on the risks of AMR, which will include resistance surveillance.[42] Specifically for gepotidacin, GSK initiated a uUTI Global Surveillance Study in 2019. The study consisted of surveilling data from 73 medical facilities across the US, Europe, the Asia-Pacific region, and Latin America.[43] GSK is also collaborating with Amref Health Africa to drive collaboration between local actors in supporting the implementation of AMR plans, including surveillance.[42]

Unclear to what extent GSK will pursue global access for gepotidacin

GSK has exclusive market rights in all 113 LMICs in scope of this report, where better access to medicine is urgently needed, including gepotidacin. Despite this potential for providing access in these countries, to both adult and paediatric populations, it is currently unclear what the delivery of gepotidacin will look like in these 113 LMICs after the product's global launch. Aside from a paediatric formulation in early-stage development, clinical trials in at least two LMICs (India and Mexico), and stewardship commitments, specific details on access plans for gepotidacin, such as registration filing and equitable pricing strategies, are lacking.

FIGURE 5 **Gepotidacin has the potential to impact lives globally**
The map indicates the countries that have the highest burden attributable to carbapenem-resistant *Escherichia coli* and fluoroquinolone-resistant *Neisserria gonorrhoea*, measured by disability adjusted life years (DALYs).* While the burden of fluoroquinolone-resistant *N. gonorrhoea* is widespread globally, the burden of carbapenem-resistant *E. coli* is particularly prevalent in South Asia, and parts of North-West Africa.



*A threshold of 0.95 DALYs per 100,000 people was used to determine countries with a high burden of fluroquinolone-resistant *N. Gonorrhoea*. DALYs were chosen as the unit of measurement because while mortality is low (0.5% to 3% of untreated infections) gonorrhoea can cause serious, lifelong consequences in men and women. To determine countries with a high burden of carbapenem-resistant *E. coli* a threshold of 27 DALYs was used. Please note that, due to the scale of the map, some countries with high burden of disease or resistance might not be visible.

Source: Burden of pathogens: IHME MICROBE database, Trial locations: NIH Clinical Trials

CASE STUDY 2

Despite varied plans, it is uncertain how recently approved aztreonam-avibactam will reach LMICs

Aztreonam-avibactam (ATM-AVI) was jointly developed by Pfizer and AbbVie, whereby AbbVie holds the commercialisation rights for the US and Canada, and Pfizer for the rest of the world.[46] While this product is a combination of two existing antibiotics, its clinical utility is significant due to its effectiveness against a variety of infections caused by multidrug-resistant gram-negative bacteria, including *Enterobacterales*, which are a main cause of respiratory and intra-abdominal infections.[46] This could make ATM-AVI a viable last-resort treatment option for patients with limited or no existing treatment options due to drug resistance and, therefore, address unmet medical need in this patient population.

Building on the positive Phase III trial results in 2023, Pfizer filed for registration in Europe in September of the same year.[47] On 22 April 2024, the European Commission approved ATM-AVI for the treatment of adult patients with complicated intra-abdominal infections (cIAI); hospital-acquired bacterial pneumonia (HABP), including ventilator-associated bacterial pneumonia (VABP); complicated urinary tract infections (cUTI), including pyelonephritis; and other infections due to aerobic gram-negative organisms in patients with limited treatment options.[48] In addition, Pfizer is planning regulatory filings in the UK and China.[46] While no early access programme is yet in place, Pfizer reports it is pursuing such programmes in multiple countries to meet patient needs.

Equitable pricing plans in place to increase affordability

Pfizer reports it will implement equitable pricing strategies for ATM-AVI. For example, pricing will be based on burden of disease data, including the local epidemiology and patient population characteristics, as well as data relating to the affordability of ATM-AVI, such as national reimbursement, potential out-of-pocket costs, gross domestic product (GDP) per capita data and healthcare benefits. In line with its internal policy, Pfizer will not file and/or enforce patents for ATM-AVI in least-developed countries (LDCs).[42]

In addition, ATM-AVI will be evaluated for Pfizer's 'Accord for a Healthier World' initiative. Through this initiative, Pfizer offers its full portfolio of medicines and vaccines, for which it holds global rights, on a not-for-profit basis to 45 LMICs.[49] The Accord covers most countries in sub-Saharan Africa (SSA), where the burden of respiratory and intra-abdominal infections due to multi-drug resistant *Enterobacterales* is especially high (see map on next page).[11] If ATM-AVI will fall under the Accord, affordability in 45 LMICs could be enhanced.

Pfizer addresses unmet medical need of children

In children under the age of five, carbapenems – currently the last-resort antibiotics – are already ineffective in 19% of all bacterial infections.[50] As such, ATM-AVI is included in the World Health Organization Paediatric Drug Optimisation for Antibiotics (WHO PADO) list, which highlights pipeline projects and products that are urgently needed for paediatric populations.[32] While an adult formulation of ATM-AVI was recently approved, Pfizer aims to accelerate access to ATM-AVI for children by developing paediatric formulations in parallel. For example, Phase II trials for ATM-AVI are ongoing in children between the ages of 9 months and 17 years.

Product
Aztreonam-avibactam (Emblaveo®)

Target pathogen(s)
Multidrug-resistant *Enterobacterales* (including MBL producing), *Stenotrophomonas maltophilia*

Target indication(s)
cIAI, HABP/VABP, cUTI (including pyelonephritis), infections due to aerobic gram-negative organisms

Mode of administration
IV

Phase
- Adult formulation: approved April 2024
- Paediatric formulation: Phase II (ongoing)

Clinical trials in LMICs in scope
Phase III: China, India, Mexico, Philippines, Thailand, and Ukraine
Phase II (paediatric): China and India

Funding partners

2015: BARDA reports it, since 2015, has provided Pfizer with USD 96 million to develop ATM-AVI.[44]	No contractual provisions on access and stewardship planning reported as part of these funding announcements
2015: European Union's IMI invests EUR 83 million through the project COMBACTE-CARE (this includes, but is not specific to, ATM-AVI).[45]	

ATM-AVI included in Pfizer's portfolio-wide antimicrobial stewardship strategy

Considering the potential impact of ATM-AVI to address unmet needs, and the scarcity of other products, safeguarding the effectiveness of ATM-AVI through stewardship is key. Instead of implementing product-specific stewardship measures, Pfizer publicly reports adopting a portfolio-wide stewardship strategy (see box-out below).[51] With ongoing data collection for Pfizer's large surveillance database, ATM-AVI is already covered by this strategy.[43]

Overall, Pfizer reports clear plans on equitable pricing, paediatric formulations, planned registration in China and portfolio-wide stewardship. Beyond this, it is unclear how ATM-AVI will be made accessible for patients living in the 113 LMICs in scope that urgently need the product to overcome resistant bacterial infections.

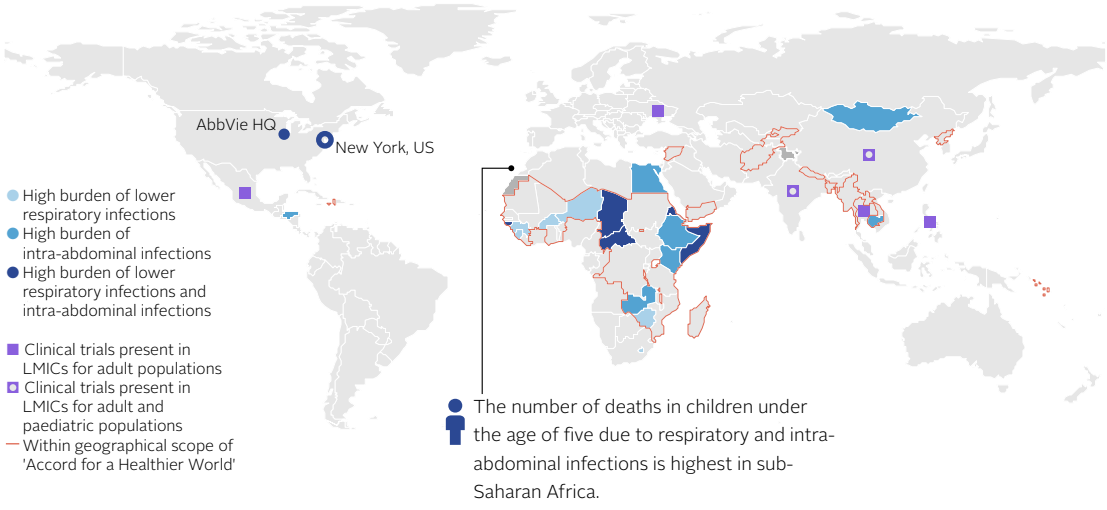
Pfizer's portfolio-wide stewardship programme

Pfizer endorses a portfolio-wide stewardship strategy, which includes:

1. Raising awareness and dissemination of information, including activities to ensure physicians understand the label indications of its anti-infectives products.
2. Surveillance through its ATLAS database – a large global AMR surveillance programme.
3. Grants to support local studies, education and other stewardship initiatives.
4. Promoting appropriate use by physicians and patients through the development of comprehensive plans for each antibiotic.

FIGURE 6 **Through the 'Accord for a Healthier World', access to ATM-AVI could be facilitated in countries with a high burden of disease**

The map depicts the countries that have the highest number of deaths due to respiratory and intra-abdominal infections.* The majority of patients that die from these infections live in LMICs, specifically sub-Saharan Africa (SSA). Pfizer covers most of SSA through its 'Accord for a Healthier World'. If included in the Accord, ATM-AVI will be offered on a not-for-profit basis to these countries.



*The map depicts the burden of disease in terms of mortality from lower respiratory infections and all related infections in the thorax (LRI+) and intra-abdominal infections (IAI). Therefore, it does not show pathogen-specific or resistance-specific burden of disease. Countries with a high burden of disease were included based on a threshold of 160 deaths per 100,000 people for LRI+ and 40 deaths per 100,000 people for IAIs, since LRI+ are more deadly. Please note that due to the scale of the map, some countries with a high burden of disease or resistance might not be visible.

Source: Burden of disease: IHME MICROBE database, trial location: NIH Clinical Trials

CASE STUDY 3

Venatorx accelerates access to new antibiotic via global licensing strategy

Cefepime-taniborbactam, a beta-lactam / beta-lactamase inhibitor (BL/BLI) combination antibiotic, is being developed for the treatment of complicated urinary tract infections (cUTIs) including pyelonephritis. Despite positive Phase III trial results, a New Drug Application (NDA) submission was rejected by the US Food and Drug Administration (FDA) in February 2024 due to insufficient data on chemistry, manufacturing, and controls (CMC), testing methods and manufacturing processes. In parallel, Venatorx is pursuing approval to treat patients with hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP). Through exclusive voluntary licensing deals and development partnerships, Venatorx is aiming to provide adult and paediatric populations with access to cefepime-taniborbactam in all regions of the world, including low- and middle-income countries (LMICs). No early access programmes are currently reported to be in place.

Product
Cefepime-taniborbactam

Target pathogen(s)
Multidrug-resistant gram-negative bacteria, most notably carbapenem-resistant *Enterobacterales* (CRE) and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA)

Target indication(s)
cUTI (including pyelonephritis), HABP/VABP

Mode of administration
IV

Phase
- Adult formulation for cUTIs, including pyelonephritis: Phase III (completed)
- Adult formulation for HABP/VABPs: Phase III (initiated, not yet recruiting)

Clinical trials in LMICs in scope
Phase III (cUTIs): Brazil, China, Mexico, Peru and Ukraine

Funding partners

2013: Up to USD 21.2 million by NIAID[52]	No contractual provisions on access and stewardship planning reported as part of these funding announcements
2013: USD 8.9 million by the Wellcome Trust[53]	
2019: USD 20.7 million by BARDA (with possible additional funding up to a total cost-share of USD 86.8 million)[54]	
2020: Up to USD 35 million by GARDP[55]	
2022: USD 72.1 million (with possible additional funding up to 318 million USD in total) by BARDA under a Project BioShield advanced development and procurement contract.[56]	

Overview of countries that are included in current strategies

2018 — In September 2018, Venatorx entered into an exclusive license agreement with China-based Everest Medicines, which has the rights to develop and commercialise cefepime-taniborbactam in China, Hong Kong, Macau, Taiwan, South Korea, Indonesia, Malaysia, Philippines, Thailand, Singapore, and Vietnam.[57]

2020 — In April 2020, Venatorx and the Global Antibiotic Research & Development Partnership (GARDP) announced a collaboration to accelerate the development of, and access to, cefepime-taniborbactam for adult and paediatric populations. This collaboration includes financial resources, paediatric development and a licensing agreement (see below).[55] GARDP holds the exclusive commercialisation rights for both the adult and paediatric formulations of cefepime-taniborbactam in 64 LMICs (the majority being low- and lower-middle-income countries) worldwide, and the public markets in India and South Africa.[55]

2023 — In November 2023, Venatorx entered into a licensing agreement with Melinta Therapeutics to facilitate a strategic partnership and commercialise cefepime-taniborbactam in the US.[58]

2024 — In January 2024, Venatorx and Menarini Group entered into an agreement under which Menarini has the exclusive rights to commercialise cefepime-taniborbactam in 96 countries in Europe, Latin America, Middle East, Turkey and North Africa and the Commonwealth of Independent States (CIS).[59]

GARDP's access pathway for cefepime-taniborbactam

In 2020, GARDP and Venatorx started a collaboration to provide access to cefepime-taniborbactam and to accelerate access to the product for paediatric populations.

To accelerate clinical development, GARDP financially supported the Phase III trial. In addition, GARDP will lead the paediatric development of cefepime-taniborbactam upon its approval by US FDA. By working with Venatorx and other key partners, such as the Penta Foundation – a global paediatric infectious diseases research network based in Italy – GARDP has taken initial steps to plan the clinical trials required by regulatory authorities such as the European Medicines Agency (EMA) and the US FDA to gain paediatric approval. Data from these trials will also be used to inform and facilitate paediatric registration filings in LMICs.

To ensure access and affordability of adult and paediatric formulations of

cefepime-taniborbactam, Venatorx has granted GARDP with a license to commercialise and distribute the product in 64 LMICs and the public markets of India and South Africa. For the 64 LMICs, GARDP reports cefepime-taniborbactam will be supplied through the support of an international procurement agency and via an export waiver. The access strategy for India and South Africa will depend on the capacity of GARDP and Venatorx to find a single commercialisation partner with knowledge of both markets to efficiently address them together.

Together with key stakeholders, GARDP started to identify the countries with a high burden of carbapenem-resistant bacteria and hospitals where cefepime-taniborbactam will have added value. Initially, a phased and monitored introduction in a few countries, where the product has been identified as high priority for hospitals, is planned to better understand how the product can be used appropriately, and for which patients. In turn, the hospitals can act as hubs to support and share learnings with less-developed healthcare facilities that plan to introduce the product further down the line. After the phased introduction, the next step would be to work with an international procurement agency to expand access and to cover parts of the distribution, which may lead to greater affordability and more sustainable supply.

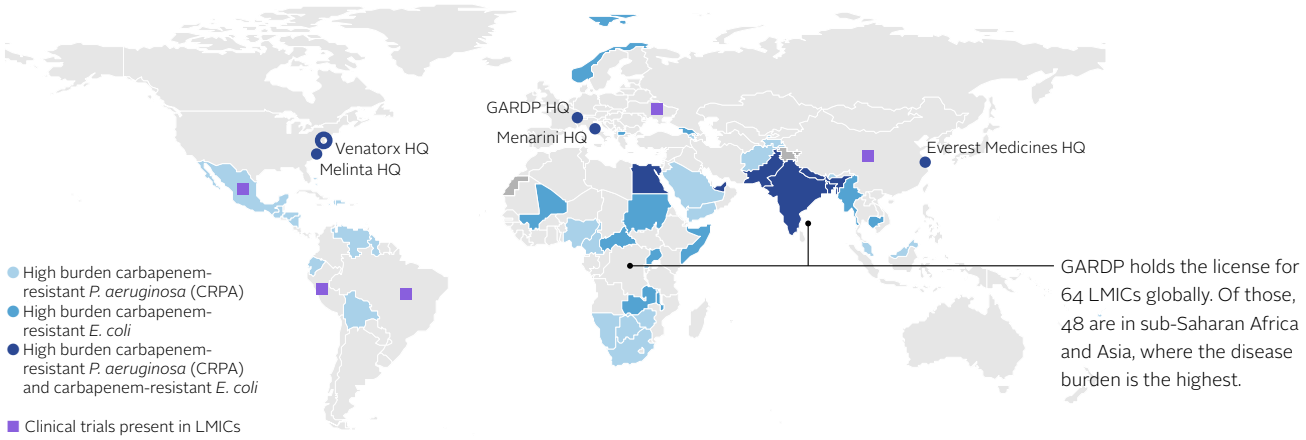
GARDP is also undertaking surveillance studies of carbapenem-resistant bacteria in select GARDP territories. In addition, Ventatorx reports it has completed a microbiological surveillance programme of five years and will continue this programme in accordance with regulatory requirements upon approval.

Licensing partners hold cards to reach patients in LMICs

Overall, Venatorx has granted exclusive licences to its partners for 105 of the 113 LMICs in scope of this report, which include all countries with the highest burden of carbapenem-resistant *E. coli* and *P. aeruginosa* (see map). While GARDP prioritises access for paediatric populations; the public markets of India and South Africa; and 64 LMICs after market approval is achieved, it is unclear how access in other LMICs within other licensing territories will be planned for. However, it is clear that through exclusive voluntary licensing deals and development partnerships, Venatorx is aiming to provide adult and paediatric populations with access to cefepime-taniborbactam in all regions of the world.

FIGURE 7 **Global partnerships broaden access to cefepime-taniborbactam for patients in need**

The map depicts the countries that have the highest number of deaths due to carbapenem-resistant *Escherichia coli* and *Pseudomonas aeruginosa.** While waiting for the approval of cefepime-taniborbactam, Venatorx entered four licensing deals and/or development partnerships. This way, Venatorx is able to accelerate access in countries with a high burden of carbapenem-resistant infections.



*A threshold of 0.69 deaths per 100,000 people due to carbapenem-resistant *E. coli* and carbapenem-resistant *P. aeruginosa* - which could cause cUTIs, HABP/VABP and other infections - was used to depict countries with a high burden. Please note that due to the scale of the map, some countries with a high burden of disease or resistance might not be visible.

Source: Burden of disease: IHME MICROBE database, Trial location: NIH Clinical Trials

CASE STUDY 4

Plans for Innoviva's oral formulation to treat gonorrhoea target countries with high burden

Innoviva is currently preparing the New Drug Application (NDA) for zoliflodacin, a first-in-class antibiotic for uncomplicated gonorrhoea, to be submitted within the upcoming year to the US Food and Drug Administration (FDA). Uncomplicated gonorrhoea is caused by *Neisseria gonorrhoeae*, which is listed as a high priority pathogen for antibacterial R&D by WHO.[7] Due to its oral formulation, zoliflodacin offers ease of administration compared to the current standard of care, which is an intramuscular injection of ceftriaxone.[18] This is especially relevant for paediatric populations.

Product
Zoliflodacin

Target pathogen(s)
N. gonorrhoeae (third-generation cephalosporin resistant and/or fluoroquinolone resistant)

Target indication(s)
Gonorrhoea

Mode of administration
Oral

Phase
Adult and paediatric formulations: Phase III (completed)

Clinical trials in LMICs in scope
Phase III: South Africa and Thailand

Funding partners

National Institute of Allergy and Infectious Diseases (NIAID) sponsored the Phase II trial	No contractual provisions on access and stewardship planning reported as part of these funding announcements
GARDP sponsored the Phase III trial	

Zoliflodacin's access and stewardship planning centred around GARDP partnership

Innoviva and the Global Antibiotic Research & Development Partnership (GARDP) formed a partnership to ensure equitable access to zoliflodacin and its appropriate use. The partnership commenced in 2017 between GARDP and Entasis Therapeutics, later acquired by Innoviva in 2022 and integrated into GARDP's core business in 2023. Within this partnership, GARDP plays a key role in the development as well as the commercialisation of zoliflodacin. In consultations for this report, Innoviva indicated that the submission of a comprehensive NDA in the US will serve as a crucial first step and springboard for subsequent registration filings in other countries, particularly within countries for which GARDP has obtained a license. To already provide patients with access to zoliflodacin prior to market approval, GARDP reports it is currently setting up an early access programme.

Partnership accelerates clinical development and prioritises access for children

The clinical development of zoliflodacin gained traction as GARDP took on the responsibility to finance and lead the Phase III trial. This trial was the largest clinical trial conducted for a new gonorrhoea treatment to date, enrolling a total of 930 patients, including women, adolescents, and people living with HIV – something that would have been a challenging undertaking without GARDP.[60] By taking the necessary preparatory steps during clinical development, GARDP aims to eliminate market inequities by ensuring accessibility for both adult and paediatric patients. GARDP's prioritisation of access for paediatric patients is evidenced by the inclusion of patients aged 12 – 17* in the Phase III trial.

GARDP secures manufacturing and commercialisation rights in all low-income countries

Through a licensing agreement, GARDP has acquired the rights to register and commercialise zoliflodacin in more than three-quarters of the world's countries, including all low-income countries, most middle-income countries, and several high-income countries. Innoviva retains the commercial rights for zoliflodacin in the major markets in North America, Europe, Asia-Pacific, and Latin America. Innoviva's first step is to pursue registration in the US while also evaluating opportunities for registration filings in Europe.

GARDP is prioritising registration filings in both South Africa and Thailand initially, given their involvement in the successful Phase III trial. These countries are situated in regions that face some of the highest burdens of drug-resistant gonorrhoea, specifically in sub-Saharan Africa and South-East Asia. Once Innoviva has filed for registration in the US, GARDP plans to seek registration in other countries battling drug-resistant gonorrhoea, with South-East Asia identified as a primary

*Patients under the age of 12 were excluded from the trial as agreed with the US FDA. The decision was based on the low prevalence of gonorrhoea in patients aged 0–12, making their inclusion in the trial impractical.

target region. GARDP reports that it intends to introduce zoliflodacin in a manner that ensures access in the public sector, and that this commitment applies to any future countries where it seeks registration.

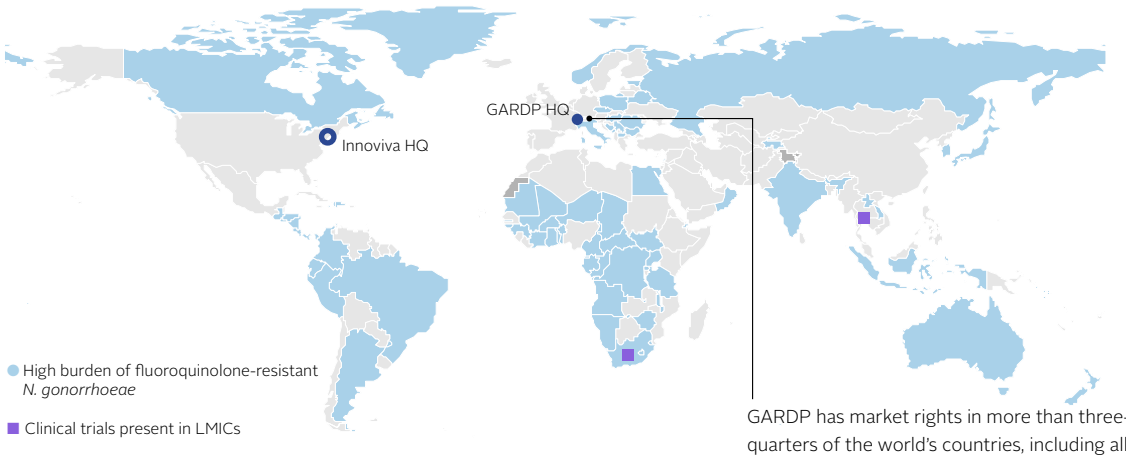
Beyond an assessment of disease burden data, GARDP collaborates closely with local ministries of health and consults local stakeholders to assess whether zoliflodacin is a priority product for countries. Some countries that GARDP has consulted already have a few indicators of sexual and reproductive health and rights (SRHR) policies in place. These indicators are helpful to understand whether zoliflodacin would be beneficial in their local context and can inform GARDP's future registration filings.

Manufacturing partnerships needed to prepare for demand

GARDP currently holds the manufacturing license for zoliflodacin and will, together with Innoviva, explore approaches to global commercialisation. While Aurigene Pharmaceutical Service Limited has been the manufacturing partner for the Phase III trial, a manufacturing partner for commercialisation has not been announced yet. Furthermore, Innoviva is actively scoping potential strategic partners who could contribute to broadening the regulatory reach of zoliflodacin, particularly in territories not covered by GARDP and not prioritised by Innoviva. Innoviva has indicated that specific market expertise in such countries, and regulatory experience, will be key attributes in a potential partner. These partnerships hold potential for improving affordability through scaling supply and expanding access to zoliflodacin beyond the geographic scope of current distribution networks.

FIGURE 8 **Global need for zoliflodacin as gonorrhoea is a widespread and growing problem**

The map indicates the countries that have the highest burden attributable to fluoroquinolone-resistant *Neisseria gonorrhoea*, measured by disability adjusted life years (DALYs).* By partnering with GARDP, Innoviva is able to expand the global reach for zoliflodacin.



*A threshold of 0.95 DALYs was used to determine countries with a high burden of gonorrhoea. DALYs were chosen as the unit of measurement because while mortality is low (0.5% to 3% of untreated infections) gonorrhoea can cause serious, lifelong consequences in men and women. Please note that due to the scale of the map, some countries with high burden of disease or resistance might not be visible.

Source: Burden of disease: IHME MICROBE database, Trial location: NIH Clinical Trials

Pre-emptive access planning but detailed stewardship planning still required

Collaborating with GARDP has accelerated the development of zoliflodacin, illustrated by the positive top-line results achieved in the Phase III trial, bringing it closer to the finish line. In similar fashion, outsourcing the commercialisation to GARDP for most LMICs has resulted in a clear approach towards access. This is illustrated by GARDP's commitment to register in clinical trial countries, including paediatric populations in clinical trials; actively searching for manufacturing partners; and identifying countries with high unmet medical need. Within GARDP's territory, it is evident that patients facing the highest disease burden will be prioritised when planning for access, irrespective of their age or where they live. In addition, GARDP is currently undertaking research to help inform affordable pricing points to support access, including in the public sector.

However, there is currently no formal stewardship plan in place for zoliflodacin. Considering that nearly 100 million people worldwide are diagnosed with gonorrhoea annually, prescriptions for zoliflodacin will be widespread.[61] It is therefore critical that Innoviva and GARDP ensure detailed stewardship plans are put in place to safeguard zoliflodacin's long-term effectiveness.

CASE STUDY 5

F2G, with its partner Shionogi, builds foundation that could shape robust access and stewardship plan for innovative antifungal agent

F2G, a UK-based small- and medium-sized enterprise (SME), is prioritising its efforts to obtain US Food and Drug Administration (FDA) approval for its Phase III product, olorofim. Targeting invasive fungal infections – including invasive aspergillosis caused by *Aspergillus fumigatus* – this antifungal aims to benefit patients who have limited or no remaining treatment options. *A. fumigatus* is listed as a critical priority pathogen for antifungal R&D and belongs to the group of fungal pathogens that have the highest public health burden according to the World Health Organization (WHO).[8] No access and stewardship plans have been developed to date. However, through a strategic partnership with Shionogi – a Japanese research-based pharmaceutical company – the two companies are collaboratively laying the foundation for what could shape up to be a robust access and stewardship plan. Specifically, the companies have contractually agreed to establishing a concrete access and stewardship plan within the first 60 days of the first global sale of olorofim.

Product
Olorofim

Target pathogen(s)
Aspergillosis spp., *Scedosporium* spp., *Lomentospora* spp. and *Coccidioides* spp.

Target indication(s)
Invasive fungal infections, including invasive aspergillosis

Mode of administration
Oral

Phase
Adult formulation: Phase III (ongoing)

Clinical trials in LMICs in scope
Phase III: Brazil, China, Egypt, Thailand and Vietnam

Funding partners
None identified

Shionogi takes on responsibility for clinical trials, registrations, manufacturing, and commercialisation across nearly 80 countries

Given that invasive fungal infections affect patients all over the world, ensuring widespread access to olorofim is critical, especially since resistance to current treatments with azoles is increasing. Anticipating this need for global access, F2G partnered with Shionogi in 2022 to plan for wider reach. As part of the partnership, Shionogi is responsible for clinical trials, subsequent registration, supply, and commercialisation of olorofim in 79 countries, spanning Europe and Asia, and including 20 low- and middle-income countries (LMICs), such as Thailand and Vietnam. In partnering, they will share responsibility for access and stewardship planning across LMICs, which can allow for wider access to olorofim when it is launched.

Choosing a partner with access and stewardship planning expertise

Small- and medium-sized enterprises (SMEs) that are considering strategic collaborations in the development and marketing phases of a project can look to potential partners with demonstrated expertise in access and stewardship planning. F2G has cited Shionogi's approach towards this as one of the key reasons for its partnership with the company, stating that Shionogi demonstrated a distinct capability in achieving a careful balance between access and stewardship in its previously devised plans for cefiderocol. For example, Shionogi prioritises working closely with healthcare facilities and physicians to ensure appropriate use of its products. In the case of cefiderocol, the company conducted questionnaires to better understand how physicians intended to use the product to choose the most suitable physicians to partner with.

Bridging barriers through licencing agreements

While Shionogi can share the risks and costs of olorofim's development, its capabilities to bring the product to local LMIC markets is limited. Shionogi lacks a global footprint, and its manufacturing is based solely in Japan. As with its access strategy for cefiderocol (also see box-out above), Shionogi is exploring collaborations, including sub-licencing agreements, with generic medicine manufacturers to address these challenges. Specifically, the company aims to address the unmet need in countries, where the burden of fungal infections targeted by olorofim is high.

In addition, an early access programme is in place to provide patients with access to olorofim prior to market approval. Due to issues of high demand and stewardship concerns, the programme was temporarily halted in 2023, but it is now running again.

Associated risks of olorofim may limit markets where drug will be registered

Due to the associated risk of drug-induced liver injury, patients undergoing treatment with olorofim need to be closely monitored, which requires a suitable

healthcare infrastructure. As a result, the markets where F2G and Shionogi will seek registration are limited. To ensure the appropriate use of olorofim, F2G and Shionogi will introduce olorofim in secondary and tertiary healthcare facilities. This is likely to impact the accessibility of olorofim in LMICs, especially in hard-to-reach rural areas that may be far from national secondary or tertiary healthcare facilities. Furthermore, F2G will implement responsible promotion to encourage stewardship; specifically, the label of olorofim will indicate that it is intended only for patients with limited or no remaining treatment options.

60-day commitment from first sale is key to reaching LMICs

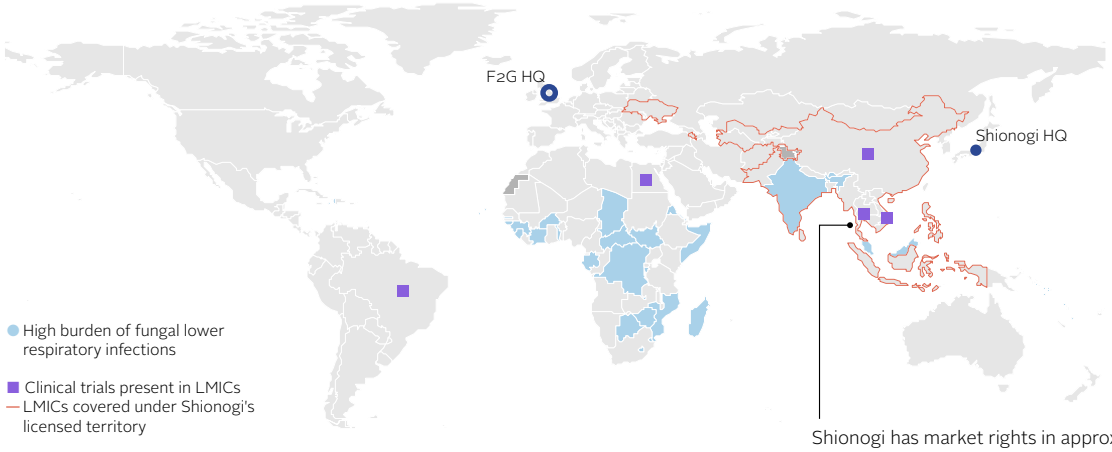
Partnering with Shionogi has spurred the development of olorofim, with both companies taking initial steps to identify barriers to access and stewardship. However, the lack of concrete access and stewardship planning during development is likely to delay access to olorofim for patients living in LMICs.

As yet, an access plan that prioritises populations and countries with high unmet medical needs and addresses patients' ability to pay is lacking. Therefore, it is unclear which LMICs will be prioritised for product registration after global launch. Although stewardship plans have not yet materialised, their importance played a crucial role in F2G's selection of Shionogi as a partner.

The commitment to develop a comprehensive access and stewardship plan within 60 days of olorofim's first sale will be key to reaching patients in LMICs. Given the potential licensing agreements with generic manufacturers; the careful considerations around stewardship; a refurbished early access programme; and Shionogi's expertise in Asian markets, there is potential to make this partnership for co-development an impactful one for patients in LMICs as well, but the uptake is anticipated to be significantly delayed.

FIGURE 9 **Respiratory infections caused by fungal pathogens costing lives in sub-Saharan Africa**

The map indicates the countries that have the highest number of deaths attributable to respiratory infections caused by fungal pathogens.* The high burden in sub-Saharan Africa underscores the need for access and stewardship planning for olorofim within this region.



*A threshold of 2.25 deaths per 100,000 people was used to determine countries with a high burden of lower respiratory infections and all related infections in the thorax caused by fungal pathogens. Please note that due to the scale of the map, some countries with a high burden of disease or resistance might not be visible.

Source: Burden of disease: IHME MICROBE database, Trial location: NIH Clinical Trials

ANALYSIS: WIDER R&D LANDSCAPE

Are funders promoting access and stewardship planning?

The majority of the projects analysed in the preceding case studies are being developed with the support of partner funding, including the Biomedical Advanced Research and Development Authority (BARDA), the Global Antibiotic Research & Development Partnership (GARDP), the National Institute of Allergy and Infectious Diseases (NIAID), the Innovative Health Initiative (IHI) and the Wellcome Trust. Public and private organisations such as these – as well as the AMR Action Fund, the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), and the Novo Repair Fund – are investing vast financial resources towards antimicrobial R&D.

By providing such 'push incentives' (see sidebar alongside) for drug discovery and product development, these players occupy a unique position in the antimicrobial R&D space, with the opportunity to set contractual provisions that foster and mandate access and stewardship plans.

Funders are uniquely placed to incentivise access and stewardship planning

Currently, CARB-X and the Wellcome Trust are the only key players for which clear access and stewardship planning requirements in contractual agreements with grantees are identified. However, GARDP typically develops and implements its own access and stewardship plans when partnering with companies. Furthermore, the Novo Repair Fund requires product developers to commit to developing such plans by the time projects enter late-stage clinical trials. While vaccines to prevent viral infections fall outside the scope of this report, the Coalition for Epidemic Preparedness Innovations (CEPI) embeds contractual provisions for equitable access into each of its vaccine development funding agreements.[62]

In the case of CARB-X, grantees are obliged to develop these plans when reaching pivotal clinical trials (see box-out below).

CARB-X requires development of access and stewardship plans for early-stage funding it provides

The Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) has clear access and stewardship planning funding requirements for its grantees. These grantees are required to develop an access and stewardship plan for low- and middle-income countries (LMICs) based on the Stewardship and Access Plan (SAP) Development Guide within 90 days their product entering Phase III trials (or Phase IIb trials, if they are intended as the pivotal trials to support registration).

If market approval is achieved, CARB-X publishes the developed access and stewardship plan on its website.[63] This accountability mechanism allows third parties, such as governments and civil society, to critically assess the plan and its implementation by the company. It must be noted that beyond the formal development of these plans, CARB-X does not evaluate the quality of these access and stewardship plans. However, CARB-X reports that its grantees are obliged to work with the Wellcome Trust, one of CARB-X's founding funders, to implement their plan.

Where companies do not live up to their contractual obligation to develop and implement an access and stewardship plan, the Wellcome Trust has the legal right to take the intellectual property for the purpose of making the product available in markets not prioritised by the company, and potentially license the product to enable generic access.

CARB-X's approach demonstrates that even if funding is only directed towards pre-clinical and early clinical development, access and stewardship requirements can still be contractually required if a project reaches pivotal clinical trials.

Antimicrobial R&D will need more than a push to catch up

Current push incentives from R&D funders are oftentimes geared towards small- and medium-sized enterprises (SMEs) that face 'valleys of death', where funding received during the earlier stages of R&D runs out. While this push funding is vital within the context of a very dry antimicrobial pipeline, it cannot serve as a replacement for the current lack of pharmaceutical companies' investment in antimicrobial development. While many pharmaceutical companies invest in the AMR Action Fund, for example, there is consensus that current push funding incentives are not sufficient to address the antimicrobial R&D gap. In the long term, push incentives need to be met with 'pull incentives', whereby successful antibiotic developers are ensured future revenues for their developed products.

The Wellcome Trust mainly provides indirect R&D funding through CARB-X, GARDP and the AMR Action Fund. It has previously made direct investments in companies, though these occurred prior to the release of the Stewardship and Access Plan (SAP) Guide in 2021 (also see p.15). In line with the Wellcome Trust's principles of honouring existing contracts, the publication of this guide did not lead to any retrofitting of these contracts to include access and stewardship planning provisions. After becoming a founding funder of CARB-X, the Wellcome Trust moved away from investing in companies directly and mandates access and stewardship planning through CARB-X. In addition, the Wellcome Trust incorporates access and stewardship requirements directly in its funding agreements with developers as part of open funding programmes. For instance, the Wellcome Trust established the Advance ID Clinical Research Network in Southeast Asia, where new funding is provided to support a clinical trial for an antibiotic.[64] As part of this funding agreement, access and stewardship planning will be required by the developer.

To increase access and guarantee stewardship, GARDP enters into collaborative agreements with antibiotic developers, particularly small- and medium-sized enterprises (SMEs), and provides expertise and financial support to help derisk drug development. While GARDP doesn't require portfolio companies to formally agree to developing access and stewardship plans, it prioritises access through these agreements whereby GARDP develops and implements the access and stewardship measures, in turn reducing the burden on SMEs.

In its operations, the AMR Action Fund sets itself apart from other funding organisations. Instead of providing non-dilutive funds, the AMR Action Fund operates as a private investing vehicle by making public health guided equity investments in SMEs. As such, the AMR Action Fund, which is mainly funded by industry, is the largest public-private partnership investing in SMEs that develop antimicrobial therapeutics. The AMR Action Fund clearly sets out access and appropriate use principles that should be agreed upon by its portfolio companies.[65] However, whether these principles are contractually binding or enforced is unclear.

Grants by US and EU lack provisions on access and stewardship

It is important to note that funders may have different reasons for the lack of access and stewardship requirements as part of funding provisions. For instance, NIAID, which is part of the National Institutes of Health (NIH), and BARDA, which is part of the Administration for Strategic Preparedness and Response, both receive appropriations from the US Congress. These appropriations mandate NIAID and BARDA to fund early-stage and late-stage R&D respectively (see Figure 10 on p.30). Requirements such as access and stewardship planning are established at the national and state level based on guidance from the US Centers for Disease Control (CDC) and state health authorities.[66] As no access and stewardship requirements are part of this mandate, BARDA does not enforce such planning in its funding requirements with grantees.

Similarly, funding by the European Union (EU) is primarily provided to target unmet medical needs of and ensure access to innovative medicines for European citizens. The funding process is organised via specific projects, such as 'COMBACTE-CARE' or the 'AMR Accelerator', under the 'Innovative Health Initiative' (former 'Innovative Medicines Initiative (IMI)). Despite the commitment by EU's Health Emergency Response Authority (HERA) to increase access to medicines in LMICs, specific access and stewardship requirements beyond the EU scope could not be identified.[67]

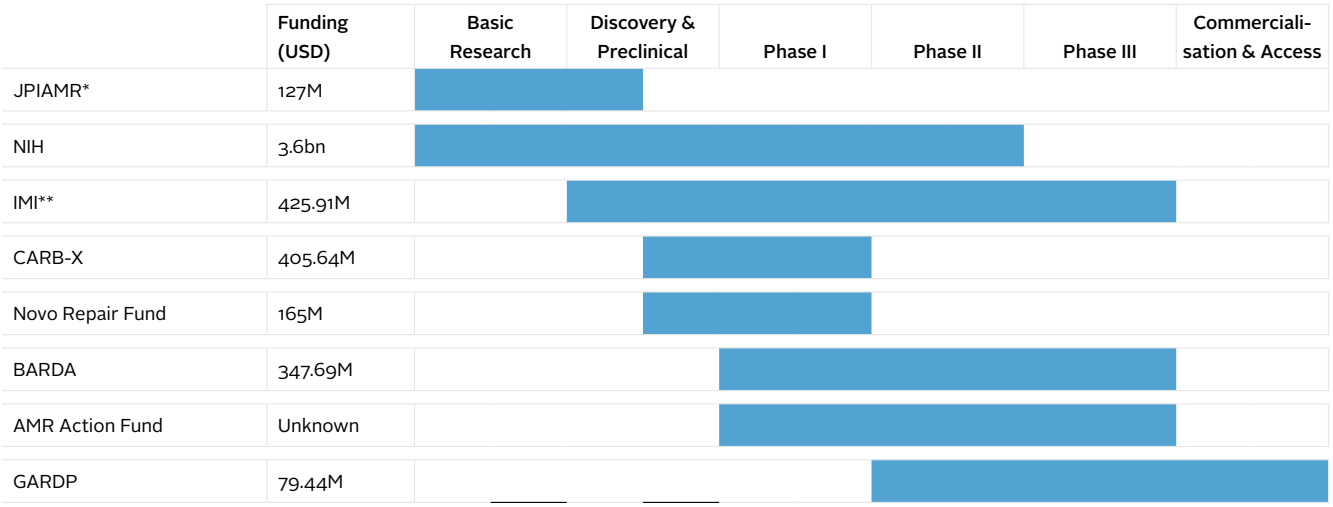
Fragmented funding requires transparency to help monitor access and stewardship planning

The various funders in the antimicrobial space tend to focus on specific phases of the R&D process, which means that funding is fragmented across the product development process (see Figure 10). As a result, the level of access and stewardship planning required by funders may vary, depending on the stage of development they are supporting. However, funders can still help guarantee access and stewardship planning, regardless of the phase that is being funded.

To ensure that qualitative access and stewardship planning will be implemented effectively throughout clinical development, funders can set provisions to be transparent on outcomes post funding. In addition, it is vital for funders themselves to transparently report on actions that have been taken. Currently, the lack of clarity in this regard makes it difficult for early-stage funders to follow up and ensure plans will be implemented; conversely, without clear information on what has been set out in the early stages, late-stage funders will find it difficult to build on what has already been done (or not). In addition, transparency on actions can offer learnings to funders who are still working to incorporate access and stewardship planning in contractual agreements. Importantly, overall transparency can help to level-set the funding landscape towards a more harmonised standard on access and stewardship planning. This will also make it easier for companies to navigate the funding landscape, as they will not have to adjust to various new funder requirements.

FIGURE 10 **Funders provide push incentives across all phases of development to refuel the antimicrobial pipeline**

This figure depicts some of the most prominent funding organisations in antimicrobial R&D.[74,75] As these organisations provide a vast number of resources to stimulate capacity building, therapeutics development, or basic research, they have the opportunity to link funding to access and stewardship provisions.



Data includes all reported AMR-related R&D funding between 2017 and 2023. As a closed-end fund, the budget of the Novo Repair Fund was set up in 2018 – however, funding is still ongoing.

*Will become part of EU One Health AMR Partnership in Q1 2025.

**Operates as IHI since November 2021.

KEY FINDINGS

Structured advance planning for access and stewardship has not become the norm yet

As has been identified in the Foundation's research through its AMR Programme, tackling the sheer scale and pace of drug resistance is a complex global health issue that will require action from pharmaceutical companies across several areas. But failure to provide appropriate access to and implement stewardship measures to safeguard the effectiveness of innovative antimicrobials anywhere will inevitably limit efforts to tackle resistance everywhere.

By acting now, companies can save lives and help address rising levels of AMR.

Gaps and opportunities: Which efforts can be scaled and what shortcomings need to be addressed?

Based on the analysis of the case studies in this report, the Foundation has identified that detailed access and stewardship planning during late-stage development of antibiotics and antifungals has not become standard yet. Four findings gleaned from the Foundation's assessment highlight examples of positive steps that are being taken, as well as gaps that need to be addressed. These insights can help to ensure that the much-needed antibiotics and antifungals in the pipeline reach the estimated 1.27 million people who die annually from drug resistant infections.

1. **Concrete plans for registration are lacking for almost all LMICs**
   Filing for registration is a vital first step towards introducing a medical product into a country, as successful registration means that a product is allowed to be imported and sold. However, for all five projects combined, concrete commitments for registration could only be identified for five low- and middle-income countries (LMICs) – China, India, Mexico, South Africa and Thailand. Most of these planned registrations are the result of post-trial commitments by developers to register in countries where clinical trials are being conducted. As a result, for 108 LMICs it is unclear whether any of the five projects in scope will be made available upon initial approval. Yet, it must be noted that the Global Antibiotic Research & Development Partnership (GARDP) plans to provide access to cefepime-taniborbactam (Venatorx) in 64 LMICs through export waivers and an international procurement agency.

2. **Affordability and stewardship in LMICs are largely overlooked during planning**
   Affordability and stewardship are challenging factors for companies to widen access to new antibiotics and antifungals in LMICs. With strict stewardship requirements but low profitability, new antibiotics and antifungals are not introduced at scale. While Pfizer applies specific pricing strategies for aztreonam-avibactam – and offers products in its portfolio at a not-for-profit basis through its 'Accord for a Healthier World' initiative – no concrete plans for making new products affordable to patients in any LMIC could be identified in the other four case studies in this report.

   In addition, besides large companies like GSK and Pfizer who have comprehensive surveillance programmes in place, detailed plans to ensure appropriate use – for example, by responsible promotion and ensuring companion diagnostics – were lacking across the board. Stewardship planning

through strategies like these not only helps with ensuring that patients receive the right treatment, but also serves companies by preserving the efficacy of their own products that are marketed.

3. **Paediatric trials prior to market approval are a hopeful sign for children**
   In 2019, 1 in 5 people who died from drug-resistant infections was a child under 5 years of age. However, market approval for paediatric use typically takes up to ten years longer than adult use, which is why it is crucial to consider paediatric populations during, and not after, drug development. Of the five companies featured in the case studies, four are conducting or initiating clinical trials involving children, including GSK, Pfizer, Innoviva, and Venatorx – with Innoviva and Venatorx doing so with support from the Global Antibiotic Research & Development Partnership (GARDP). This is especially notable for the projects by Venatorx and Pfizer, as both are listed on the World Health Organization Paediatric Drug Optimisation for Antibiotics (WHO PADO) list, which prioritises the antibiotics in development that are urgently needed for children. The efforts from these four companies to prioritise children early on are positive developments in closing the gap between adult and paediatric access and set an example of what can be done by other developers.

4. **Partnerships help scale efforts, but other tools to broaden access and stewardship plans are underutilised**
   Small and medium-sized enterprises (SMEs) rely heavily on partners to help commercialise products and drive global access. Not only are partnerships necessary for survival, but they are also used as a strategy to outsource the challenging task of providing access in LMICs. For example, F2G co-develops its antifungal project with Shionogi, who in turn receives licensing rights in the Asia Pacific region and Europe. Furthermore, organisations like GARDP – funded by governments and charitable funds – are increasingly taking on the task of access and stewardship planning for LMICs. Without constraints of commercial profitability requirements, GARDP can prioritise access to new antibiotics for those patients who need them the most. This is reflected in GARDP's partnerships for zoliflodacin (Innoviva) and cefepime-taniborbactam (Venatorx), with both case studies demonstrating great detail on country and population prioritisation, supply chain planning and the development of additional formulations.

   Aside from partnerships with GARDP, companies can set up their own plans based on the Stewardship and Access Plan (SAP) Development Guide in 2021. This Guide – developed by the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) in collaboration with key partners, including the Wellcome Trust and the Access to Medicine Foundation – supports companies in planning ahead for access and stewardship. However, while this Guide has been in existence for three years, the companies assessed in this report are underutilising the recommendations in this guide.

SPOTLIGHT

Without the resources and efforts of big pharma, innovation might never reach all eligible patients sustainably

Most large pharmaceutical companies have closed their doors on antibacterial and antifungal R&D and minimised their investments to acquire promising small- and medium-sized enterprises (SMEs). This has not only left a major gap in innovation, but also a major gap in delivering new products to patients.

While SMEs have become the powerhouses of developing innovative antibiotics and antifungals, these SMEs do not have the resources to commercialise new products and provide global access. Therefore, early development of innovative products by SMEs must go hand in hand with late-stage development and scaling of access in low- and middle-income countries (LMICs) by large pharmaceutical companies. These large multinational companies hold a vast array of expertise, capacity and financial resources that are needed to foster late-stage R&D commercialisation. However, without being acquired by these companies, SMEs are unable to tap into their much-needed resources. As a result, SMEs seek public funding and collaborations to survive and to outsource the responsibility of ensuring access in LMICs.

To address the gap in R&D left by industry, public and private funders are increasingly offering push and pull incentives. This funding is vital in stimulating antimicrobial R&D, however, linking it with access and stewardship provisions is not common practice. To bolster access in LMICs, partnerships like the Global Antibiotic Research & Development Partnership (GARDP) – funded by governments and charitable funds – have stepped in to alleviate the burden of access and stewardship planning for SMEs. Without constraints of commercial profitability requirements, GARDP can prioritise access to new antibiotics for those patients who need them the most. However, leaving patient access to innovative products in LMICs entirely in the hands of public and private funders is not a sustainable solution.

Large pharmaceutical companies need to re-enter the ring and make their unique expertise on access and commercialisation available. While there is a need for more push and pull incentives to revive the R&D pipeline and make innovation in the AMR space financially sustainable, these companies have a duty to commercialise innovative late-stage projects currently in the pipeline and provide access in LMICs.

By financially supporting the AMR Action Fund, many large pharmaceutical companies invest in the development of a few novel antibiotics, but this is not enough. Active engagement is critical – even if that is by actively supporting SMEs. Without active engagement from more pharmaceutical companies, there is a real risk that the world will be left without any antibiotics and antifungals that will be effective against drug-resistant infections. Not only will this put the lives of millions at risk, but it will have a direct impact on companies. Without effective antibiotics, many profitable products that are at the core of companies' business model – such as oncology drugs – will be threatened. Therefore, investing in R&D and providing access to new antibiotics and antifungals will not only help curb AMR, but it will also safeguard large pharmaceutical companies' business (also see 'Recommendations' in the next section of this report).

It is critical for companies to act now and make sure the few antimicrobials are made available to patients on the frontlines of drug resistance.

RECOMMENDATIONS

Prioritising access and stewardship: How to rethink and redesign R&D

Large pharmaceutical companies and small- and medium-sized enterprises

- Pursue access and stewardship planning for all late-stage clinical projects for antibiotics and antifungals, both innovative and adaptive.
- Increase the depth and breadth of access and stewardship plans. Utilise the Stewardship and Access Plan (SAP) Development Guide to guide the quality of developed plans

▶ **Access planning**

- Develop strategy to file for registration in LMICs. Be inclusive of countries, especially low-income countries, with particularly high burdens of disease and disproportionally affected populations, such as children, women and immuno-suppressed patients.
- Conduct clinical trials in low- and middle-income countries (LMICs). These trials must be followed by post-trial access commitments, such as filing for registration.
- Conduct paediatric clinical trials in a timely manner to develop and register formulations for children.
- Prioritise LMICs for access planning based on public health needs by engaging with stakeholders on the ground to better understand for which countries this could be a priority product.
- Set up early access programmes that allow patients with no or limited treatment options to access antibiotics and antifungals that are not registered yet.
- Establish pricing strategies that consider patients' ability to pay in LMIC settings.

▶ **Stewardship planning**

- Set up surveillance programmes for projects in the pipeline and publicly share this data, or support and engage with external surveillance programmes run by other organisations.
- Ensure companion diagnostics and susceptibility testing are available as soon as possible. For example, by collaborating with diagnostics companies.
- Commit to responsible promotion either by avoiding the use of sales agents for antibacterial and antifungal medicines, or by removing the financial incentive linked to sales volumes of these medicines.

Large research-based pharmaceutical companies

- Remain engaged in antibacterial and antifungal R&D and align R&D investments to address the most critical public health needs. R&D investments must target public health priorities and the global burden of disease, for example, by consulting the World Health Organization's (WHO's) Priority Pathogen lists for antibacterials and antifungals. Investing in R&D includes acquisitions of small- and medium-sized enterprises (SMEs) with promising pipeline candidates.
- Leverage local offices and regional hubs in LMICs to facilitate connections and partnerships for improved access and stewardship.
- Implement not-for-profit models in LMICs where products have low financial viability, with the necessary stewardship provisions to ensure safeguarding the long-term effectiveness of new products, and commit to measuring patient reach with a clear methodology.
- Support access and stewardship planning by SMEs either through licensing deals, co-development partnerships or acquisitions.

Small- and medium-sized enterprises	• Consider partnerships with large pharmaceutical companies and public partners for co-development, voluntary licensing agreements and access and stewardship planning in LMICs. • Prioritise partners with a strong presence and a proven track record of successfully bringing products to market in LMICs.
Public funders, including governments of high-income countries	• Mandate contractual provisions as part of push incentives that require access and stewardship planning from Phase II onwards. In addition, develop enforcement mechanisms that guarantee quality and implementation of the developed access and stewardship plans. Existing tools such as the SAP Development Guide can be leveraged by all funders to harmonise expectations from companies and limit fragmentation of funder requirements. • Enable direct communication and transparency about agreed-upon access and stewardship obligations between funders to ensure that commitments made in the past are upheld. • Foster a secure and sustainable market for antibiotics and antifungals and develop policies that encourage and incentivise companies to remain engaged in the R&D space. Push and pull incentives must be aligned with public health priorities identified by WHO while acknowledging country-by-country differences. • Support improved transparency and data to measure access in LMICs, such as the Access to Medicine Foundation.
Governments in low- and middle-income countries	• Support clinical trials by companies and reduce the time to issue marketing authorisation. • Set up or support surveillance systems to monitor resistance and the use of antibiotics and antifungals. Governments can help build an ecosystem that allows for accurate data collection, for example through implementation of electronic patient records. If there are financial barriers, explore options for investments, such as from the World Bank or high-income countries. • Invest and engage in regulatory harmonisation schemes, such as collaborative registration procedures or mutual recognition procedures, to accelerate registration filings by pharmaceutical companies. • Identify key priority products that are still in late-stage clinical development and signal the importance of these products internally to regulatory agencies and externally to companies and key partners, such as the Access to Medicine Foundation.
Public-private partnerships	• Support companies with limited resources and R&D projects that target priority pathogens to ensure novel interventions with low commercial viability reach the most affected patients. • Prioritise licensing agreements and/or commercial partnerships, particularly for countries or regions where there is no commercial interest to seek registration for a product.

LIST OF ABBREVIATIONS

3CGR Third-generation cephalosporin-resistant
A. fumigatus *Aspergillus fumigatus*
AMR Antimicrobial resistance
AmpR Ampicillin resistance
ATM-AVI Aztreonam-avibactam
BARDA Biomedical Advanced Research and Development Authority
BIO Biotechnology Innovation Organization
BL Beta-lactam
BLI Beta-lactamase inhibitor
BSI Blood stream infection
Campylobacter spp. *Campylobacter species*
CARB-X Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator =
CDC Centers for Disease Control
CIS Commonwealth of Independent States
CEPI Coalition for Epidemic Preparedness Innovations
cIAI Complicated intra-abdominal infection
ClaR Clarithromycin-resistant
CMC Chemistry, manufacturing, and controls
CR Carbapenem-resistant
CRAB Carbapenem-resistant *Acinetobacter baumannii*
CRE Carbapenem-resistant *Enterobacterales*
CRPA Carbapenem-resistant *Pseudomonas aeruginosa*
cUTI Complicated urinary tract infection
DHSC Department of Health and Social Care
E. coli *Escherichia coli*
E. faecium *Enterococcus faecium*
EMA European Medicines Agency
ESBL Extended spectrum beta-lactamase
EU European Union
FDA Food and Drug Administration
FQR Fluoroquinolone-resistant
GAMRIF Global AMR Innovation Fund
GARDP Global Antibiotic Research & Development Partnership
GDP Gross domestic product
GNI Gross national income
HABP Hospital-acquired bacterial pneumonia
HERA European Health Emergency Response Authority
HHS Department of Health and Human Services
IAI Intra-abdominal infection
ICU Intensive care unit
IHI Innovative Health Initiative
IHME Institute for Health Metrics and Evaluation
IMI Innovative Medicines Initiative
IV Intravenous
JPIAMR Joint Programming Inititaive on Antimicrobial Resistance
LMICs Low- and middle-income countries
LRBs Large research-based pharmaceutical companies
LRI Lower respiratory infection
LRI+ Lower respiratory infections and all related infections in the thorax
MBL Metallo beta-lactamase
MoA Mode of action
MR Methicillin-resistance
NDA New drug application

N. gonorrhoeae *Neisseria gonorrhoeae*
NIAID National Institute of Allergy and Infectious Disease
NIH National Institutes of Health
OGA Office of Global Affairs
P. aeruginosa *Pseudomonas aeruginosa*
PDUFA Prescription Drug User Fee Act
PNS Penicillin non-susceptible
R&D Research and development
Salmonella spp. *Salmonella species*
SAP Stewardship and Access Plan
S. aureus *Staphylococcus aureus*
Shigella spp. *Shigella species*
SME Small and medium sized enterprise
S. pneumoniae *Streptococcus pneumoniae*
SRHR Sexual and reproductive health and rights
SSA Sub-Saharan Africa
STI Sexually transmitted infection
UK United Kingdom
US United States
USD US dollar
US FDA US Food and Drug Administration
UTI Urinary tract infection
uUTI Uncomplicated urinary tract infection
VABP Ventilator-associated bacterial pneumonia
VR Vancomycin-resistance
WHO BPPL World Health Organization bacterial Priority Pathogen List
WHO FPPL World Health Organization fungal Priority Pathogen List
WHO PADO World Health Organization Pediatric Drug Optimization for Antibiotics
WHO World Health Organization

DEFINITIONS

Access plan
Plans to ensure that access needs in low- and middle-income countries are taken into consideration during the R&D stage. Access plans can be developed in-house or in collaboration. They can include commitments and strategies, as well as more concrete access provisions, such as specific measures developed in partnership with other organisations that can enforce accountability. Potential components of an access plan include registration commitments, equitable pricing strategies, sufficient supply commitments, and applying for World Health Organization prequalification. Access plans facilitate availability, affordability and supply for patients in countries within the scope of the Programme.

AMR surveillance
[Working definition, used for analysis]
The continuous and systematic collection, analysis and interpretation of antimicrobial infection and resistance-trend data needed for the planning, implementation, and evaluation of antimicrobial stewardship activities.

Antibacterial medicine
Antimicrobial medicine used to treat bacterial infections by directly targeting the bacteria that causes the infection or the disease process (as opposed to targeting the symptoms of the infection). Biocides are not considered antibacterial medicines. See also Antibiotics.

Antibiotics
Equivalent to Antibacterial medicine. The term "antibiotic" is often used inconsistently in literature to denote either a drug that targets any type of microorganism in the body or, alternatively, a drug that targets bacteria specifically.

Antifungal medicine
Antimicrobial medicine used to treat fungal infections by directly targeting the fungi that causes the infection (as opposed to targeting the symptoms of the infection or toxins produced by the pathogen).

Antimicrobial resistance (AMR)
Antimicrobial resistance is the ability of microbes such as bacteria, viruses, fungi and parasites (protozoa or helminths) to grow in the presence of an antimicrobial substance (e.g., a medicine) that would normally kill them or limit their growth. Resistance is a consequence of evolution via natural or artificial selection.

Antimicrobial stewardship
A systematic and comprehensive process that aims to ensure that all aspects of prescribing, (e.g., drug, dose, duration), dispensing, and the use of antimicrobial medicines are consistent with the available evidence on how to minimise the emergence of antimicrobial resistance.

Appropriate use of antimicrobials
The cost-effective use of antimicrobials, which maximises clinical therapeutic effect while minimising both drug-related toxicity and the development of antimicrobial resistance.[68]

Companion diagnostic
A companion diagnostic is a medical device, often an in vitro diagnostic (IVD), which provides information that is essential for the safe and effective use of a corresponding drug or biological product. If the diagnostic test is inaccurate, then the treatment decision based on that test may not be optimal.[69]

Cross-resistance
Cross-resistance refers to the resistance developed to a usually effective antimicrobial medicine through exposure to a similarly acting substance. Cross-resistance can occur among human antimicrobials and is also observed between human antimicrobials and products used in animal health or agriculture (e.g., pesticides, herbicides or fungicides).

Disability-Adjusted Life Year (DALY)
A measure of disease burden that combines disease-associated mortality and morbidity. It is the sum of the number of years of life lost (YLLs) and years lived with disability (YLDs). DALYs allow the comparison of disease burden across different populations and health conditions across time. One DALY equals one lost year of healthy life.

Early Access Programme
An Early Access Programme is a pathway allowing patients to access medicines that are yet unregistered in a country. These programmes typically include medicines for serious or life-threatening diseases when there are no other treatment options available, until marketing authorisation has been granted.

Equitable pricing strategy
A targeted pricing strategy which aims to improve access to medicine for those in need by considering the relevant payer's ability to pay, and by taking healthcare systems' needs and characteristics into account.

Gram-negative bacteria
Gram-negative bacteria are bacteria that do not retain the crystal violet stain used in the Gram staining method of bacterial differentiation due to their bacterial cell wall.

Innovative project
[Working definition, used for analysis]
A novel candidate meets at least one of the four criteria defined in WHO's report "2021 Antibacterial agents in clinical and preclinical development" (2022): (1) new chemical class; (2) new target; (3) new mode of action (MoA); (4) absence of cross-resistance.

Pooled procurement
A process through which a buyer pulls together demand to increase the total quantity of a specific product to include in a tender, in order to benefit from better procurement conditions and economies of scale.

Post-trial access
The continued provision of an investigational product or comparator to clinical trial participants following the end of the clinical trial in which they participated when continued treatment is beneficial.

Priority pathogen
[Working definition, used for analysis]
Priority pathogens are pathogens for which new medicines and vaccines are highly needed. Priority pathogens are informed by the bacterial and antifungal priority pathogens lists published by WHO and are based on unmet R&D needs and public health importance.

Product Development Partnership (PDP)
[Working definition, used for analysis]
Product Development Partnerships (PDPs) take the form of centralised non-profit organisations that facilitate financial risk-sharing across the public and private sectors by pooling and sharing resources, both tangible and intangible, for the development of medicines, vaccines, and other health tools.

Public-private partnership
A partnership between one or more public organisation(s) and a private sector company or companies for providing a public asset or service, in which the private party bears significant risk and management responsibility, and remuneration is linked to performance. The Programme also considers a partnership between a non-profit organisation and the private sector to be a PPP.

Pull incentive
Pull incentives, in the form of extended exclusivity periods, higher reimbursement or market entry rewards, reward companies for bringing new drugs to the market through lowering the uncertainty for return on investment.

Push incentive
Push incentives, in the form of grants, partnerships or tax credits, are employed to lower the cost of and de-risk research and development of a new medicine.

Small- and medium-sized enterprise
Enterprises can be classified in different categories according to their size; for this purpose, different criteria may be used, but the most common is number of people employed. Small and medium-sized enterprises (SMEs) employ fewer than 250 people and can be subdivided into micro enterprises (fewer than 10 employees), small enterprises (10 to 49 employees), medium-sized enterprises (50 to 249 employees).[70]

Stewardship plan
[Working definition, used for analysis]
A stewardship plan is a plan set up to ensure that AMR-relevant public health needs are taken into consideration during R&D. These plans may be developed in-house or through collaborations and include commitments, strategies, concrete provisions, and other agreed-upon measures (typically developed in partnership) to enforce accountability. Stewardship plans facilitate the appropriate use of antimicrobial medicines and reduce the emergence of resistance. Examples include (but are not limited to) appropriate promotional practices and conducting surveillance studies.

Voluntary licensing
[Working definition, used for analysis]
A voluntary license is an authorization given by the patent holder to a generic company, allowing it to produce the patented medicine or vaccine, often at a lower cost. The license usually sets quality requirements and defines the countries in which the licensee can sell the product.[71]

Vulnerable populations
People at greater risk of facing barriers to accessing medicines due to social, economic and/or health considerations.

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