Antimicrobial Resistance Benchmark 2020

METHODOLOGY 2019

access to medicine FOUNDATION

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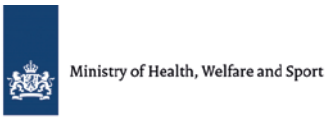

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ACCESS TO MEDICINE FOUNDATION

The Access to Medicine Foundation is an independent non-profit organisation based in the Netherlands. It aims to advance access to medicine in low- and middle-income countries by stimulating and guiding the pharmaceutical industry to play a greater role in improving access.

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METHODOLOGY REPORT 2019

ACCESS TO MEDICINE FOUNDATION

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Table of contents

The blueprint towards progress on AMR

Modern medicine depends on our ability to control and cure infections. The role for pharmaceutical companies in this is clear: develop life-saving new products, produce quality antimicrobials, take responsibility for manufacturing waste and appropriately market antimicrobial medicines.

This report sets out the path ahead to measure pharmaceutical companies' responses to the growing threat from antimicrobial resistance (AMR). It is the latest framework for action from the Access to Medicine Foundation, and provides a tool for guiding and incentivising pharmaceutical companies to limit AMR.

AMR has topped global political agendas since at least 2016. Since then, international agencies, governments and policy shapers have swung into action. Global AMR strategies are now being implemented. Pharmaceutical companies have also committed to limiting AMR.

Going forward, the recent recommendations from the UN Interagency Coordination Group (IACG) on AMR will catalyse further progress. Our shared aim is to replace medicines that are losing effectiveness, while conserving the ones that still work through good stewardship, and promoting vaccines.

Perhaps the toughest challenge is to secure sustainable supply and responsible access to quality antimicrobials for the millions of people who still have no access today – without encouraging overuse and misuse.

The backdrop is complex. Today's markets for antibiotics, antifungals and vaccines are riskier and less profitable than other therapeutic areas. Many critical medicines are no longer being produced, causing shortages in mature and developing markets alike. As vaccines are increasingly politicised, it becomes harder to ensure adequate coverage and protection.

In 2018, the first AMR Benchmark independently mapped companies' actions on AMR. In 2020, the second edition of the Benchmark will track their progress to date. There's still much work to do in combating AMR. By tracking progress and sharing best practice, we reveal the blueprint for achieving the global goals on AMR.

Jayasree K. Iyer
Executive Director
Access to Medicine Foundation

Executive summary

This report sets out the methodology for the 2020 Antimicrobial Resistance Benchmark. It is an updated framework for tracking how a cross-section of the pharmaceutical industry is responding to antimicrobial resistance (AMR). In 2019, the Access to Medicine Foundation will use it to benchmark 30 companies against society's expectations of where they can and should be making progress.

Antimicrobials are essential life-saving medicines that have revolutionised medical care. Yet, most will eventually become obsolete as pathogens develop resistance, making it increasingly difficult to treat infections. AMR can only be tackled through joint action, with the engagement of international agencies, governments, health workers, farmers, veterinarians, the general public and the pharmaceutical industry. A range of advocacy- and policy-oriented initiatives have succeeded in driving AMR up the political agenda. The most recent milestone is the inclusion of AMR in the 2017 G20 Leader's Declaration.

The first AMR Benchmark was published in 2018, as a tool for guiding and incentivising pharmaceutical companies to do more to limit AMR. Published every two years, the Benchmark evaluates the largest players in the global antibacterials market and companies with promising clinical-stage pipelines, to show where progress is being made and where critical action is still required.

THE METHODOLOGY REVIEW

The methodology for the 2020 AMR Benchmark has been updated through a consensus-building and review process, which confirmed the global health priorities regarding AMR and pharmaceutical companies' role in slowing its growth.

The review began with a fine-grained evaluation of the indicators and data sets for the 2018 AMR Benchmark, checking the robustness, relevance and capacity for trend analysis of each metric in turn. Throughout this process, the team discussed aspects of the methodology with experts from multilateral organisations, governments, academic research institutions, non-governmental organisations (NGOs), policy research centres and pharmaceutical companies. Strategic guidance was provided by the Foundation's Expert Committee (EC), an independent body of experts from, among others, the World Health Organization (WHO), governments, NGOs, patient organisations, the industry, academia and investors.

ANALYSIS SCOPES IN 2020

The 2020 AMR Benchmark will measure 30 pharmaceutical companies, representing a cross-section of the pharmaceutical industry active in antibacterials and antifungals. This includes eight companies that are newly in scope this cycle. Selection criteria included the volume and value of global antibacterials sales, and the maturity and novelty of clinical-stage R&D projects targeting high-risk pathogens for AMR. Three types of companies are in scope: large R&D-based pharmaceutical companies, generic medicine manufacturers and clinical-stage biopharmaceutical companies, referred to as small and medium-sized enterprises, or SMEs.

Companies are assessed depending on their focus and business model – each type of company has a different but necessary role to play in curbing AMR. For instance, generic medicine manufacturers are not evaluated in R&D metrics, as they are not typically active in R&D; SMEs are only evaluated in R&D, as they generally do not yet have products on the market (see figure 1).

The 2020 AMR Benchmark will assess companies' activities worldwide, except when looking at issues relating to access to antibacterials and antifungals. Access metrics will capture companies' activities in 102 mainly low- and middle-income countries where people have a particularly acute need for greater access. These countries were identified using criteria such as gross national income, the scale of inequality and infectious disease burden. The 2020 AMR Benchmark will focus on companies' actions to limit resistance in bacteria and fungi, particularly priority pathogens.

Analysis scopes for the 2020 AMR Benchmark

Table 1

Company scope	30 companies
	8 large research-based pharmaceutical companies
	9 generic medicine manufacturers
	13 small and medium-sized enterprises (SMEs)
Disease scope	Bacterial and fungal infections
Product scope	Antibacterial and antifungal medicines and vaccines
Geographic scope	Global, with access indicators focusing on 102 countries where greater access is needed

RESEARCH AREAS IN 2020

The Benchmark uses a framework of 19 indicators organised into three Research Areas. These correspond to pharmaceutical companies' core responsibilities for limiting AMR: developing new medicines to replace ones that no longer work, and finding new ways to ensure antibiotics are produced and promoted responsibly, i.e., through 'stewardship'.

A Research & Development

This area will capture companies' R&D activities to develop new medicines and vaccines targeting pathogens posing the greatest threat to human health. It will also highlight where gaps remain, and assess how companies plan to ensure new products are swiftly accessible for people in need.

B Responsible Manufacturing

This area will assess strategies for limiting the impact of antibiotic manufacturing on resistance. It will evaluate how thorough and transparent companies' environmental risk-management strategies are and how they apply to suppliers.

C Appropriate Access & Stewardship

This Research Area will look at how companies aim to responsibly increase access to antibacterial and antifungal medicines and vaccines while also limiting their overuse and misuse. Issues of both access and stewardship are closely interlinked as the need to enhance access where necessary must be balanced with that of ensuring optimal and appropriate use.

KEY CHANGES

The methodology review led to a number of refinements for the 2020 AMR Benchmark. Key changes are:

2020 focus will be on bacterial and fungal infections

The 2020 AMR Benchmark will zero in on bacterial and fungal infections, particularly those identified as particular threats due to resistance. This is where pharmaceutical companies have the most urgent role to play in addressing AMR. They correspond to the largest need for antimicrobial R&D and strong stewardship policies.

Eight companies are newly in scope

To track key companies with important antibacterial and antifungal assets, and considering the most recent market intelligence data, eight companies are newly in scope for the 2020 AMR Benchmark.

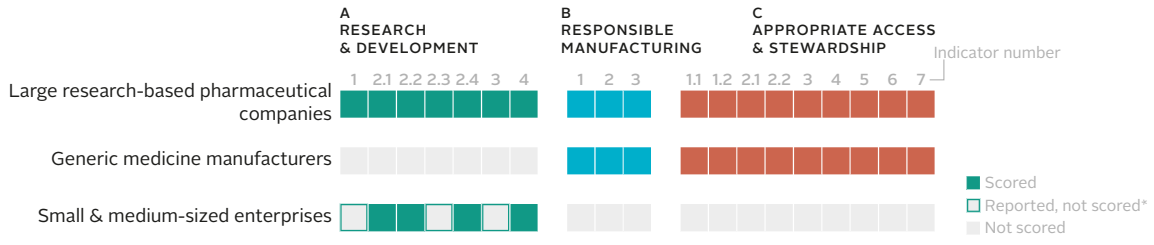
Access metrics will be tailored to products' patent status

When assessing registration and access strategies, the Benchmark will look for different behaviours depending on whether products are still on-patent or are now available as off-patent or generic products. The access issues that affect on-patent and off-patent/generic products differ significantly, and the 2020 AMR Benchmark will examine and report on how companies respond to these nuances.

Analytical Framework for the 2020 AMR Benchmark

The AMR Benchmark analyses three groups of companies using an analytical framework of three Research Areas and 19 indicators. Whether a company is scored in a Research Area depends on its pipeline and portfolio.

Figure 1



*SMEs will be scored in four of the Research & Development indicators. The Benchmark will report on, but not score, their activities in the remaining three R&D indicators

INTRODUCTION: TOWARD A 2ND AMR BENCHMARK

Where is action by pharmaceutical companies most critical in curbing AMR?

Antimicrobial medicines are essential life-saving medicines that have revolutionised medical care as we know it today – particularly antibacterials, commonly known as antibiotics. However, most bacteria and fungi, among other pathogens, develop resistance to medicines, hampering the treatment of infections. Eventually, most pathogens will become resistant to antimicrobials, making it extremely difficult and, in many cases, impossible to treat infections. This scenario is all the more worrying considering that aging populations and climate change are expected to further drive up the burden of infectious diseases in the future.

Antimicrobial resistance (AMR) is now widely recognised as having a significant impact on human health and the global economy. It has been on the agenda of the G20 and the United Nations General Assembly since 2016. A range of advocacy- and policy-oriented organisations and initiatives have been prominent in driving AMR up the political agenda, including the Alliance for the Prudent Use of Antibiotics (APUA), Doctors without Borders (MSF), the Global Antibiotic Resistance Partnership (GARP), ReAct and the World Alliance Against Antibiotic Resistance (WAAR), as has the Ministerial Alliance of Champions against AMR, which includes 14 countries. The most recent political milestone is the inclusion of AMR in the 2017 G20 Leader's Declaration, in which the G20 Heads of State and global leaders made a historic commitment to combatting AMR. The Declaration acknowledges that AMR can only be tackled by taking shared responsibility, including by international agencies, governments, the pharmaceutical industry, health workers, farmers, veterinarians and the general public.

To follow up on these political commitments, global AMR strategies are now being developed by international agencies, such as the World Health Organization (WHO), the UN Interagency Coordination Group on Antimicrobial Resistance and others, to research and develop new antimicrobials to replace those that are losing effectiveness, and to conserve those that still work through stewardship. Global AMR strategies must address access and stewardship issues in tandem. People living in less developed and resource-limited settings are on the frontlines for AMR – they generally face higher rates of resistance and infectious diseases. They are more likely to receive poor healthcare advice and often struggle to access appropriate antimicrobials when they need them, which can drive up rates of resistance. Efforts to increase access must include measures to limit resistance, while efforts to curb resistance must also include measures to enable appropriate access. The pharmaceutical industry has a key role to play in these different areas.

AMR threatens all countries

In recent decades, AMR has become widespread, irrespective of national income levels. In Europe, drug-resistant bacteria are responsible for more than 670,000 infections and 33,000 deaths annually, costing EUR 1 billion in annual healthcare expenditure.[1] Each year in the US, at least 2 million people get an antibacterial-resistant infection leading to at least 23,000 deaths.[2] This costs over USD 20 billion in direct healthcare costs and as much as USD 35 billion in lost productivity.[2,3] There is less data available generally on AMR in low- and middle-income countries (LMICs), due to, for example, the absence of local disease surveillance systems. Nevertheless, cost estimates of AMR for Thailand, which do exist, can be assumed to apply to many LMICs: the total economic cost of AMR due to five key pathogens in Thailand is estimated at USD 0.5 billion.[4]

To follow up on these political commitments, global AMR strategies are now being developed by international agen Local disease surveillance systems are critical for monitoring and preventing the rise and spread of diseases. For instance, information on antibacterial consumption, resistance levels and transmission patterns is still scarce or completely absent in many countries. Nevertheless, we know that mortality rates due to bacterial infections, such as untreated pneumonia and sepsis/meningitis, continue to be a public health problem in LMICs due to poor and/or limited access to relevant medicines, especially in children under five years of age.[5] To address gaps in surveillance, WHO and the Wellcome Trust are now supporting programmes that aim to advance global surveillance, including the Global Antimicrobial Resistance Surveillance System (GLASS) and the AMR Register.

Multiple factors influence AMR

AMR affects human health when infections become difficult to treat or life-threatening, and the appropriate medicines either do not exist, are unavailable, are of poor quality or come at a prohibitively high cost to individuals and society.

The exact impact of AMR on people and their communities depends on an interplay of factors including the distribution of pathogens such as bacteria and fungi, the prevalence of resistance to each and the availability of economic and healthcare delivery resources.

Weaknesses in healthcare delivery systems can limit appropriate access to antimicrobial medicines while also promoting their overuse. The issues of limited access and overuse are closely interlinked. Measures to increase access can lead to overuse, which leads in turn to greater resistance. As resistance increases, demand for second- and third-line treatments also increases. These products are often more expensive than first-line treatments, and thus harder to access. The need for new strategies and programmes to appropriately increase access to antimicrobial medicines remains particularly acute in LMICs, where healthcare delivery systems are generally weaker.[6]

Weaknesses in regulatory oversight can also promote overuse. They can lead to easy over-the-counter access to antimicrobial medicines and to the widespread availability of poor-quality antimicrobials with subtherapeutic levels of the active ingredient. Over-the-counter access encourages self-diagnosis and self-medication, leading to overuse. Exposure to subtherapeutic levels of an active ingredient can promote the development of resistant bacterial strains and increased virulence, which leads to the threat of deadlier infections.[7]

Globally, the burden of non-communicable diseases (NCDs) is increasing, including for cardiovascular disease and cancer. At the same time, the infections that now persist in higher-income countries tend to occur among sicker and often older patients in challenging settings such as hospital intensive care units and nursing homes. The resistant pathogens that emerge in such settings are not as common as the underlying conditions and invasive procedures that set the stage for their presence, yet the consequences of such infections for those with otherwise treatable conditions are life-threatening. Unless addressed early, the probability of a dramatic increase in high-risk infections in aging populations is substantial.

Growing but varied demand

The antibacterial market is expected to grow to USD 55.8 billion by 2023 (up from USD 38.3 billion in 2018).[8] This is in step with the growing demand for generic antibacterials from emerging markets. Human consumption of antibacterials is growing primarily in LMICs (e.g., China and India) where antibacterials are often accessed over-the-counter rather than by prescription. The growing demand coupled with poor surveillance and stewardship is likely to drive the emergence of resistant strains.

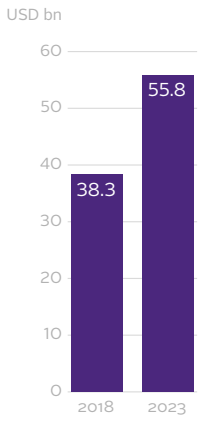
The majority of antibacterials are generic; only a small number remain on patent, with small profit margins. In general, new antibacterials are developed by either large research-based pharmaceutical companies or smaller biotechnology companies. Some larger research-based pharmaceutical companies have generic medicine divisions while some generic medicine manufacturers also invest in R&D.

Need for new products, low market promise

Appropriate access to antimicrobials is needed more urgently than ever by communities around the world, and the pharmaceutical industry has a critical role to play here. There is an evolutionary arms race occurring between pathogens and the medicines we use against them. This means novel products must be developed at at least the same rate as the existing ones are becoming obsolete due to resistance. New antibacterials in particular are urgently needed. Yet, antibacterials offer low profit margins,

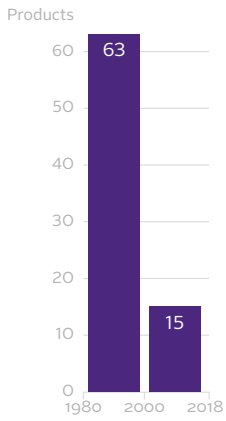
Projected growth in antibacterial market

Figure 2



New antibiotics reaching the market

Figure 3



their R&D is risky and expensive and growth in demand comes mainly from the poorest. Plus, new antibacterials must be used conservatively, as part of stewardship strategies, in order to limit resistance. This makes high-volume, high-return markets unlikely to develop. These factors have contributed to several companies, including large research-based pharmaceutical companies and smaller companies, leaving this market since 2000, halting their production and engagement in R&D.

The result is a drying up of the global antibacterial pipeline; only 15 new antibacterials have been approved since 2000, compared to 63 that were put to clinical use between 1980 and 2000.[9] Only 16 new antibacterial candidates targeting priority pathogens (those that pose the highest public health risk from AMR) are now in development.[10] Nevertheless, a core group of companies remain committed with dedicated antimicrobial R&D divisions, and a growing number of smaller biopharmaceutical companies demonstrate a strong focus on antimicrobial R&D.

Incentives for antimicrobial R&D

To incentivise pharmaceutical companies to invest in R&D for new antimicrobial medicines and vaccines, the global AMR community established "push" incentives that share R&D costs between partners to reduce the costs of necessary inputs for developers. These push incentives include research grants (e.g., from the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB X), the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR), and the AMR Accelerator Programme), as well as tax incentives, public-private partnerships (such as GARDP) and data-sharing initiatives.

On its own, push funding is not enough to create a functioning antimicrobials market, particularly for antibacterials.[10] The call for "pull' funding has become louder in recent years. Pull mechanisms guarantee or increase the revenue generated by a new antibacterial either by: 1) accelerating the regulatory pathway; 2) extending market exclusivity; or 3) offering premium pricing. For instance, the United States' Generating Antibiotic Incentives Now (GAIN) Act grants an additional five years of market exclusivity to companies developing antibacterials that target a selected group of qualifying pathogens. Many different ideas for pull mechanisms have recently been discussed in various fora around the world and consensus is emerging that a mix of incentives could provide a sustainable long-term outcome. To demonstrate the viability of the approach, governments and pharmaceutical companies now need to collaborate on designing concrete pull incentives.

Multiplayer solution

Ultimately, novel and existing antimicrobial medicines need to be affordably priced and prudently used. The challenge will be to ensure affordable, sufficient and appropriate access to these medicines while also advancing antimicrobial stewardship – and all within a viable business model.[11] Successfully limiting AMR requires a consolidated, concerted effort by multiple stakeholders, including governments, pharmaceutical companies, international health organisations and academic institutions, to name a few. AMR is a public health issue that impacts not only human health, but animal health and the agricultural industry as well. Addressing AMR requires a "One Health" approach that stimulates increased access and affordability and ensures stewardship to limit overuse, as well as innovative R&D in next generation medicines and a higher level of environmental care in the management of antibacterial manufacturing and discharge.

Pharmaceutical companies are critical players in the innovation of new and improved medicines and vaccines, in the safe manufacturing of high-quality products and in ensuring appropriate access to and stewardship of their products. The role they play in these different areas can have a profound effect on the usage of antimicrobials and, ultimately, on resistance.

AMR BENCHMARK DEEPENS PHARMACEUTICAL INDUSTRY ENGAGEMENT IN AMR

The goal of the Antimicrobial Resistance (AMR) Benchmark is to guide and incentivise pharmaceutical companies to limit AMR. It is published every two years and tracks how a cross-section of the industry is responding to AMR by benchmarking them against the consensus view on where they can and should be making progress.

Identifying the consensus view

Before each new iteration of the Benchmark, the Foundation conducts a methodology review to refine the scopes and analytical framework that form the basis of this research. The Foundation conducts this review following its proven process for building consensus on the role of pharmaceutical companies in tackling global health priorities. The review draws on input and feedback from a variety of stakeholders, including governments, non-governmental organisations (NGOs), academia and research organisations, pharmaceutical companies and industry associations, investors, product development partnerships (PDPs) and relevant international organisations. The methodology is finalised in consultation with global experts on AMR. This report describes the 2019 methodology review and its outcomes.

The first AMR Benchmark report was published in January 2018. It was the first independent assessment of pharmaceutical company action on AMR. The Benchmark gives companies, governments, investors, NGOs and others a tool for deepening industry engagement in global efforts to curb AMR. The Benchmark metrics and analyses highlight where good practice and progress are expected and can be expanded upon, and where companies and other stakeholders can take action together, while pointing towards where new ideas are needed.

The second Benchmark report will be published early in 2020, and will provide an updated, refined map of how 30 pharmaceutical companies are responding to the global threat of AMR in three key areas: R&D, responsible manufacturing, and appropriate access and stewardship.

REFERENCES

1 Cassini A, Högberg LD, Plachouras D, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis. 2018;19(1):56-66. doi:10.1016/S1473-3099(18)30605-4

2 U.S. Centers for Disease Control and Prevention (CDC). (April, 2013.) Antibiotic resistance threats in the United States, 2013. https://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf

3 Prestinaci F, Pezzotti P, Pantosti A. Antimicrobial resistance: a global multifaceted phenomenon. Pathog Glob Health. 2015;109(7):309-318. doi:10.1179/2047773215Y.0000000030

4 Shrestha P, Cooper BS, Coast J, et al. Enumerating the economic cost of antimicrobial resistance per antibiotic consumed to inform the evaluation of interventions affecting their use. Antimicrob Resist Infect Control. 2018;7(1). doi:10.1186/s13756-018-0384-3

5 Liu L, Oza S, Hogan D, et al. Global, regional, and national causes of under-5 mortality in 2000–15: an updated systematic analysis with implications for the Sustainable Development Goals. Lancet. 2016;388(10063):3027-3035. doi:10.1016/S0140-6736(16)31593-8

6 Laxminarayan R, Matsoso P, Pant S, et al. Access to effective antimicrobials: A worldwide challenge. Lancet. 2016;387(10014):168-175. doi:10.1016/S0140-6736(15)00474-2

7 Andersson DI, Hughes D. Microbiological effects of sublethal levels of antibiotics. Nat Rev Microbiol. 2014;12(7):465-478. doi:10.1038/nrmicro3270

8 BCC Research Reference Staff. Antibiotics: Global Markets to 2023.; 2018. https://cdn2.hubspot.net/hubfs/308401/PHM Report Overviews/PHM209A Report Overview.pdf. Accessed January 2, 2019.

9 Tomasi F. Less of the Same: Rebooting the antibiotic pipeline. Science in the News - Harvard Medical School. http://sitn.hms.harvard.edu/flash/2018/less-rebooting-antibiotic-pipeline/. Published 2017. Accessed January 2, 2019.

10 (WEF) World Economic Forum. Antimicrobial Resistance Tackling the Gap in R&D Resources with Pull Incentives In collaboration with Wellcome. World Econ Forum. 2018. http://www3.weforum.org/docs/Antimicrobial_Resistance_pagers_2018.pdf. Accessed January 2, 2019.

11 Theuretzbacher U, Årdal C, Harbarth S. Linking sustainable use policies to novel economic incentives to stimulate antibiotic research and development. Infect Dis Rep. 2017;9(1):28-31. doi:10.4081/idr.2017.6836

REVIEWING THE METHODOLOGY

How the Benchmark defines what pharmaceutical companies can do to curb AMR

The Antimicrobial Resistance (AMR) Benchmark is an analytical tool for comparing how pharmaceutical companies are ensuring appropriate access and to antimicrobials while curbing the rise of AMR. It is developed independently by the Access to Medicine Foundation and translates the consensus view on the role of pharmaceutical companies in tackling AMR into a set of ambitious yet achievable expectations for action.

Developing the framework for the 2020 AMR Benchmark began with a targeted review of the Benchmark methodology. The aim of the review is to confirm the global health priorities regarding AMR and to define pharmaceutical companies' role in halting its rise. The review draws on the Foundation's experience in building consensus on where pharmaceutical companies can take action, before translating it into robust metrics. The Foundation uses the methodology review to reaffirm the robustness of the Benchmark analysis and maintain its capacity for trend analysis between reports.

The primary principles of the methodology review are: (1) that all metrics are robust, and data can efficiently and feasibly be collected; (2) that the Benchmark is responsive to changing access and AMR needs; and (3) that all metrics are relevant to the appropriate role of the different types of pharmaceutical companies in tackling AMR.

Internal and external reviews

The process for the methodology review includes a series of internal checks on indicators, data sets and analytical approaches. This is followed by an external review during which the consensus view is sought between a range of expert stakeholders on specific AMR topics and the role for pharmaceutical companies, as well as on the analytical scopes.

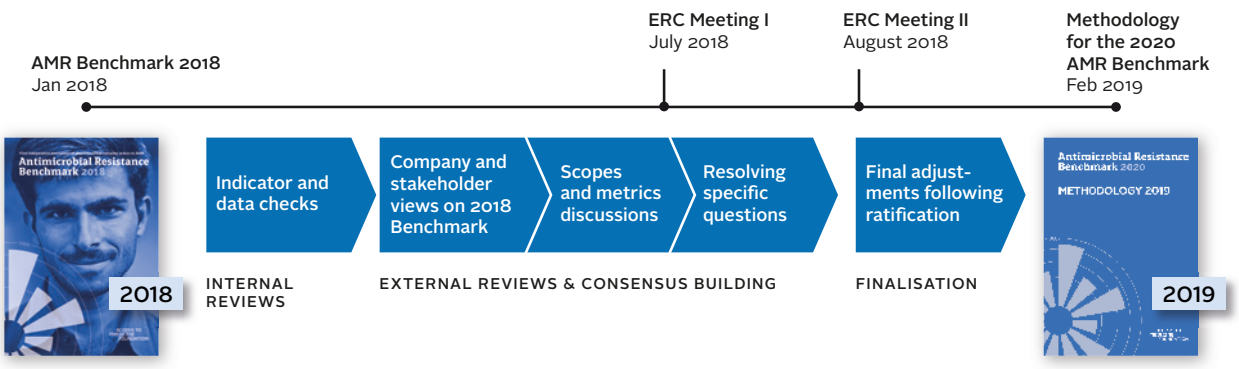
Internal reviews of indicators and data

The Foundation's research team reviewed each of the indicators of the 2018 AMR Benchmark for robustness, response quality and the potential for companies to improve performance through a series of quantitative and qualitative analyses:

- Distribution analysis: Assessing the distribution of scores per indicator to check the spread of company behaviour in the 2018 AMR Benchmark. Large clusters of low scores indicate the extent of room for improvement in general, but may mask differences between better and worse performances.
- Qualitative indicator review: A battery of qualitative assessments of each indicator, including clarity of expectations and roles for companies, relevance to AMR, potential for longitudinal comparisons and the 'change-making' potential of each indicator.

Methodology Review for the 2020 Antimicrobial Resistance Benchmark

Figure 4



External review and consensus building

Aspects of the methodology were discussed and evaluated with a range of international organisations, governments, NGOs, leading research centres and other relevant groups and initiatives addressing AMR. The research team gathered feedback from the companies evaluated in the 2018 Benchmark, as well as those from industry organisations and alliances such as the AMR Industry Alliance, the Biotech companies in Europe combating AntiMicrobial Resistance (BEAM) Alliance, Biotechnology Innovation Organization (BIO) and the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA). The research team also used the views gathered from a dedicated discussion at the World Health Organization (WHO) headquarters on the methodology for the 2020 AMR Benchmark. The team used the feedback and insights gathered from this process to inform its proposals for modifying the methodology.

The Expert Committee

These proposals formed the basis of discussion at the Expert Committee (EC) meeting. The EC is made up of ten independent experts, including from the WHO, top-level academic centres, governments in low- and middle-income countries, as well as investors and pharmaceutical industry representatives. The EC's recommendations and strategic guidance helped to identify ways forward, especially in areas where consensus was difficult to reach on the exact role of the industry and what good practice would look like.

The research team adjusted the proposed methodology following the recommendations from the EC. The EC then ratified the refined framework, resulting in the methodology for the 2020 AMR Benchmark.

The Expert Committee members

Hans Hogerzeil (Chair)	University of Groningen
Gregory Frank	BIO
Nina Grundmann	IFPMA
Magdalena Kettis	Nordea
Joakim Larsson	University of Gothenburg
Marc Mendelson	University of Cape Town
Margareth Ndomondo-Sigonda	African Union-NEPAD Planning & Coordinating Agency
Katarina Nedog	Medicines for Europe
Sarah Paulin	WHO (observer)
Andrew Singer	NERC Centre for Ecology & Hydrology

OUTCOME: REFINED SCOPES AND INDICATOR SET

Through its year-long methodology review, the Foundation has now finalised the methodology for the next AMR Benchmark. The Foundation will use this methodology to evaluate 30 pharmaceutical companies selected based on either the volume and value of their global antibacterial sales or on their clinical pipelines targeting priority pathogens (as identified by the Centers for Disease Control and Prevention (CDC) and WHO. The 30 companies will be assessed using 19 indicators across three Research Areas, in relation to bacteria and fungi. Their actions will be assessed globally in most areas, with indicators relating to access looking at a narrower set of 102 countries where better access is most needed.

The three Research Areas

A RESEARCH & DEVELOPMENT

This Research Area maps companies' R&D activities that target priority bacterial and fungal pathogens posing significant threats due to AMR.

B RESPONSIBLE MANUFACTURING

This Research Area compares companies' strategies for limiting the environmental impact of antibacterial manufacturing on resistance.

C APPROPRIATE ACCESS & STEWARDSHIP

This Research Area assesses companies' access strategies for antibacterial and antifungal medicines and vaccines for 102 countries where greater access is most needed, alongside their global stewardship initiatives.

For references, see appendices.

REVIEWING THE METHODOLOGY

Key decisions and discussions

Discussions held during the methodology review covered a wide range of areas and were rich in detail and context. In many cases, there was alignment on the behaviours that the 2020 AMR Benchmark should measure and how. In others, it was difficult to find consensus. In these cases, the Benchmark team, with the Expert Committee, identified workable ways forward, balancing the evidence and viewpoints gathered. This section highlights discussions where the appropriate decision was contested, or where discussions led to new areas of measurement.

In this section:

▶DISEASE SCOPE

Should the AMR Benchmark cover all infectious diseases, or focus on a subset of diseases and pathogens?

Context

The 2018 AMR Benchmark provided a baseline analysis of company action against AMR – the disease scope was deliberately broad, with all infectious diseases in scope, in order to capture the full range of companies' policies and practices. This included all bacterial (including tuberculosis [TB]) and fungal infections, as well as HIV/AIDS and malaria, which have been defined by WHO as AMR priority areas. Yet, these diseases and pathogens differ in two main ways: 1) R&D needs; and 2) market structure.

Given the disparities that exist across all these areas, the Foundation asked stakeholders and the Expert Committee to consider whether HIV/AIDS, malaria and TB should be analysed alongside bacteria and fungi.

Discussion

Regarding R&D needs, the public and private support for the R&D of new or improved products for HIV/AIDS, malaria and TB is much more extensive compared to antibacterial and antifungal R&D.[1] This is in part reflected by the number of product development partnerships (PDPs) that have been established since the late 1990s, aimed specifically at devel oping and delivering these new products. PDPs take the form of centralised non-profit organisations that bring together resources and investments for the advancement of new med icines and vaccines. To date, only a few partnerships have been created for the development of innovative antibacteri als (except for those targeting TB) and antifungals. As such, the R&D gap for the development of innovative antibacterials and antifungals is much larger in comparison to HIV/AIDS and malaria.

Regarding market structure, the markets for HIV/AIDS, malaria and TB products are supported by a wide range of organisations including global procurement agents, donors and national and international organisations such as the Global Fund and the President's Emergency Plan for AIDS Relief (PEPFAR). These organisations pool investments and coordinate procurement processes with local partners to ensure treatments can be made available and accessible for communities in need. Yet, no such global procurement part nerships or alliances are limited for the antibacterial (excluding those targeting TB) and antifungal markets.

DECISION: FOCUS SOLELY ON BACTERIAL AND FUNGAL INFECTIONS

The 2020 AMR Benchmark will compare pharmaceutical companies solely on their activities as related to antibacterials (including TB) and antifungals.

Stakeholders agree that the disease areas differ vastly in their markets and R&D needs and advised the Foundation to focus solely on bacterial and fungal infections. Such steps would help ensure a comparable and clear picture on the current state of pharmaceutical company action on antibacterials and antifungals.

TB will be included as part of the Benchmark analysis, despite progress in R&D, as it continues to face the same challenges in its market structure as other antibacterials. More action is needed, in particular, for multi-drug resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB).

However, different approaches are required from the public and private sectors to combat resistance to HIV/AIDS and malaria treatment. The actions taken by large pharmaceutical companies to improve access to innovative HIV/AIDS and malaria treatments are included in the Access to Medicine Index. The Foundation is currently exploring ways to address access and resistance issues for HIV/AIDS and malaria on specific topics supported by stakeholders, including generic medicine manufacturers.

▶STEWARDSHIP EDUCATION

How can pharmaceutical companies responsibly support educational activities for healthcare professionals about antimicrobial stewardship?

Context

A key step in halting the rise of AMR is to raise awareness and build knowledge – among the public, policy makers, healthcare professionals (HCPs) and more – about how to prevent resistance from emerging. Governments shoulder the main responsibility in this regard, but pharmaceutical companies can also play an important role.

The 2018 AMR Benchmark asked companies about their efforts to educate HCPs on the stewardship of antibacterials. In future Benchmarks, it is important to clearly distinguish between companies' activities solely aimed towards education from activities that also involve promotion. The Benchmark aims to guide pharmaceutical companies to support or undertake educational activities in an objective way, and to proactively identify, mitigate and avoid conflicts of interest. As companies often engage with HCPs about the usage of their products, they can help HCPs ensure their products are used appropriately: i.e., by providing doctors with accurate guidance on prescribing the right product, at the right time, at the right dose and for the right duration.

During the methodology review, discussions were held with expert stakeholders and the Expert Committee on the role companies should play in educating HCPs about antimicrobial stewardship.

Discussion

Discussions with stakeholders and the Expert Committee revealed two main viewpoints. The first viewpoint emphasised that companies have the expertise and extensive product knowledge, and therefore the responsibility, to educate HCPs on the appropriate use of their products and/or to support continuing medical education. However, this viewpoint also held that companies must acknowledge and act upon the need to address and mitigate conflicts of interest. The second viewpoint held that, because of inherent conflicts of interest, pharmaceutical companies should only ever play a limited role in educating HCPs.

DECISION: THE BENCHMARK WILL MEASURE COMPANIES ON HOW THEY MANAGE CONFLICTS OF INTEREST

The Foundation concluded that, in this area, the consensus view is that pharmaceutical companies should proactively mitigate conflict of interest if they aim to play a role in educating HCPs about AMR.

The 2020 AMR Benchmark will evaluate companies on how they manage conflicts of interest if/when they engage with HCPs. For example, it will look at whether companies' use non-branded material, issue unrestricted grants for educational activities to independent third parties; and pledge not to provide financial or material incentives to participants. This analysis will enable the Benchmark to assess whether companies are enagaging with HCPs in an objective way.

How should a product's patent status affect the actions companies take to improve access?

Context

To curb AMR, new antibacterial and antifungal medicines are needed to replace those that are becoming less effective. Once these products are approved for sale, the people who need them must rapidly be given responsible accessibility, wherever they live. Whether such new and on-patent products are available and affordable to those in need depends on the choices pharmaceutical companies make when registering, pricing and distributing their products.

However, the market dynamics for older, off-patent and generic antibacterial and antifungal medicines differ substantially. Ensuring access to such may require pharmaceutical companies to take a different approach.

During the methodology review, the Foundation asked expert stakeholders about the potential benefits of taking different approaches to evaluating companies' access activities for on- or off-patent products.

Discussion

Factors that currently affect access to off-patent and generic antibacterial and antifungal medicines are multiple and complex, and include fragmented supply chains, limited availability of active pharmaceutical ingredients (APIs)[2] and an increasing demand from countries where health coverage and ability to pay might be lower.[3,4] This is important to note as many off-patent and generic antibacterial and antifungal medicines are listed on the 2017 WHO Model List of Essential Medicines (EML)[5] — a list of medicines that are deemed essential for all healthcare systems — specifically in the Access, Watch and Reserve categories of antibacterials. The three categories describe which antibacterials should be used more readily (Access) and which ones need to be carefully conserved (Watch and Reserve).

Further, several pharmaceutical companies, including large research-based pharmaceutical companies and smaller companies, have left the anti-infectives market in recent years.[6] This has particularly affected the antibacterials market, mainly due to low profit margins, but also to other factors, such as the opportunity cost of using a production line for less profitable products.

In order to capture what companies are doing to solve the different access issues relating to on- and off-patent/generic products, the Foundation consulted with stakeholders and the Expert Committee. Further, the expectations and roles for companies that produce Access and Watch antibacterials (used as first- and second-line treatments) and Reserve antibacterials (frequently used as a last resort in resistant infections) were also discussed and clarified.

Stakeholders and the Expert Committee identified availability and affordability as well as substandard and falsified products, shortages and weak supply chains as the main issues affecting access to off-patent and generic products.

As part of the consultation process, stakeholders and the Expert Committee also gave their views on priorities for improving access to on-patent products: namely, countries where there the burden of disease is high and where access is limited.

DECISION: ACCESS STRATEGIES FOR ON- AND OFF-PATENT/GENERIC PRODUCTS ASSESSED SEPARATELY

Stakeholders and the Expert Committee agreed that the Benchmark should separate its measurement of access approaches for on- and off-patent/generic products. This will allow the Benchmark to identify best practices around access barriers and incentivise companies to take different perspectives to inform their access-related activities.

For 2020, the Benchmark will assess companies' plans for access depending on the patent status of products and according to the issues identified above. For on-patent products, the Benchmark will look at all antibacterial and antifungal medicines and vaccines. For off-patent products, it will explore how pharmaceutical companies facilitate access to antibacterials listed on the WHO EML's Access, Watch and Reserve categories as well as vaccines.

To address access issues for on-patent products, the Benchmark expects companies to prioritise registration and access in countries where the burden of disease is higher. Additionally, it expects companies to have access plans in place that aim to improve affordability and availability. These access plans can include not only pricing strategies, but also voluntary licensing agreements, or participation in pooled procurement mechanisms, which enable treatments to be provided in larger volumes and at more affordable prices.

For off-patent products, some of which have been on the market for 20 years, the Benchmark expects companies to make these treatments available as widely as possible in countries in scope, for example through broad registration. Additionally, companies are expected to engage in mechanisms such as pooled procurement mechanisms that ensure large volumes of high-quality products are available in these countries, and are affordable to all population segments.

▶AMR SURVEILLANCE

How can company data on consumption of antimicrobial medicines and vaccines assist national surveillance systems?

Context

Surveillance systems are critical for monitoring, controlling and preventing the rise and spread of diseases and resistance. These systems track and monitor data about how antimicrobials are being consumed, which means they play an important role in reducing their misuse. For the purpose of AMR-related stewardship, each country needs to track and monitor consumption trends to develop and implement strategies that can help to reduce inappropriate use. When companies provide data about imports, sales, donations and production records, this can enhance national surveillance programmes to monitor antimicrobial consumption.

In 2016, WHO published the methodology for a global programme on surveillance of antimicrobial consumption[7] to facilitate the analysis of antimicrobial consumption. This methodology guides governments in implementing national surveillance programmes of antimicrobial consumption which can be integrated into the WHO surveillance programme.

Following its publication, the Foundation held discussions with the Expert Committee on whether the Benchmark could aid WHO in its efforts to gain insight into the consumption of antimicrobials.

Discussion

Information on antibacterial consumption, resistance levels and transmission patterns is still scarce or completely absent in many countries, particularly in low- and middle-income countries. Nevertheless, we know that mortality rates due to bacterial infections, such as untreated pneumonia and sepsis/meningitis, continue to be a public health problem in LMICs due to poor and/or limited access to relevant medicines, especially in children under five years of age. To address gaps in surveillance, WHO and the Wellcome Trust are now supporting programmes that aim to advance global surveillance, including the Global Antimicrobial Resistance Surveillance System (GLASS) and the AMR Register.

During the discussion, the Expert Committee expressed contrasting views. On the one hand, that the added value in expecting companies to engage with governments to provide consumption data is unclear; and on the other hand, that consumption data from companies could be helpful in guiding governments' policy making decisions. This second viewpoint also held that any data provided by companies could lead to important insights at the national level.

DECISION: BROADER MEASUREMENT OF SURVEILLANCE PROGRAMMES

The 2020 AMR Benchmark will ask companies whether they share antimicrobial consumption data with national governments and other public health authorities or initiatives and, if so, to provide further details on the type of data they share.

For references, see appendices.

What the Benchmark measures

The AMR Benchmark assesses company behaviour regarding specific diseases and product types and within a specific geographic scope, depending on the Research Area in question. The following pages set out the rationale for these analytical scopes and how they have been defined.

Table 1. Analysis scopes for the AMR Benchmark

Company scope	30 companies
	8 large research-based pharmaceutical companies
	9 generic medicine manufacturers
	13 small and medium-sized enterprises (SMEs)
Disease scope	Bacterial and fungal infections
Product scope	Antibacterial and antifungal medicines and vaccines
Geographic scope	Global, with access indicators focusing on 102 countries where greater access is needed

WHAT WE MEASURE

Company scope

The AMR Benchmark evaluates 30 pharmaceutical companies with the ability to address AMR through the products they market and R&D projects in their pipelines. They include today's largest players in the global antibacterials market, by volume and value of sales, as well as companies with relevant and mature projects in their clinical pipelines. The Benchmark compares companies in three groups: large-research-based pharmaceutical companies, generic medicine manufacturers and clinical-stage biopharmaceutical companies (referred to as small and medium-sized enterprises, or SMEs).

Since the publication of the first Benchmark in 2018, major changes in the market landscape for antibacterials have occurred. Several pharmaceutical companies have left the antibacterials market, divested part or all of their antibiotic assets or ceased investing in R&D for new antibacterials. As such, the companies in scope of this Benchmark are the remaining major actors that play a key role in shaping a market that is becoming more fragile.

Pharmaceutical companies that develop and market antibacterials and antifungals to improve human health can be grouped broadly into three categories: large research-based pharmaceutical companies, generic medicine manufacturers and clinical-stage biopharmaceutical companies, referred to as small and medium-sized enterprises (SMEs). While there is some overlap, there are key differences in expertise and capacity, notably in the size and nature of product portfolios, and in R&D focus and expertise. As a result, each group is able to address the challenges of AMR in varying ways.

Companies assessed per Research Area

Table 2

A RESEARCH & DEVELOPMENT
• Large R&D-based pharmaceutical companies
• SMEs

B RESPONSIBLE MANUFACTURING
• Large R&D-based pharmaceutical companies
• Generic medicine manufacturers

C APPROPRIATE ACCESS & STEWARDSHIP
• Large R&D-based pharmaceutical companies
• Generic medicine manufacturers

Defining the scope

Specific criteria are used to select the companies in scope. The 2020 AMR Benchmark makes it a priority to assess companies that focus on antibacterial and antifungal medicines and vaccines. Of all the resistant pathogens, bacteria represent the greatest proportion and have the widest geographic scope of resistance.

The 2020 AMR Benchmark includes large research-based pharmaceutical companies including global leaders in antibacterials with rankings in the top five for either the volume or value of their sales, as identified using IQVIA data (see table 3). It also includes companies with antibacterial pipelines that have at least one antibacterial drug or vaccine candidate targeting a priority pathogen in scope, as identified by the Pew Charitable Trusts[8] or WHO[9] (see table 3). Candidates must be in Phase II or more advanced stages of clinical development.

For generic medicine manufacturers, the 2020 AMR Benchmark selected those ranking in the global* top five by antibacterial sales volume and/or sales value, as identified using IQVIA data (see table 3), and/or whether they are a large vendor of active pharmaceutical ingredients (API).[10]

While the selection of large research-based pharmaceutical companies and generic medicine manufacturers was done on antibacterials, these companies will also be analysed on the vaccines and antifungals they develop and produce.

SMEs that were included in the 2018 AMR Benchmark were also included in the 2020 AMR Benchmark if they had at least one traditional antibacterial or antifungal candidate targeting a priority pathogen that was in Phase II or more advanced stages of clinical development. In addition, SMEs that were not included in 2018 were included in the 2020 AMR Benchmark if they had at least one candidate as described above that was novel according to the criteria set out by WHO.[9] Traditional antibacterials are medicines that target one or more essential pathways to directly kill or inhibit the growth of bacteria. A novel candidate meets at least one of the four criteria defined by WHO: new chemical class; new target; new mode of action; or absence of cross-resistance. Information on the clinical antibacterial pipeline was obtained using reports from the Pew Charitable Trusts[8] and WHO.[9] Information on the antifungal clinical pipeline was obtained using the publication titled, "The antifungal pipeline: a reality check" by John R. Perfect in 2017.[11]

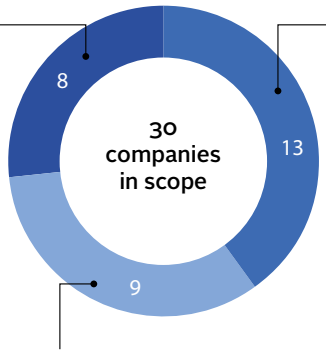
* 'Global' refers to aggregate sales in 75 countries.

Key changes for 2020

To define the company scope for the 2020 AMR Benchmark, IQVIA Midas intelligence data on consumption of antibiotics globally (2017) was used. The data indicated that the companies with highest antibiotic sales (in volume and value) has changed slightly. As a result, five companies included in the 2018 AMR Benchmark — Aspen, Dr. Reddy's, Lupin, Macleods and Roche — are not in scope for the 2020 AMR Benchmark. In addition, the 2018 Benchmark included SMEs with at least one antibacterial or antifungal candidate in Phase I or beyond. In 2020, the Benchmark will assess only those companies with candidates in Phase II or more advanced clinical development. As a result, MGB Biopharma – previously included – is no longer in scope. Companies newly in scope of the Benchmark are Abbott, Alkem, Cidara, Debiopharm, Amplyx, Hainan Hailing, Otsuka and Scynexis. In a further change, the 2020 AMR Benchmark will not include the signatories to the 2016 Declaration by the Pharmaceutical, Biotechnology and Diagnostics Industries on Combating Antimicrobial Resistance (known as the Davos Declaration) as a selection criteria for the company scope. Instead of tracking action to commitments made, it is now more critical to track key players with important antibacterial and antifungal assets; 20 out of the 30 companies have signed the Davos Declaration.

Companies in scope for the 2020 Antimicrobial Resistance Benchmark by company type

Figure 5



LARGE RESEARCH-BASED PHARMACEUTICAL COMPANIES

GlaxoSmithKline plc
Johnson & Johnson
Merck & Co., Inc.
Novartis AG
Otsuka Holdings
Pfizer Inc.
Sanofi
Shionogi & Co., Ltd.

SMALL & MEDIUM-SIZED ENTERPRISES

Achaogen Inc.
Amplyx Pharmaceuticals Inc.
Cidara Therapeutics
Debiopharm
Entasis Therapeutics Inc.
Melinta Therapeutics Inc.
Motif Bio plc
Nabriva Therapeutics plc
Polyphor Ltd.
Scynexis
Summit Therapeutics
Tetraphase Pharmaceuticals Inc.
Wockhardt Ltd.

GENERIC MEDICINE MANUFACTURERS

Abbott Laboratories
Alkem Laboratories Ltd.
Aurobindo Pharma Ltd.
Cipla Ltd.
Fresenius Kabi AG
Hainan Hailing Chemipharma Corporation Ltd.
Mylan NV
Sun Pharmaceutical Industries Ltd.
Teva Pharmaceutical Industries Ltd.

Erratum

After this report was initially published, the company scope has been further revised and this section of the report (pages 20-22) has been corrected to show that Amplyx is now in scope of the 2020 AMR Benchmark. The initial version showed that F2G was also in scope of the 2020 AMR Benchmark, but this is no longer the case and has been corrected.

Companies in scope for the 2020 Antimicrobial Resistance Benchmark – 30 companies

Table 3

LARGE RESEARCH-BASED PHARMACEUTICAL COMPANIES

	Company	Country	Ticker	Stock Exchange	Revenue (billion USD)*	Global antibiotic sales volume (SU million)**	Global antibiotic sales value (million USD)**
1	GlaxoSmithKline plc	GBR	GSK	London	40.8	6,589.8	1,353.1
2	Johnson & Johnson	USA	JNJ	New York	76.5	Inclusion based on R&D pipeline: ExPEC4V vaccine	
3	Merck & Co., Inc.	USA	MRK	New York	40.1	Not available	2,497.4
4	Novartis AG	CHE	NOVN	Six Swiss Exchange	49.1	3,749.2	1,630.3
5	Otsuka Holdings	JPN	4578	Tokyo	11.7	Inclusion based on R&D pipeline: OPS-2071	
6	Pfizer Inc.	USA	PFE	New York	52.5	2,490.2	4,019.0
7	Sanofi	FRA	SAN	Euronext Paris	42.1	1,142.4	787.3
8	Shionogi & Company, Limited	JPN	4507	Tokyo	3.2	Inclusion based on R&D pipeline: Cefiderocol	

GENERIC MEDICINE MANUFACTURERS

	Company	Country	Ticker	Stock Exchange	Revenue (billion USD)*	Global antibiotic sales volume (SU million)**	Global antibiotic sales value (million USD)**
1	Abbott Laboratories	USA	ABT	New York	27.4	2,162.6	Not available
2	Alkem Laboratories Limited	IND	ALKEM	NSE	1.0	2,695.8	432.2
3	Aurobindo Pharma Limited	IND	AUROPHARMA	NSE	2.5	1,020.1	Company included based on significance of API production
4	Cipla Limited	IND	CIPLA	NSE	2.3	2,491.1	386.5
5	Fresenius Kabi AG	DEU	FRE***	Frankfurt	7.6	Not available	991.3
6	Hainan Hailing Chemipharma Co. Ltd.	CHN	-	-	-	Not available	472.7
7	Mylan N.V.	USA	MYL	NASDAQ	11.9	1,033.2	809.5
8	Sun Pharmaceutical Industries Ltd.	IND	SUNPHARMA	NSE	4.1	3,053.3	513.7
9	Teva Pharmaceutical Industries Ltd.	ISR	TEVA	New York/Tel Aviv	22.4	2,604.9	1,253.0

Data sources:
* Revenue from latest fiscal year data available (Exchange rates from www.x-rates.com, the exchange rate of the last day of the fiscal year was used).
** Source: IQVIA (based on MIDAS 2017 anti-infectives data).
*** Fresenius SE & Co. KGaA, the parent company of Fresenius Kabi

SMALL AND MEDIUM-SIZED ENTERPRISES

	Company	Country	Ticker	Stock Exchange	Revenue (mn USD)*	Antibacterial or antifungal candidates in phase II or III or approved in or after 2015†‡§¶
1	Achaogen Inc.	USA	AKAO	NASDAQ	11.2	1: Zemdri™
2	Amplyx Pharmaceuticals Inc.	USA	-	-	-	1: APX001
3	Cidara Therapeutics	USA	CDTX	NASDAQ		1: Rezafungin (CD101)
4	Debiopharm	CHE	-	-	-	1: Afabicin (Debio-1450)
5	Entasis Therapeutics Inc.	USA	ETTX**	NASDAQ	-	2: ETX2514SUL; zoliflodacin
6	Melinta Therapeutics Inc.	USA	MLNT	NASDAQ	33.9	2: Baxdela™; Vabomere™
7	Motif Bio plc	GBR/USA	MTFB	London / NASDAQ	-	1: Iclaprim
8	Nabriva Therapeutics plc	IRL	NBRV	NASDAQ	5.3	1: Lefamulin
9	Polyphor Ltd.	CHE	POLN**	Six Swiss Exchange	-	1: Murepavidin (POL-7080)
10	Scynexis	USA	SCYX	NASDAQ	0.3	1: Ibrexafungerp
11	Summit Therapeutics	GBR	SMMT	London / NASDAQ	39.9	1: Ridinilazole
12	Tetraphase Pharmaceuticals Inc.	USA	TTPH	NASDAQ	9.7	1: Eravacycline
13	Wockhardt Ltd.	IND	WOCKPHARMA	NSE	604.0	5: Alalevonadifloxacin; cefepime & zidebactam; nafithromycin; WCK 771; WCK 5222

Data sources:
* Revenue from latest fiscal year data available (Exchange rates from www.x-rates.com, the exchange rate of the last day of the fiscal year was used).
** This company recently had its IPO

† The PEW Charitable Trusts. (March 2016). Antibiotics currently in clinical development.
‡ WHO. (2017). Antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline, including tuberculosis.
§ Perfect, J. R. (2017). The antifungal pipeline: a reality check. Nature Reviews. Drug Discovery, 16(9), 603–616.
¶ Development phase validated on 10 August 2018

WHAT WE MEASURE

Disease scope

The 2020 AMR Benchmark will evaluate pharmaceutical companies actions to limit AMR regarding bacterial and fungal infections. This is a refined disease scope, and will lead to a more focused comparison of companies' actions surrounding antibacterials and antifungals in terms of AMR and their market structure.

The 2018 AMR Benchmark provided a baseline analysis of company action against AMR by using a deliberately broad disease scope covering all infectious diseases. As well as all bacterial and fungal infections, this included viral infections such as HIV/AIDS and malaria (defined by WHO as AMR priority areas). In terms of R&D needs and market structure, these diseases and pathogens differ in important ways.

Key changes for 2020

The change in scope has been recommended by the Expert Committee and a wide range of external stakeholders. While the Foundation recognises that resistance to HIV/AIDS and malaria treatments constitutes a global threat, the role of the pharmaceutical industry in addressing AMR challenges for these diseases is rather different than for antibacterial and antifungal diseases.

In two of the three Research Areas (Research & Development and Responsible Manufacturing) the Benchmark will further narrow its focus with regard to disease scope – a narrowing mandated by scientific evidence and stakeholder recommendations that prioritises specific pathogens or products for these Research Areas (see table 4).

A Research & Development

In this Research Area, the Benchmark will limit its assessment to priority pathogens that include bacteria and fungi that pose the greatest threat to human health because of their widespread resistance against the existing standard of care. The Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) have published priority pathogens lists (see appendix I), and both will be covered in this R&D Research Area.

B Responsible Manufacturing

As in 2018, this Research Area will maintain a focus on antibacterials. Because the Benchmark selected companies in scope on the basis of antibacterial product sales, the action of these companies on managing antibacterial discharge is expected to have a sizeable impact on resistance. In contrast, there is no comparable level of certainty around the management of antifungal discharge. However, this is an emerging area of concern, and the Benchmark will therefore seek to identify and highlight best practices in environmental risk management that also take into account antifungal discharge.

C Appropriate Access & Stewardship

Having appropriate access to antibacterials and antifungals is important for all bacterial or fungal infections, and therefore, the disease scope of this Research Area is broad and not restricted to priority pathogens or antibacterials only.

Diseases and pathogens assessed per Research Area

Table 4

A RESEARCH & DEVELOPMENT

- Priority bacteria as defined by CDC and WHO (see appendix I)
- Priority fungi as defined by CDC and WHO (see appendix I)

B RESPONSIBLE MANUFACTURING

- All bacteria

C APPROPRIATE ACCESS & STEWARDSHIP

- All bacteria
- All fungi

WHAT WE MEASURE

Product scope

The product scope of the 2020 Antimicrobial Resistance Benchmark Report covers antimicrobial medicines and vaccines that target bacterial and fungal infections in humans:

- Medicines: Includes all innovative and adaptive medicines, branded generics and generic medicines that are used for direct treatment of target bacterial and fungal pathogens or disease processes, regardless of formulation. Products such as medicines used only for symptomatic relief are not included.
- Vaccines: Includes both preventive and therapeutic vaccines targeting bacteria and fungi.

Each of the Benchmark's three Research Areas has a tailored product scope as shown in table 5.

Products assessed per Research Area

Table 5

A RESEARCH & DEVELOPMENT

- Antibacterial medicines and vaccines that target priority pathogens (see appendix I) in discovery, preclinical and clinical phases I-III, or approved
- Antifungal medicines and vaccines that target priority pathogens (see appendix I) in discovery, preclinical and clinical phases I-III, or approved

B RESPONSIBLE MANUFACTURING

- Manufactured and/or marketed antibacterial medicines
- Manufactured and/or marketed antibacterial APIs

C APPROPRIATE ACCESS & STEWARDSHIP

- Marketed antibacterial medicines and vaccines
- Marketed antifungal medicines and vaccines

Appropriate Access

- Off-patent/generic products listed on the WHO EML (for access indicators C.1.2, C.2.2)

Stewardship

- Marketed antibacterial and antifungal medicines

WHAT WE MEASURE

Geographic scope

Antibacterial and antifungal resistance is emerging across the globe. The need for new medicines and responsible manufacturing practices are global priorities. Efforts to improve rational use of antibacterial and antifungal products already on the market are needed wherever these products are available. For that reason, the geographic scope of the 2020 Antimicrobial Resistance Benchmark is global (218 countries or territories*).

Yet, the challenges of appropriate access and affordability are significantly higher in resource-limited countries. This is why a group of indicators (A.4, C.1.1, C.1.2, C.2.1, C.2.2 and C.3) measure how companies either plan for or already address access to antibacterial and antifungal medicines and vaccines in 102 countries where better access is most needed. Further, two indicators (C.1.1 and C.2.1) will focus solely on companies' registration and pricing practices for on-patent products in countries with the highest need for the product in question.

Access metrics focus on where access is most needed

The 102 countries relevant to access indicators have been defined using four criteria: (1) countries' level of income (gross national income [GNI] per capita); (2) their levels of development; (3) the scope and scale of inequality in each country; and (4) their infectious disease burden.** These assessments are based on data from the World Bank,[12] the United Nations Economic and Social Council (ECOSOC),[13] the United Nations Development Programme (UNDP),[14] and the Institute for Health Metrics and Evaluation (IHME),[15] respectively. The Benchmark consulted the most recent available version of each of these datasets, published up to and including November 1st 2018.

In relation, to the methodology used in 2018, the first four methodological steps used for determining the geographic scope of access metrics remain unchanged, with the exception of the threshold used to select countries based on value of inequality-adjusted human development index (IHDI). This threshold is now the median of the IHDI distribution in UNDP's report "Human Development Indices and Indicators: 2018 Statistical Update".[14] In addition, a new fifth step now takes into account countries' infectious disease burden, measured in disability-adjusted life years (DALYs), as reported by IHME.[15] These and other updates in the data from the World Bank and UNDP resulted in countries moving in or out of scope for the 2020 AMR Benchmark. One country - Georgia - has moved into scope: it is now classified as a lower-middle-income country by the World Bank. Five countries have moved out of scope: Armenia, Ecuador, Iran, Samoa and Tonga. Out of these, Armenia, Samoa and Tonga are now classified as upper-middle-income countries by the most recent World Bank data, whereas Ecuador and Iran have IHDI values above the threshold considered; none fulfil any of the other inclusion criteria.

Table 6. Geographic scope assessed per Research Area

Table 6

A RESEARCH & DEVELOPMENT

- Pipeline: Global
- Stewardship Plans: Global
- Access Plans: 102 countries where better access is needed.

B RESPONSIBLE MANUFACTURING

- Global

C APPROPRIATE ACCESS & STEWARDSHIP

- Appropriate Access: 102 countries where better access is needed
- Stewardship: Global

*The Benchmark considers all countries or territories listed in the World Bank Country and Lending Groups (June 2018). The World Bank warns that the term "country" (used interchangeably with "economy"), does not imply political independence but refers to any territory for which authorities report separate social or economic statistics.
**Calculated as the sum of the burden of disease for 24 infectious diseases included in IHME's Global Burden of Disease Study (2017).

HOW THE SCOPE IS DEFINED FOR ACCESS INDICATORS

Step 1.
Include all countries classified as low income or lower middle-income countries based upon the latest available World Bank data.[12] For the 2020 Benchmark, this brings 81 countries into scope - three countries fewer than in the 2018 AMR Benchmark (see page 25 for full listing of countries). Countries no longer in scope of the 2020 AMR Benchmark include Armenia, Samoa and Tonga, now classified as upper-middle-income countries. Georgia, previously classified as an upper-middle-income country, is now classified as a lower-middle-income country and is therefore in scope.

Step 2.
Include all countries classified as least developed countries (LDCs) by the Committee for Development Policy of ECOSOC.[13] This results in the inclusion of Tuvalu in the 2020 AMR Benchmark scope.

Step 3.
Include all countries classified as low or medium human development based upon UNDP's Human Development Index (HDI) latest data.[14] This brings an additional six countries into scope, namely Equatorial Guinea, Guatemala, Guyana, Iraq, Namibia and South Africa.

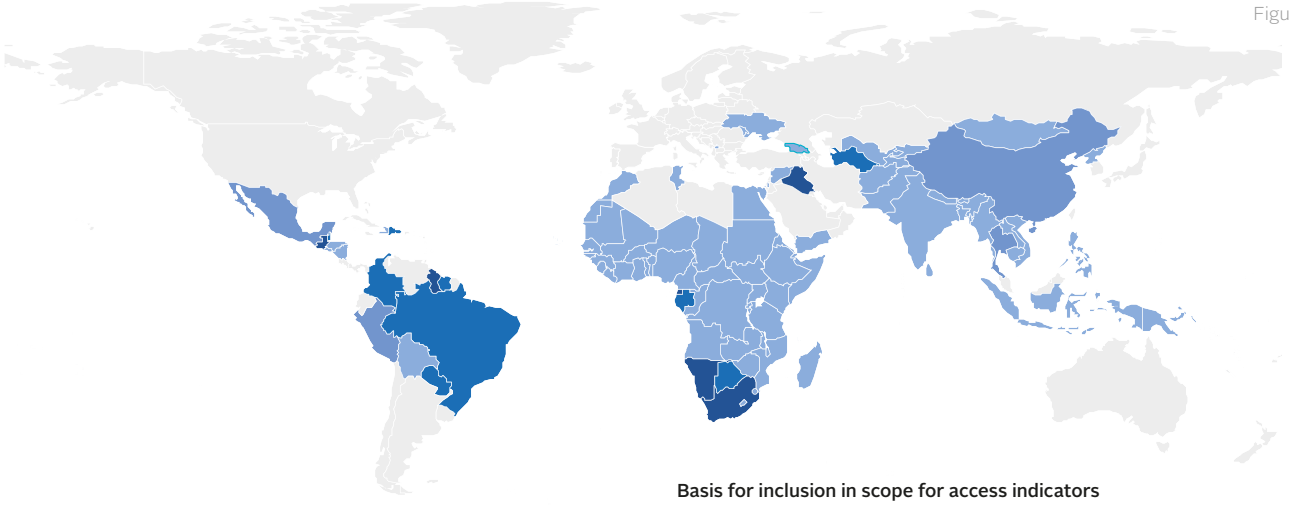
Step 4.
Include all countries with an Inequality-adjusted Human Development Index (IHDI) lower or equal to 0.583, the median of the IHDI distribution in UNDP's "Human Development Indices and Indicators: 2018 Statistical Update".[14] This step results in the inclusion of 10 more countries in the Benchmark scope: Belize, Botswana, Brazil, Colombia, Dominican Republic, Gabon, Maldives, Paraguay, Suriname and Turkmenistan.

Step 5.
Include all countries with a high bacterial and fungal infectious disease burden (measured in DALYs) as assessed by IHME in its "Global Burden of Disease Tool" (2017).[15] All countries above the third quartile of the data distribution are included unless they are classified by the World Bank as high-income, or by the UNDP as having a "Very high" HDI or being above the third quartile of the IHDI distribution. This step results in the inclusion of China, Mexico, Peru and Thailand in the scope of the Benchmark.

When countries had missing HDI or IHDI values in UNDP's 2018 report, past reports (published as far back as 2013) were also taken into account (this resulted in the inclusion of Botswana).

Countries in scope for access metrics in the 2020 Antimicrobial Resistance Benchmark - 102 countries

Figure 6



Basis for inclusion in scope for access indicators

- World Bank list of economies (June 2018)
- ECOSOC/UNDP Human Development Indices and Indicators (2018): HDI
- UNDP Human Development Indices and Indicators (2018): IHDI
- Global Burden of Disease Study (GBD 2017): bacterial and fungal infections
- Newly in scope for access indicators
- Not in scope for access indicators

Due to scaling, countries may not be visible on the map e.g., Tuvalu.

List of countries covered by access metrics for the 2020 Antimicrobial Resistance Benchmark – 102 countries

Table 7

East Asia & Pacific	
Cambodia	LMIC
China	HIDBC
Indonesia	LMIC
Kiribati	LMIC
Korea, Dem. People's Rep.	LIC
Lao PDR	LMIC
Micronesia, Fed. Sts.	LMIC
Mongolia	LMIC
Myanmar	LMIC
Papua New Guinea	LMIC
Philippines	LMIC
Solomon Islands	LMIC
Thailand	HIDBC
Timor-Leste	LMIC
Tuvalu	LDC
Vanuatu	LMIC
Vietnam	LMIC
Europe & Central Asia	
Georgia	LMIC
Kosovo	LMIC
Kyrgyz Republic	LMIC
Moldova	LMIC
Tajikistan	LIC
Turkmenistan	HIHDC
Ukraine	LMIC
Uzbekistan	LMIC
Latin America & Caribbean	
Belize	HIHDC
Bolivia, Plurinat. State	LMIC
Brazil	HIHDC
Colombia	HIHDC
Dominican Republic	HIHDC
El Salvador	LMIC
Guatemala	MHDC
Guyana	MHDC
Haiti	LIC
Honduras	LMIC
Mexico	HIDBC
Nicaragua	LMIC
Paraguay	HIHDC
Peru	HIDBC
Suriname	HIHDC
Middle East & North Africa	
Djibouti	LMIC
Egypt, Arab Rep.	LMIC
Iraq	MHDC
Morocco	LMIC
Syrian Arab Republic	LIC
Tunisia	LMIC
Palestine, State / West Bank and Gaza	LMIC
Yemen, Rep.	LIC
South Asia	
Afghanistan	LIC
Bangladesh	LMIC
Bhutan	LMIC
India	LMIC
Maldives	HIHDC
Nepal	LIC
Pakistan	LMIC
Sri Lanka	LMIC
Sub-Saharan Africa	
Angola	LMIC
Benin	LIC
Botswana	HIHDC
Burkina Faso	LIC
Burundi	LIC
Cabo Verde	LMIC
Cameroon	LMIC
Central African Republic	LIC
Chad	LIC
Comoros	LIC
Congo, Dem. Rep.	LIC
Congo, Rep.	LMIC
Côte d'Ivoire	LMIC
Equatorial Guinea	MHDC
Eritrea	LIC
Ethiopia	LIC
Gabon	HIHDC
Gambia, The	LIC
Ghana	LMIC
Guinea	LIC
Guinea-Bissau	LIC
Kenya	LMIC
Lesotho	LMIC
Liberia	LIC
Madagascar	LIC
Malawi	LIC
Mali	LIC
Mauritania	LMIC
Mozambique	LIC
Namibia	MHDC
Niger	LIC
Nigeria	LMIC
Rwanda	LIC
São Tomé and Príncipe	LMIC
Senegal	LIC
Sierra Leone	LIC
Somalia	LIC
South Africa	MHDC
South Sudan	LIC
Sudan	LMIC
Swaziland	LMIC
Tanzania	LIC
Togo	LIC
Uganda	LIC
Zambia	LMIC
Zimbabwe	LIC

● Newly in scope for the 2020 Benchmark

LIC	Low-income country World Bank income classifications (June 2018)
LMIC	Lower middle-income country World Bank income classifications (June 2018)
LDC	Least Developed Country UN ECOSOC LDC list (March 2018)
LHDC	Low Human Development Country UNDP Human Development Indices and Indicators (September 2018)
MHDC	Medium Human Development Country UNDP Human Development Indices and Indicators (September 2018)
HIHDC	High Inequality in Human Development Country UNDP Human Development Indices and Indicators (September 2018)
HIDBC	High Infectious Disease Burden Country IHME Global Burden of Disease Study 2017 Results

How the Benchmark measures

The AMR Benchmark will map how 30 large research-based companies, generic medicine manufacturers and small and medium-sized enterprises are responding to the rise of AMR. It will assess their policies and practices for addressing drug resistance and for improving appropriate access to medicines and vaccines for people living in countries where greater access is needed. The Benchmark will compare companies' approaches, where relevant and appropriate, with reference to their pipelines and portfolios.

The analytical framework is structured along three Research Areas:

A Research & Development
B Responsible Manufacturing
C Appropriate Access & Stewardship

HOW WE MEASURE

Analytical framework

The 2020 AMR Benchmark will evaluate company action using an analytical framework of three Research Areas: Research & Development, Responsible Manufacturing and Appropriate Access & Stewardship. The three Research Areas have been confirmed by stakeholders as those areas where pharmaceutical companies have core responsibilities to limit AMR. In each Research Area, companies' policies and practices are measured by indicators that correspond to priority actions for pharmaceutical companies.

19 indicators

The framework for the 2020 AMR Benchmark comprises 19 indicators: three are new additions and one has been removed. Two new indicators were developed to capture companies' access strategies for on- and off-patent/generic products separately, and one new indicator was established to analyse R&D for unmet needs. The indicator used to measure companies' efforts to reduce non-prescription sales in the 2018 AMR Benchmark (C.8 "Over-the-counter sales control") was removed as the role that pharmaceutical companies can play in this area is not yet clear. However, some aspects previously included in the C.8 indicator are now being assessed in other indicators; an example is traceability of products on the market, which is assessed in indicator C.3 "Ensuring continuous supply". The other 16 indicators have been modified or refined, either to tailor the metric more closely to stakeholders' expectations of company behaviour or to improve data capture to enhance comparison between companies and to conduct additional analyses.

Analysing companies only where relevant

Whether a company is assessed in a certain Research Area depends on the size and nature of its R&D pipeline and marketed product portfolio. For example, large research-based pharmaceutical companies will be assessed across all Research Areas, whereas generic medicine manufacturers will be assessed only in the Responsible Manufacturing and Appropriate Access and Stewardship areas. Following stakeholder consensus, small and medium-sized enterprises (SMEs) will be evaluated in four indicators of the Research & Development Research Area only: pipeline size (A.2.1); public health value of R&D candidates (A.2.2 and A.2.4); and access and stewardship planning for late-stage candidates (A.4). The remaining three indicators in this Research Area will report on data provided but not scored (see figure 7).

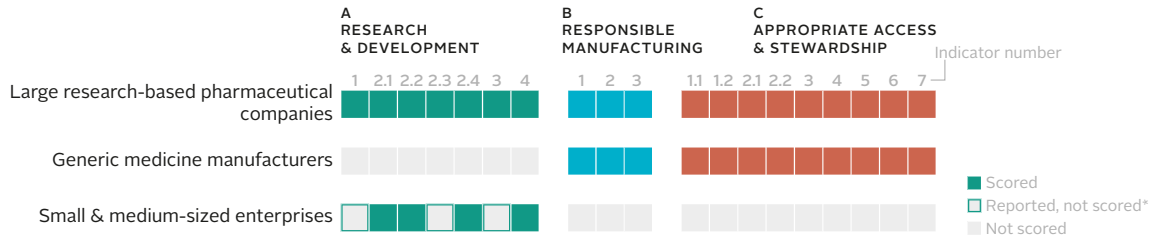
Where the data comes from

The Benchmark will collect data from public sources and from a detailed survey of pharmaceutical companies regarding their actions across the 19 indicators. Public sources will include the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), ClinicalTrials.gov, annual filings and reports from companies, among others. Data submitted by companies will be verified, cross-checked and clarified by the research team using public sources and supporting documentation provided by the companies. Companies will be asked to verify the accuracy of publicly sourced data and to provide additional necessary information.

Analytical Framework for the 2020 AMR Benchmark

The AMR Benchmark analyses three groups of companies using an analytical framework of three Research Areas and 19 indicators. Whether a company is scored in a Research Area depends on its pipeline and portfolio.

Figure 7



*SMEs will be scored in four of the Research & Development indicators. The Benchmark will report on, but not score, their activities in the remaining three indicators

RESEARCH AREAS

A Research & Development

Company scope: Large R&D-based companies, SMEs • Disease scope: Bacterial, fungal infections • Product scope: Medicines, vaccines • Geographic scope: Global/other

This Research Area captures companies' R&D activities to develop new medicines and vaccines that target pathogens posing the greatest threat to human health (referred to as priority pathogens, as identified by CDC and WHO - see appendix I). It will map R&D pipelines, highlighting areas of focus and where gaps remain, and assess how companies plan ahead to ensure new products can swiftly be made available and accessible for people in need. Further, it also examines whether companies share intellectual capital (e.g., molecules, patented compounds, technologies) with third-party researchers.

As AMR increases, there is a pressing need for new products to be developed to replace those losing their effectiveness. New vaccines will also play a part in slowing the emergence of resistance by preventing disease and the overuse of antibacterial and antifungal medicines.

Once a new clinical project is approved for sale by regulatory authorities, it should be introduced in a way that (a) ensures its rapid and appropriate accessibility for patients in need while (b) conserving its use to slow the inevitable emergence of resistance. This requires advance planning. Before new products are approved, pharmaceutical companies are encouraged to engage with others during the development process to achieve these twin aims.

In this Research Area, the Benchmark assesses pharmaceutical companies engaged in antibacterial and antifungal R&D for new medicine and vaccine development and/or adapting existing medicines and vaccines, including those in pre-clinical and clinical development (e.g., to develop new formulations or label extensions). These are the large R&D-based pharmaceutical companies in scope and small and medium-sized enterprises (SMEs). SMEs will only be assessed on indicators, A.2.1, A.2.2, A.2.4 and A4, with the Benchmark collecting data and reporting their activities under other indicators in this Research Area.

KEY CHANGES FOR 2020

In order to guide and incentivise companies to conduct R&D for infections that pose the greatest threat to human health, a new indicator has been introduced that will analyse R&D projects targeting the most critical priority pathogens (i.e. those defined as "Urgent" or "Critical" in the CDC and WHO lists of priority pathogens, respectively). In addition, the Benchmark will recognise R&D that looks to fulfil specific needs. In particular, it will consider R&D that addresses the need for certain types of formulations, such as paediatric, oral and heat-stable formulations; formulations for use in pregnancy; and formulations that are environmentally friendly. Further, it has adjusted the indicator that examines how companies work in collaboration. This indicator will now look at how companies collaborate and share intellectual capital[16] with third-parties (e.g., research institutions and universities) in order to catalyse antibacterial and antifungal R&D.

WHICH ACTIVITIES WILL BE ANALYSED?

R&D investments

The Benchmark will capture the financial resources that a company dedicates to antibacterial and antifungal R&D. However, as the resources of companies in scope differ considerably, the Benchmark will focus on the proportion of total revenue derived from pharmaceuticals that a company invests in the R&D dedicated to the development of antibacterial and antifungal medicines and vaccines.

R&D pipelines

The Benchmark examines how many projects a company has in its R&D pipeline to address priority pathogens in scope, including innovative and adaptive medicines and vaccines. It will also consider the degree to which products are of value for public health, as judged against four criteria: 1) candidates that target the most critical priority pathogens (see appendix I); 2) medicines that are novel; 3) medicines that can improve take-up in countries in scope; and 4) vaccines in general.

Intellectual capital sharing

Often, needed pharmaceuticals are unavailable because they target diseases that predominantly affect vulnerable populations in resource-limited countries, and therefore commercial market incentives are too low to drive R&D. Pharmaceutical companies can help accelerate R&D by sharing intellectual capital[16] (e.g., unpublished data, compound libraries, compound sets) with third-party researchers working to develop new and adapted products that address the needs of low- and middle-income populations. Intellectual capital is the intangible value of a company, covering its employees (human capital), its relationships (relational capital) and the infrastructure (e.g, data, processes, patents) that supports the work of its employees (structural capital) and gives it a competitive advantage. The Benchmark assesses how each company discloses their intellectual capital and whether it allows research institutions and other initiatives access to its intellectual capital relating to antibacterial and antifungal R&D in scope.

Access and stewardship planning

Planning ahead for access helps ensure public health needs are taken into consideration during product development. As a result, such planning early on can help to ensure more rapid access to new products at more affordable prices following market entry. Access plans can include equitable pricing strategies, wide-spread registration strategies and non-exclusive voluntary licensing agreements. These access plans must be coupled with stewardship plans to ensure that new products can be used appropriately and remain effective over time. Companies are expected to have plans in place for pipeline projects in Phase II and beyond. The Benchmark assesses the extent to which a company creates and discloses plans to make new products swiftly accessible upon market entry and ensure they will be used appropriately.

	Indicator	Change since 2018	Rationale
A.1	**R&D investments**		
	R&D investments (including in-kind) dedicated to the development of antibacterial and antifungal medicines and vaccines targeting priority pathogens in fiscal years 2017 and 2018.	No change	To characterise the overall financial resources dedicated to R&D of antibacterial and antifungal medicines and vaccines, focusing on priority pathogens.
A.2.1	**Pipeline size**		
	The size of a company's R&D pipeline targeting priority pathogens, including antibacterial and antifungal medicines, vaccines and adaptations (developed in-house or through collaborations).	No change	To characterise the degree to which a company focuses on antibacterial and antifungal R&D, in addition to financial information.
A.2.2	**Novelty of pipeline**		
	The novelty of investigational clinical antibacterial and antifungal medicines targeting priority pathogens that the company is developing (in-house or through collaborations). A novel candidate meets at least one of the four criteria defined by WHO: new chemical class; new target; new mode of action; or absence of cross-resistance. Additionally, other pipeline projects that fulfil one or more of the following criteria will be recognised: 1) paediatric formulation and formulation for pregnancy; 2) oral formulation; 3) heat-stable formulation; 4) environmentally friendly formulation; or 5) other special formulations or conditions that help to improve usage in low- and middle-income countries.	Modified	Innovative antibacterial and antifungal medicines are needed to overcome (cross-) resistance and companies actively developing novel candidates should be recognised. Adaptations, such as Paediatric formulations, also play an important role in limiting AMR.
A.2.3	**Vaccines in the pipeline**		
	The number of new vaccines that the company is developing for priority pathogens in scope (in-house or through collaborations).	No change	Vaccines are shown to have a positive impact in mitigating AMR. By preventing infectious diseases from spreading, vaccines reduce the need for antibacterial and antifungal medicines.
A.2.4	**Projects targeting critical priorities**		
	The number of projects that target a 'critical' pathogen (as defined by WHO) and/or 'urgent' pathogen (as defined by the CDC). These pathogens include carbapenem-resistant (CR) *Acinetobacter baumannii, CR Pseudomonas aeruginosa*, CR or ESBL-producing *Enterobacteriaceae, Clostridioides difficile* and drug-resistant *Neisseria gonorrhoeae.*	New	There is an urgent need for products that target multidrug-resistant bacteria (predominantly those that are Gram-negative). Through this indicator, the Benchmark aims to provide incentives to companies to direct R&D efforts to medicines and/or vaccines that address these pathogens.
A.3	**Intellectual capital sharing**		
	The company provides evidence of sharing its intellectual capital (e.g., molecule libraries, patented compounds, processes and technologies) with research institutions and drug discovery initiatives to foster the development of products that target priority pathogens.	Modified	Sharing intellectual capital can accelerate R&D and consequently increase the availability of new products.
A.4	**Access and stewardship planning**		
	The proportion of late-stage antibacterial and antifungal R&D projects, targeting priority pathogens, for which the company provides information about having plans in place for (1) access in countries in scope and (2) stewardship on a global basis. Late-stage R&D includes projects in Phase II and III of clinical development (developed in-house or through collaborations) and recently approved products.	No change	To describe efforts to ensure that successful antibacterial and antifungal medicine and vaccine candidates, targeting priority pathogens, are made available rapidly and affordably and are used appropriately where needed.

RESEARCH AREAS

B Responsible Manufacturing

Company scope: Large R&D-based companies, generic medicine manufacturers • Disease scope: Bacterial infections • Product scope: Medicines • Geographic scope: Global

This Research Area (previously Manufacturing & Production) compares companies' strategies for limiting the impact of antibacterial manufacturing on resistance. It evaluates how thorough their environmental risk-management strategies are and how these apply to the companies' suppliers; if companies' strategies include limits on antibacterial discharge; and their transparency regarding strategies, audit results, discharge limits and levels and the identities of third-party suppliers of APIs and drug products. Further, it assesses the specific policies and actions companies can take to uphold high-quality manufacturing practices.

Antibacterials released into the environment through factory wastewaters are increasingly thought to be contributing to AMR.[17] The exposure of bacteria in soil and water to discharged antibacterial ingredients can trigger the emergence and/or selection of resistance genes. There are two main roles that the pharmaceutical industry can play to limit the risk of resistance with respect to their manufacturing operations: 1) implement a clear environmental risk-management strategy that applies to their own manufacturing sites, to third-party manufacturers of APIs and/or drug products and to external waste-treatment plants; and 2) manufacture antibacterial products of high quality following international standards accepted by recognised authorities.

In this Research Area, the Benchmark assesses manufacturers of antibacterial products in scope (i.e., large R&D-based pharmaceutical companies and generic medicine manufacturers). The volumes of sales of these companies indicate that they are prominent players in multiple manufacturing chains, with significant influence upon upstream suppliers. Consequently, their policies and practices in these areas have stronger impacts than those of other companies on the emergence of antibacterial resistance.

KEY CHANGES FOR 2020

The Benchmark will assess how companies monitor levels of antibacterial discharge, and evaluate their approach to the disposal of solid waste that may contain antibacterial residue, resistant bacteria or resistance genes. In addition, the Benchmark will look at whether companies publish the limits they set for antibacterial discharge across their manufacturing sites. The Benchmark will also assess the quality of manufacturing. It will evaluate not just drug products but also APIs, examining the ways companies engage with their suppliers to identify needs and to provide training in areas where suppliers find it difficult to meet quality standards.

WHICH ACTIVITIES WILL BE ANALYSED?

Environmental risk-management strategy

During manufacturing, antibacterials can be released into the environment. This risks promoting the development of resistant bacteria and the spread of resistance genes. Additionally, some of the processes used to treat wastewaters may produce materials (such as sludge) that contain antibacterial residues and/or resistance genes, which must be disposed of properly. The Benchmark will assess how companies dispose of antibacterial waste and how they implement relevant policies and/or processes to third-party suppliers and waste-treatment plants.

Disclosure on environmental risk management

As companies work to implement targeted strategies to manage environmental AMR risks associated with antibacterial discharge from their manufacturing operations, it is crucial that such strategies - as well as their outcomes - be made publicly available. Public disclosure can ensure accountability and provide insight and understanding on the epidemiology of AMR in the environment and its impact on human health.[18,19] It also gives procurers of antibacterial medicines, such as governments and other public institutions, the information they need to identify companies that manufacture responsibly. The Benchmark will look at whether companies are transparent about: (a) their overall strategy to manage environmental risk; (b) the results of strategy audits (both at company sites and sites of third parties); (c) the limits companies set for antibacterial discharge; (d) the amount of antibacterials discharged from their manufacturing sites; and (e) whether they disclose the identities of first-tier suppliers of APIs, drug products and waste treatment services.

Manufacturing high-quality antibacterial products

Human consumption of subtherapeutic doses (below the amount required for therapeutic effect) of antibacterial products can accelerate the development of antibacterial resistance. While some bacteria may be eliminated at this level, others become resistant. To help limit the emergence of resistance due to subtherapeutic levels of antibacterial ingredients, it is important for companies to make products of high quality, with doses sufficient to produce the intended therapeutic effect. The Benchmark will assess the mechanisms companies have in place to maintain high-quality production at their own sites and at third-party manufacturing facilities.

Indicator	Change since 2018	Rationale
B.1 Environmental risk-management strategy		
The company has an environmental risk-management (ERM) strategy to minimise the environmental impact of manufacturing discharge of antibacterials. This applies to: (a) its own manufacturing sites; (b) third-party suppliers of antibacterial active pharmaceutical ingredients (APIs) and drug products; and (c) external private waste treatment plants. The strategy includes, for (a), (b) and (c), the following elements: (i) implementation of appropriate waste-treatment practices for both liquid and solid antibacterial-containing wastes; (ii) on-site auditing of compliance with the strategy; (iii) setting of antibacterial discharge limits based on predicted no-effect concentrations (PNECs) for resistance selection; and (iv) appropriate monitoring of the levels of antibacterials discharged and implementation of corrective procedures as needed.	Modified	To assess how a company incorporates auditing and discharge limits in its ERM strategy for each phase of manufacturing and production, in order to minimise impacts of antibacterial production on resistance.
B.2 Disclosure on environmental risk management		
The company publicly discloses: (i) its ERM strategy to minimise environmental impact of manufacturing discharge of antibacterials; (ii) results of strategy audits at the company's manufacturing sites; (iii) results of strategy audits at third-party sites manufacturing antibacterial APIs and drug products and/or external private waste treatment plants; (iv) identities of third parties manufacturing antibacterial APIs and drug products and/or of external private waste-treatment plants; (v) levels (concentrations) of antibacterial discharge and discharge monitoring technique(s); and (vi) limits set for antibacterial discharge, along with methodological and evidential bases.	Modified	To assess how much information a company makes publicly available to allow independent third parties to analyse and compare companies' environmental risk-management processes and performance.
B.3 Manufacturing high-quality antibacterials		
The company makes commitments, has systems in place and promotes initiatives to ensure, maintain and/or improve the production of high-quality antibacterial APIs and drug products at its own and third-party manufacturing sites, in a manner consistent with the international standards developed and accepted by recognised national and international authorities.	Modified	To assess risks that a company will produce antibacterial medicines with subtherapeutic dose levels, and/or of sub-optimal quality, which can contribute to the development and spread of antibacterial resistance.

RESEARCH AREAS

C Appropriate Access & Stewardship

Access Company scope: Large R&D-based companies, generic medicine manufacturers • Diseases: Bacterial, fungal infections • Products: Medicines, vaccines • Geographic scope: 102 Countries

Stewardship Company scope: Large R&D companies, generic manufacturers • Disease scope: Bacterial, fungal infections • Product scope: Medicines • Geographic scope: Global

This Research Area looks at how companies aim to increase access to antibacterial and antifungal medicines and vaccines while also limiting their misuse (stewardship). Issues of both access and stewardship are closely interlinked as the need to enhance access where necessary must be balanced with that of ensuring optimal and appropriate use. It will assess companies' access strategies for antibacterial and antifungal medicines and vaccines in 102 countries where better access is most needed, alongside their global stewardship initiatives.

Antibacterial and antifungal medicines and vaccines are essential tools in treating the burden of infectious diseases worldwide. Yet, millions of people currently live without reliable access to these medicines or do not have sufficient information on how to use them. Issues of both access and stewardship are especially relevant in countries where healthcare systems have limited resources and the burden of infectious diseases is high, as their capacity to prevent and control these diseases (including resistant infections) is lower.[20]

Reasons why access to quality-assured antibacterial and antifungal medicines and vaccines may be restricted in these countries include low availability (e.g., when new and on-patent medicines are not registered in countries in need) and affordability of on- and off-patent/generic products, disruptions in the supply chain and other issues such as weaker regulatory systems. This may lead to doctors prescribing suboptimal medicines which can increase the risk of resistance emerging.[21,22] To delay the emergence of resistance, stewardship activities must be in place.

In this Research Area, the Benchmark assesses pharmaceutical companies with antibacterials and antifungals on the market (i.e., the large R&D-based pharmaceutical companies and generic medicine manufacturers). Companies with on-market products have a dual role in solving the issues of both access and stewardship. To ensure access, they can put in place strategies relating to product registration, pricing and improving supply chains. Regarding stewardship, the role for pharmaceutical companies spans a range of areas such as surveillance and ensuring marketing practices take account of the risks of overuse and misuse.

KEY CHANGES FOR 2020

The 2020 Benchmark will assess companies' strategies for access to on- and off-patent/generic products separately, in order to gain a more focused understanding of how companies consider access for these products. It will prioritise the analysis of access plans for on-patent products and for off-patent/generic products listed on the WHO EML. In particular, it will consider antibacterials, antifungals categorised by WHO as Access, Watch and Reserve and vaccines. In addition, the Benchmark will take a deeper look at how companies aim to improve supply chain efficiencies following the publication of the Foundation's white paper on antibiotic shortages published in May 2018.[23] A further change includes the removal of the C.8 indicator "Over-the-counter sales control," as the role that pharmaceutical companies can play in this area is not yet clear.

WHICH ACTIVITIES WILL BE ANALYSED?

▶ACCESS

Registration

For products to become available, they must first be filed for registration (and then approved for sale) by a regulatory authority. This step must be taken as widely and rapidly as possible, particularly if a product is innovative or superior to those already on the market. The Benchmark will look for evidence that companies file their antibacterial and antifungal medicines and vaccines for registration in countries with a high burden for the disease in question.

Accessibility

For antibacterial and antifungal medicines and vaccines, the Benchmark will consider how companies are setting prices, at a country level and for populations within a given country. Since the issues around accessibility and affordability of medicines are diverse, it may not be enough to solely measure pricing strategies for new medicines and vaccines. Therefore, the Benchmark will also look at how companies work with the public sector and global health donors and organisations to offer access strategies that could reduce the financial burden of countries in scope. Examples might include licensing patented medicines to promote generic competition or collaborating with those who procure medicines on a global or regional basis (e.g., Global Drug Facility, the Global Fund or Pan American Health Organization's [PAHO] Revolving Fund).

Ensuring continuous supply
When antibacterials and antifungals are out of stock (due to fragile supply chains or unexpected increases in the demand), this can have a profound impact on access, especially in resource-limited settings. For antibacterial and antifungal medicines and vaccines, the Benchmark will examine the mechanisms companies have implemented to prevent stock-outs, improve forecasts for demand, build capacity and collaborate with other parties.

▶STEWARDSHIP

Educational stewardship activities
The first step in changing how antimicrobial medicines are prescribed is to raise awareness of antimicrobial resistance and its prevention. As companies often engage with healthcare professionals (HCPs) about the usage of their products, they can help ensure appropriate product use. In order to assess if companies do this in an objective way, the Benchmark will measure companies on how they manage conflicts of interest if and/or when they engage with HCPs. For example, it will look at whether companies' use non-branded material, issue unrestricted grants for educational activities to independent third parties; and pledge not to provide financial or material incentives to participants.

Appropriate promotional practices
One of the strategic pillars of the global effort to address AMR is to ensure that antibacterials are used appropriately and only when needed in order to prolong their effectiveness. The Benchmark will look at whether companies have non-sales-related incentives for its sales staff, among others. For example, companies can adopt non-sales-related targets for their sales agents based on quality of service, behaviour and other competencies. By minimising the focus on sales volume, there is less incentive for sales agents to behave unethically by mis-selling or overselling products.

Stewardship-oriented packaging adaptations
When medicines are prescribed or bought over the counter, the quality of information provided with them can improve the likelihood of appropriate use. The Benchmark will assess whether companies have adapted their brochures and packaging to encourage appropriate use of antibacterials and antifungals. For example, by providing brochures in local languages or with pictograms for illiterate populations.

Antimicrobial surveillance
To monitor, control and prevent the rise and spread of diseases and resistance, surveillance systems are critical. They are also important in tracking and monitoring data on antimicrobial consumption to reduce misuse. The Benchmark examines whether companies have their own AMR surveillance system; are involved in capacity building for new surveillance activities; or whether they support or contribute to existing local, national and global systems (such as the AMR Register of the Open Data Institute and Wellcome Trust). Further, it will assess whether companies share antibacterial and antifungal consumption data with national governments and other public health authorities.

	Indicator	Change since 2018	Rationale
C.1.1	**Registration of on-patent products** The company files to register its on-patent antibacterial and antifungal medicines and vaccines in those countries in scope with the highest public health need (defined as the highest burden of disease).	New	Registration of innovative products is the first step to ensure these products will be available where needed. When a company files to register its new products in countries where disease burden and inequality are higher, it demonstrates a commitment to enter markets in need and provide access to products in these markets.
C.1.2	**Registration of off-patent/generic products** The company files to register its off-patent and generic antibacterial and antifungal medicines and vaccines in countries in scope.	Modified	Registration of off-patent and generic antibacterial and antifungal products is a prerequisite to ensure availability. When a company files to register relevant products in the countries in scope, it demonstrates a commitment to enter and to provide access to their products in these markets.
C.2.1	**Accessibility of on-patent products** The company implements an appropriate access strategy to ensure that its on-patent antibacterial and antifungal medicines and vaccines are affordable. Examples may include: • Policies enabling a company to take account of needs-based affordability, equity and relevant socioeconomic factors when making decisions about inter- and/or intra-country pricing • Ensuring products are available and affordable through mechanisms such as voluntary licences and/or non-assert declarations (committing not to enforce patents in certain circumstances and countries in scope), including stewardship-oriented terms and conditions for patented products in scope, in countries within scope.	New	The extent to which a company is committed to providing access to its most innovative therapies is evident in its policies, pricing and other commitments. Access to such therapies is essential to tackling resistant infections.
C.2.2	**Accessibility of off-patent/generic products** The company implements an appropriate access strategy to ensure off-patent and generic anti-bacterial and antifungal medicines and vaccines are accessible. Examples may include: • Engagement with large global procurers to lower product prices in countries in scope • Policies enabling a company to take account of needs-based affordability, equity and relevant socioeconomic factors when making decisions about inter- and/or intra-country pricing.	New	Access to off-patent and generic antibacterial and antifungal products gives low- and middle-income countries the tools to reduce the burden of infectious diseases, including resistant infections.
C.3	**Ensuring continuous supply** The company has mechanisms in place to improve supply chain efficiency for antibacterial and antifungal medicines and vaccines, addressing the following gaps: • Buffer stock and supplier diversity: the company manages a buffer stock of relevant antibacterial and antifungal medicines and vaccines and works with several API suppliers to prevent shortages. • Information systems: the company engages with governmental agencies and other relevant stakeholders to inform on issues that may affect the supply chain, such as API shortages and demand forecasting. • Capacity building: the company engages with governmental agencies and other stakeholders to improve supply capacity and ensure the quality of medicines. • Supply of old or "forgotten antibiotics": the company commits to ensuring the continuous supply of any such antibacterials, making these medicines accessible and available in markets where the company operates.	Modified	Making medicines accessible not only reduces the burden of infectious diseases, it also decreases any incentive to manufacture falsified medicines, which in turn reduces the spread of resistant infections and the emergence of resistant bacteria and fungi. Fundamental to accessibility are companies' strategies to ensure a continuous supply of on-patent, off-patent and generic antibacterial and antifungal medicines and vaccines.

C.4 Educational stewardship activities

The company has a clear strategy to mitigate any conflicts of interest (COI) in its support of antibacterial and antifungal stewardship educational activities directed at healthcare professionals.	Modified	Companies organise congresses and other educational activities that can influence and/or change the behaviour of prescribers and potentially affect access to appropriate treatment as well as the use of antibacterials and antifungals. Therefore, companies involved in educational stewardship activities need to have robust strategies, policies and procedures in place to avoid and/or mitigate conflicts of interest and safeguard appropriate use.

C.5 Appropriate promotional practices

In its promotional activities for healthcare professionals, the company adopts marketing practices that advance stewardship of antibacterials and antifungals. It implements mechanisms to incentivise in-house and/or third-party sales representatives to engage in responsible marketing practices, and thus avoid overselling of antibacterials and antifungals.	Retained	Marketing practices promoting the sale of antibacterial and antifungal medicines could lead to bias in prescribers' practices and potentially inappropriate prescription of products. Mediating these marketing practices by altering sales incentives can limit prescriber bias and reduce the inappropriate prescription of medicines, thereby limiting resistance.

C.6 Stewardship-oriented packaging adaptations

The company adapts its brochures and/or its packaging to facilitate the appropriate use of antibacterial and antifungal products by patients. The company considers needs, such as literacy or language, and adaptations that improve paediatric use and/or adherence to treatment.	Retained	Adapting brochures and the packaging of medicines to guide patients on product usuage, for example by writing the brochure in their native language, may increase appropriate use and subsequently limit antimicrobial resistance.

C.7 Antimicrobial surveillance

The company has, supports and/or contributes to antibacterial and antifungal surveillance programmes, and/or shares antibacterial and antifungal medicine and vaccine consumption data with national governments and other public health authorities.	Modified	By providing data on resistance and consumption, companies assist in the effort to monitor how resistance against antibacterial and antifungal medicines is spreading and how these medicines are used. This is essential not only for measuring the burden of resistant infections, but also for forecasting and prioritising objectives in the design of stewardship policies.

Appendices

APPENDIX I. PRIORITY PATHOGENS INCLUDED FOR ANALYSIS IN R&D

In the Research & Development Research Area, the Benchmark will assess the size and public health value of a company's pipeline of investigational antibacterial and antifungal medicines and vaccines. This assessment will be limited to medicines and vaccines targeting priority pathogens, which include families of bacteria and fungi that pose the greatest threat to human health because of their widespread resistance against the existing standard of care. The Centers for Disease Control and Prevention (CDC) and World Health Organization have published priority pathogens lists and both will be covered in the R&D Research Area.

Specifically for indicator A.2.4, newly introduced in 2020, the Benchmark will assess companies' projects targeting the most critical priorities in these lists, i.e. targeting the pathogens classified in the CDC and WHO lists as "Urgent" or "Critical", respectively.

Pathogen	Specific resistance	WHO Priority List*	CDC Biggest Threats**
BACTERIA			
Acinetobacter spp.		Critical	Serious
Campylobacter spp.		High	Serious
Clostridioides difficile			Urgent
Enterobacteriaceae	Carbapenem / Extended-Spectrum ß-Lactamase (ESBL)	Critical	Urgent / Serious
Enterococcus spp. (*E. faecalis* & *E. faecium*)	Vancomycin	High	Serious
Haemophilus influenzae type b (Hib)	Ampicillin	Medium	
Helicobacter pylori	Clarithromycin	High	
Mycobacterium tuberculosis		R&D priority	Serious
Neisseria gonorrhoeae		High	Urgent
Pseudomonas aeruginosa		Critical	Serious
Salmonella spp.		High	Serious
Shigella spp.		Medium	Serious
Staphylococcus aureus	Methicillin / Vancomycin	High	Serious / Concerning
Streptococcus (group A)	Erythromycin		Concerning
Streptococcus (group B)	Clindamycin		Concerning
Streptococcus pneumoniae		Medium	Serious
FUNGI			
Candida spp.	Fluconazole		Serious

REFERENCES

* WHO. (2017). Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics.
**U.S. Centers for Disease Control and Prevention (CDC). (April, 2013). Antibiotic resistance threats in the United States, 2013.

APPENDIX II. PRODUCTS IN SCOPE FOR ACCESS INDICATORS

In order to capture the different strategies and practices that companies implement to improve access to medicines in scope, the Benchmark separates these products into on-patent and off-patent/generic medicines. For patented products, all patented antibacterial and antifungal medicines and vaccines are in scope for indicators C1.1 and C2.1.

For off-patent and generic products, the Benchmark will assess those antibacterial and antifungal medicines and vaccines that are on the following table based on the 2017 WHO Model List of Essential Medicines (EML).[5] These products are deemed essential by WHO to the basic functioning of any health system. Access to these medicines, particularly in low- and middle-income countries, must be considered alongside efforts to curb AMR.

Moreover, in 2017 WHO developed the Access, Watch and Reserve classification. In this classification, Access antibacterials are those that need to be widely available, affordable and quality assured. Watch antibacterials are those with higher resistance potential and therefore those that most stewardship programmes need to focus on. Finally, Reserve antibacterials includes those that should be treated as "last resort", for example, because of lack of therapeutic alternatives due to resistance. When possible, the Benchmark will prioritise access plans for these products.

Product (defined by WHO EML)	Dose and route of administration (defined by WHO EML)	Access/Watch/ Reserve (defined by WHO EML)
6. ANTI-INFECTIVES		
6.2. Antibacterials		
amoxicillin	Powder for oral liquid: 125 mg (as trihydrate)/5 mL; 250 mg (as trihydrate)/5 mL Solid oral dosage form: 250 mg; 500 mg (as trihydrate) Powder for injection: 250 mg; 500 mg; 1 g (as sodium) in vial	Access
amoxicillin + clavulanic acid	Oral liquid: 125 mg amoxicillin + 31.25 mg clavulanic acid/5 mL; 250 mg amoxicillin + 62.5 mg clavulanic acid/5 mL Tablet: 500 mg (as trihydrate) + 125 mg (as potassium salt) Powder for injection: 500 mg (as sodium) + 100 mg (as potassium salt); 1000 mg (as sodium) + 200 mg (as potassium salt) in vial	Access
ampicillin	Powder for injection: 500 mg; 1 g (as sodium salt) in vial	Access
benzathine benzylpenicillin	Powder for injection: 900 mg benzylpenicillin (= 1.2 million IU) in 5- mL vial; 1.44 g benzylpenicillin (= 2.4 million IU) in 5 mL vial.	Access
benzylpenicillin	Powder for injection: 600 mg (= 1 million IU); 3 g (= 5 million IU) (sodium or potassium salt) in vial.	Access
cefalexin	Powder for reconstitution with water: 125 mg/5 mL; 250 mg/5 mL (anhydrous). Solid oral dosage form: 250 mg (as monohydrate).	Access
cefazolin	Powder for injection: 1 g (as sodium salt) in vial.	Access
cefixime	Capsule or tablet: 200 mg; 400 mg (as trihydrate). Powder for oral liquid: 100 mg /5 mL	Access, Watch
cefotaxime	Powder for injection: 250 mg per vial (as sodium salt)	Access, Watch
ceftriaxone	Powder for injection: 250 mg; 1 g (as sodium salt) in vial.	Access, Watch
cloxacillin	Capsule: 500 mg; 1 g (as sodium salt). Powder for injection: 500 mg (as sodium salt) in vial. Powder for oral liquid: 125 mg (as sodium salt)/5 mL.	Access
phenoxymethylpenicillin	Powder for oral liquid: 250 mg (as potassium salt)/5 mL. Tablet: 250 mg (as potassium salt).	Access
piperacillin + tazobactam	Powder for injection: 2 g (as sodium salt) + 250 mg (as sodium salt); 4 g (as sodium salt) + 500 mg (as sodium salt) in vial	Access, Watch
procaine benzylpenicillin	Powder for injection: 1 g (=1 million IU); 3 g (=3 million IU) in vial. Powder for injection: 250 mg or 1 g (as pentahydrate) in vial.	Access
ceftazidime	Powder for injection: 250 mg or 1 g (as pentahydrate) in vial.	Watch
meropenem	Powder for injection: 500 mg (as trihydrate); 1 g (as trihydrate) in vial	Access, Watch
aztreonam	Powder for injection: 1 g; 2 g in vial	Reserve
fifth generation cephalosporins (with or without beta-lactamase inhibitor) e.g., ceftaroline	Powder for injection: 400 mg; 600 mg (as fosamil) in vial	Reserve
fourth generation cephalosporins (with or without beta-lactamase inhibitor) e.g., cefepime	Powder for injection: 500 mg; 1g; 2g (as hydrochloride) in vial	Reserve
amikacin	Injection: 250 mg (as sulfate)/mL in 2- mL vial	Access

Product (defined by WHO EML)	Dose and route of administration (defined by WHO EML)	Access/Watch/ Reserve (defined by WHO EML)
azithromycin	Capsule: 250 mg; 500 mg (anhydrous). Oral liquid: 200 mg/5 mL.	Access, Watch
chloramphenicol	Capsule: 250 mg. Oily suspension for injection: 0.5 g (as sodium succinate)/ mL in 2- mL ampoule. Oral liquid: 150 mg (as palmitate)/5 mL. Powder for injection: 1 g (sodium succinate) in vial.	Access
ciprofloxacin	Oral liquid: 250 mg/5 mL (anhydrous). Solution for IV infusion: 2 mg/ mL (as hyclate). Tablet: 250 mg (as hydrochloride).	Access, Watch
clarithromycin	Solid oral dosage form: 500 mg. Powder for oral liquid: 125 mg/5 mL; 250 mg/5 mL Powder for injection: 500 mg in vial	Access, Watch
clindamycin	Capsule: 150 mg (as hydrochloride). Injection: 150 mg (as phosphate)/ mL. Oral liquid: 75 mg/5 mL (as palmitate)	Access
doxycycline	Oral liquid: 25 mg/5 mL; 50 mg/5 mL (anhydrous). Solid oral dosage form: 50 mg; 100 mg (as hyclate). Powder for injection: 100 mg in vial	Access
gentamicin	Injection: 10 mg; 40 mg (as sulfate)/ mL in 2- mL vial.	Access
metronidazole	Injection: 500 mg in 100- mL vial. Oral liquid: 200 mg (as benzoate)/5 mL. Suppository: 500 mg; 1 g. Tablet: 200 mg to 500 mg.	Access
nitrofurantoin	Oral liquid: 25 mg/5 mL. Tablet: 100 mg.	Access
spectinomycin	Powder for injection: 2 g (as hydrochloride) in vial.	Access
sulfamethoxazole + trimethoprim	Injection: 80 mg + 16 mg/ mL in 5- mL ampoule; 80 mg + 16 mg/ mL in 10- mL ampoule. Oral liquid: 200 mg + 40 mg/5 mL. Tablet: 100 mg + 20 mg; 400 mg + 80 mg; 800 mg + 160 mg.	Access
vancomycin	Capsule: 125 mg; 250 mg (as hydrochloride).	Access, Watch
daptomycin	Powder for injection: 350 mg; 500 mg in vial	Reserve
fosfomycin	Powder for injection: 2 g; 4 g (as sodium) in vial	Reserve
oxazolindinones e.g., linezolid	Injection for intravenous administration: 2 mg/ mL in 300 mL bag. Powder for oral liquid: 100 mg/5 mL. Tablet: 400 mg; 600 mg.	Reserve
polymyxins e.g., colistin	Powder for injection: 1 million I.U. (as colistemethate sodium) in vial	Reserve
tigecycline	Powder for injection: 50 mg in vial	Reserve
clofazimine	Capsule: 50 mg; 100 mg.	
dapsone	Tablet: 25 mg; 50 mg; 100 mg.	
rifampicin	Solid oral dosage form: 150 mg; 300 mg.	
ethambutol	Oral liquid: 25 mg/ mL. Tablet: 100 mg to 400 mg (hydrochloride).	
ethambutol + isoniazid	Tablet: 400 mg + 150 mg	
ethambutol + isoniazid + pyrazinamide + rifampicin	Tablet: 275 mg + 75 mg + 400 mg + 150 mg.	
ethambutol + isoniazid + rifampicin	Tablet: 275 mg + 75 mg + 150 mg.	
isoniazid	Oral liquid: 50 mg/5 mL. Tablet: 100 mg to 300 mg. Tablet (scored): 50 mg.	
isoniazid + pyrazinamide + rifampicin	Tablet: 75 mg + 400 mg + 150 mg. 150 mg + 500 mg + 150 mg (For intermittent use three times weekly). Tablet (dispersible): 50 mg + 150 mg + 75 mg	
isoniazid + rifampicin	Tablet: 75 mg + 150 mg; 150 mg + 300 mg. 60 mg + 60 mg (For intermittent use three times weekly). 150 mg + 150 mg (For intermittent use three times weekly). Tablet (dispersible): 50 mg + 75 mg.	
pyrazinamide	Oral liquid: 30 mg/ mL. Tablet: 400 mg. Tablet (dispersible): 150 mg. Tablet (scored): 150 mg.	
rifabutin	Capsule: 150 mg.	
rifampicin	Oral liquid: 20 mg/ mL. Solid oral dosage form: 150 mg; 300 mg.	

Product (defined by WHO EML)	Dose and route of administration (defined by WHO EML)	Access/Watch/ Reserve (defined by WHO EML)
rifapentine	Tablet: 150 mg	
amikacin	Powder for injection: 100 mg; 500 mg; 1 g (as sulfate) in vial.	
bedaquiline	Tablet: 100 mg.	
capreomycin	Powder for injection: 1 g (as sulfate) in vial.	
clofazimine	Capsule: 50 mg; 100 mg.	
cycloserine	Solid oral dosage form: 250 mg.	
delamanid	Tablet: 50 mg.	
ethionamide	Tablet: 125 mg; 250 mg.	
kanamycin	Powder for injection: 1 g (as sulfate) in vial.	
levofloxacin	Tablet: 250mg; 500 mg; 750 mg.	Watch
linezolid	Injection for intravenous administration: 2 mg/ mL in 300 mL bag. Powder for oral liquid: 100 mg/5 mL. Tablet: 400 mg; 600 mg.	Reserve
moxifloxacin	Tablet: 400 mg.	Watch
p-aminosalicylic acid	Granules: 4 g in sachet. Tablet: 500 mg.	
streptomycin	Powder for injection: 1 g (as sulfate) in vial.	
6.3 ANTIFUNGAL MEDICINES		
amphotericin B	Powder for injection: 50 mg in vial (as sodium deoxycholate or liposomal complex).	
clotrimazole	Vaginal cream: 1%; 10%. Vaginal tablet: 100 mg; 500 mg.	
fluconazole	Capsule: 50 mg. Injection: 2 mg/ mL in vial. Oral liquid: 50 mg/5 mL	
flucytosine	Capsule: 250 mg. Infusion: 2.5 g in 250 mL.	
griseofulvin	Oral liquid: 125 mg/5 mL. Solid oral dosage form: 125 mg; 250 mg.	
itraconazole	Capsule: 100 mg. Oral liquid: 10 mg/mL.	
nystatin	Lozenge: 100 000 IU. Oral liquid: 50 mg/5 mL; 100 000 IU/ mL. Pessary: 100 000 IU. Tablet: 100 000 IU; 500 000 IU	
voriconazole	Tablet: 50 mg; 200 mg Powder for injection: 200 mg in vial Powder for oral liquid: 40 mg/mL	
13. DERMATOLOGICAL MEDICINES		
13.1 Antifungal medicines		
miconazole	Cream or ointment: 2% (nitrate).	
selenium sulfide	Detergent-based suspension: 2%	
sodium thiosulfate	Solution: 15%.	
terbinafine	Cream: 1% or Ointment: 1% terbinafine hydrochloride.	
13.2 Anti-infective medicines		
mupirocin	Cream (as mupirocin calcium): 2%. Ointment: 2%.	
potassium permanganate	Aqueous solution: 1:10 000	
silver sulfadiazine	Cream: 1%.	
19. VACCINES		
BCG vaccine	diphtheria vaccine	
Haemophilus influenzae type b vaccine	pertussis vaccine	
pneumococcal vaccine	cholera vaccine	
meningococcal meningitis vaccine	typhoid vaccine	
21. OPHTHALMOLOGICAL PREPARATIONS		
21.1 Anti-infective agents		
azithromycin	Solution (eye drops): 1.5%.	
erythromycin	Ointment: 0.5%	
gentamicin	Solution (eye drops): 0.3% (sulfate).	
natamycin	Suspension: (eye drops): 5%	

ofloxacin	Solution (eye drops): 0.3%.
tetracycline	Eye ointment: 1% (hydrochloride).
28.EAR, NOSE AND THROAT MEDICINES	
ciprofloxacin	Topical: 0.3% drops (as hydrochloride).

Finally, the Benchmark will assess where possible, the plans developed by the pharmaceutical companies to ensure continuous supply for a list of old antibiotics with high potential to treat resistant infectious diseases, but that are shown to be widely unavailable.

aztreonam	benzylpenicillin
cefepime	cefoperazone + sulbactam
cefoxitin	cefpodoxime
ceftibuten	chloramphenicol
cloxacillin	colistin
dicloxacillin	ertapenem
flucloxacillin	colistin
ertapenem	fosfomycin
fusidic acid	mecillinam
methenamine	nafcillin
nitrofurantoin	oxacillin
phenoxymethylpenicillin	pivmecillinam
pristinamycin	quinupristin + dalfopristin
spectinomycin	teicoplanin
temocillin	thiamphenicol
tobramycin	trimethoprim

APPENDIX III. DEFINITIONS

Access plan
[Working definition, used for analysis]
An access plan is a plan set up to ensure that 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. Access plans facilitate availability, accessibility and affordability for patients in countries within the scope of the Benchmark (e.g., registration commitments, equitable pricing strategies, sufficient supply commitments, non-exclusivity in specified territories, waiving of patent rights, royalty-free provisions and applying for WHO prequalification).

Active pharmaceutical ingredient (API)
The active pharmaceutical ingredient (API) is the active pharmaceutical component of a medicine that carries out its intended effects. Some medicines, such as combination therapies, have multiple active ingredients that target multiple disease pathways and/or symptoms. The inactive ingredients of a medicine are referred to as excipients.

Adaptive R&D
[Working definition, used for analysis]
R&D adaptations to existing medicines and/or vaccines. This includes new formulations, new fixed-dose combinations of existing chemical or biological entities, a new target demographic, or the repurposing of an existing product for additional indications.

Affordability
[Working definition, used for analysis]
The measure of a payer's ability to pay for a product (whether or not they are the end user). The Benchmark takes this into account when assessing pharmaceutical companies' pricing strategies.

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
[Working definition, used for analysis]
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). See also Antibiotic medicine.

Antibacterial resistance
Antimicrobial resistance occurring specifically in bacteria. This resistance renders the medicines normally used to treat bacterial infections (e.g., urinary tract infections, pneumonia, bloodstream infections) ineffective. Sometimes also referred to as antibiotic resistance. See also antimicrobial resistance.

Antibiotic medicine
[Working definition, used for analysis]
Equivalent to Antibacterial medicine. The term "antibiotic" is used inconsistently in the literature to denote either a drug that targets any type of microorganism in the body or, alternatively, a drug that targets bacteria specifically. Given the ambiguity, the Benchmark preferably avoids use of this term, referring to the more general category as "antimicrobial" and to the more specific one as "antibacterial".

Antifungal medicine
[Working definition, used for analysis]
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 medicine
[Working definition, used for analysis]
A medicine used to treat an infectious disease by directly targeting the bacteria, fungi, helminths, protozoa or viruses that cause the infection (as opposed to targeting the symptoms of the infection or toxins produced by the pathogen).

Antimicrobial resistance
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 promotional practices
[Working definition, used for analysis]
Promotional activities targeting the general public, patients and healthcare professionals in such a way that transparency, integrity, accuracy, clarity and completeness of information can be ensured.

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 [WHO Global Strategy for Containment of Antimicrobial Resistance, 2001].

Broad-spectrum antibacterial
Broad-spectrum antibacterial medicines are active against a wide range of bacterial types and may be used to treat a wide range of bacterial infections.

Clinical-stage drug development
[Working definition, used for analysis]
Clinical-stage drug development comprises phases I through III of clinical development. Products approved (or awaiting approval) between 9 September 2017 (end of the period of analysis for the previous edition of the Benchmark) and 21 June 2019 are also categorised as late-stage.

Conflict of interest
[Working definition, used for analysis]
Within the context of pharmaceutical companies' engagement in public health-oriented initiatives, a conflict of interest potentially arises when the commercial interests of the company conflict with the primary interest of protecting and promoting public health.

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)
The disability-adjusted life year (DALY) is 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 comparison of disease burden across different populations and health conditions across time. One DALY equals one lost year of healthy life.

Drug product
The finished dosage form of a medicine obtained at the end of the manufacturing process, (e.g., the tablet, capsule, or solution containing the active pharmaceutical ingredient(s), generally, but not necessarily, in association with one or more other ingredients). Also referred to as a finished drug product, finished product or formulation.

Environmental risk management (ERM)
[Working definition, used for analysis]
In the context of antibacterial product manufacturing, environmental risk management (ERM) seeks to determine and manage environmental risks resulting from the production of antibacterials, such as the emergence of antibacterial resistance, to protect human health and the environment.

Falsified medicine
A medicine which is deliberately and fraudulently mislabelled with respect to identity and/or source. Falsified medicines may contain no active ingredient, the wrong active ingredient or the wrong amount of the correct active ingredient.

Generic medicine
A medicine that is created to be the same as a known marketed brand-name drug (the originator medicine) in dosage form, strength, route of administration, quality and performance characteristics, and intended use. See also Originator medicine.

Good Manufacturing Practices
Good manufacturing practice (GMP) is a system employed to ensure that products are consistently produced and controlled according to appropriate quality standards. Within pharmaceutical production this serves to minimise risks such as unexpected contamination, incorrect labelling or incorrect dose of the active ingredient. GMP covers all aspects of pharmaceutical production (e.g., starting materials, premises, equipment, training and personal hygiene of staff) and includes processes that provide documented proof that correct procedures are consistently followed at each step of the manufacturing process. GMP guidelines are established and overseen by regulatory agencies in individual countries or regions, as well as the WHO.

Healthcare Professional
Any specialised worker in any branch of healthcare that provides preventive, curative or rehabilitative services to the community.

Intellectual capital
[Working definition, used for analysis]
Intellectual capital is the intangible value of a company, covering its employees (human capital), its relationships (relational capital) and the infrastructure (e.g. hardware, software, databases, processes, patents) that supports the work of its employees (structural capital). A company's intellectual capital gives it a competitive advantage. In the context of the Benchmark, the intellectual capital of a pharmaceutical company may comprise of, for example, molecule libraries, patented compounds, processes and technologies or unpublished data on pharmacological characteristics of compounds.

International non-proprietary name (INN)
The International non-proprietary name (INN) is a common, generic name selected by designated experts for the unambiguous identification of a pharmaceutical substance or active pharmaceutical ingredient. The selection process is coordinated by World Health Organization (WHO) via its INN Programme. Each INN is a unique name that is globally recognised and is public property.

Late-stage drug development
[Working definition, used for analysis]
In the context of the pharmaceutical R&D pipeline, medicine and vaccine candidates in Clinical phase II or Clinical phase III are considered to be in late-stage clinical development. Products approved (or awaiting approval) between 9 September 2017 (end of the period of analysis for the previous edition of the Benchmark) and 21 June 2019 are also categorised as late-stage by the Benchmark.

Narrow-spectrum antibacterial
Narrow-spectrum antibacterials are antibacterial medicines that are active against a selected group of bacterial types. Examples include colistin, an antibacterial that selectively targets gram-negative bacteria, and vancomycin, an antibacterial that selectively targets gram-positive bacteria.

Novel drug candidate
[Working definition, used for analysis]
A novel candidate meets at least one of the four criteria defined in WHO's report "Antibacterial agents in clinical development" (2017): (1) new chemical class; (2) new target; (3) new mode of action; (4) absence of cross-resistance. This assessment is applied only to candidates in clinical stage and validated by WHO and/or external experts.

Off-patent medicine
[Working definition, used for analysis]
A medicine whose granted patent protection has expired. Patent protection typically lasts for 20 years and is specific to each country.

On-patent/patented medicine
[Working definition, used for analysis]
A patented or on-patent medicine is one which has received exclusivity rights, allowing the patent holder to prevent or stop others from making, using, selling or importing the medicine within the country that granted the patent. The Benchmark determines patent status for its products in scope through a process that combines data from selected regulatory authority websites (e.g. FDA) and participating companies.

One Health
An approach used to design and implement public health programmes, policies, legislation and research in which multiple sectors communicate and work together to achieve better

outcomes. The areas for which a One Health approach is particularly relevant include food safety, the control of zoonosis, and combating antimicrobial resistance. [WHO, 2017]

Originator medicine
The medicine that was first authorised worldwide for marketing, normally as a patented product, on the basis of its documented efficacy, safety and quality, according to requirements at the time of authorisation. The originator medicine always has a brand name; this name may, however, vary among countries.

Over-the-counter medicine
A medicine that can be purchased without prescription from a healthcare professional.

Period of analysis
[Working definition, used for analysis]
The 2020 AMR Benchmark report will assess company activities taking place during a period of analysis going from 9 September 2017 to 21 June 2019. For the R&D research area, projects need to be ongoing, approved or awaiting approval by the end of the period of analysis.

Preclinical-stage drug development
[Working definition, used for analysis]
Preclinical-stage drug development comprises the discovery and preclinical phases of drug development.

Predicted no-effect concentration (PNEC)
In the context of environmental risk assessment, the predicted no-effect concentration (PNEC) is the concentration of a substance in any environment below which adverse effects will most likely not occur. The PNEC can be based on acute (short-term) or chronic (long-term) toxicity data and usually takes account of the uncertainty in extrapolating from collected/available data to the entire ecosystem.

Priority pathogen
[Working definition, used for analysis]
Priority pathogens are pathogens for which new medicines and vaccines are highly needed. The Benchmark identified this set of priority pathogens based on the WHO priority pathogens list as of 25 February 2017 and the CDC's US Biggest Threats list as of April 2013.

Product Development Partnership
[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
[Working definition, used for analysis]
A public-private partnership (PPP) is a partnership between one or more public organisations and the private sector 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 Benchmark 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.

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.

Substandard medicine
Also referred to as "out of specification", these are market-authorised medicines that fail to meet either quality standards or specifications, or both. [based on WHO, 2017]

APPENDIX IV: REFERENCES

References for the Introduction are on page x.

1 Chapman N, Doubell A, Oversteegen L, et al. G-FINDER 2018 Neglected Disease Research and Development: Reaching New Heights.; 2019. https://www.policycuresresearch.org/g-finder/. Accessed January 23, 2019.

2 Seuring SA. Has factory consolidation for pharma companies heightened risk of drug shortages? https://medcitynews.com/2017/03/drug-shortages/. Published 2017. Accessed December 20, 2018

3 Klein EY, Boeckel TP Van, Martinez EM, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. Proc Natl Acad Sci. 2018;115(15):E3463-E3470. doi:10.1073/PNAS.1717295115

4 Laxminarayan R, Matsoso P, Pant S, et al. Access to effective antimicrobials: A worldwide challenge. Lancet. 2016;387(10014):168-175. doi:10.1016/S0140-6736(15)00474-2

5 WHO Model List of Essential Medicines (20th List, March 2017, Amended August 2017). http://www.who.int/medicines/publications/essentialmedicines/en/.

6 Pulcini C, Bush K, Craig WA, et al. Forgotten Antibiotics: An Inventory in Europe, the United States, Canada, and Australia. Clin Infect Dis. 2012;54(2):268-274. doi:10.1093/cid/cir838

7 World Health Organization. WHO Report on Surveillance of Antibiotic Consumption: 2016-2018 Early Implementation.; 2018.

8 The Pew Charitable Trusts. Antibiotics Currently in Global Clinical Development. 2018. https://www.pewtrusts.org/-/media/assets/2018/09/antibiotics_currently_in_global_clinical_development_sept2018.pdf. Accessed January 9, 2019.

9 World Health Organization. Update of Antibacterial Agents in Clinical Development.; 2018. doi:10.1016/S1473-3099(18)30513-9

10 Technavio. Global Active Pharmaceutical Ingredients Market 2017-2021.; 2016. https://www.technavio.com/report/global-plastics-polymers-and-elastomers-global-active-pharmaceutical-ingredients-market-2017. Accessed November 5, 2018.

11 Perfect JR. The antifungal pipeline: a reality check. Nat Rev Drug Discov. 2017;16(9):603-616. doi:10.1038/nrd.2017.46

12 World Bank list of economies (June 2018). https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups. Accessed December 7, 2018.

13 LDCs at a Glance | Development Policy & Analysis Division. (March 2018). https://www.un.org/development/desa/dpad/wp-content/uploads/sites/45/page/LDC_data.xls. Accessed December 7, 2018.

14 Human Development Indices and Indicators: 2018 Statistical Update. http://hdr.undp.org/sites/default/files/2018_statistical_annex_all.xlsx. Accessed December 7, 2018.

15 Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2017 (GBD 2017) Results. 2018. http://ghdx.healthdata.org/gbd-results-tool. Accessed January 10, 2019.

16 Luthy DH. Intellectual capital and its measurement. In: Proceedings of the Asian Pacific Interdisciplinary Research in Accounting Conference (APIRA). Osaka, Japan; 1998.

17 Singer AC, Shaw H, Rhodes V, Hart A. Review of Antimicrobial Resistance in the Environment and Its Relevance to Environmental Regulators. Front Microbiol. 2016;7:1728. doi:10.3389/fmicb.2016.01728

18 Larsson DGJ, Andremont A, Bengtsson-Palme J, et al. Critical knowledge gaps and research needs related to the environmental dimensions of antibiotic resistance. Environ Int. 2018;117:132-138. doi:10.1016/J.ENVINT.2018.04.041

19 Larsson DGJ, Fick J. Transparency throughout the production chain—a way to reduce pollution from the manufacturing of pharmaceuticals? Regul Toxicol Pharmacol. 2009;53(3):161-163. doi:10.1016/j.yrtph.2009.01.008

20 Tomson G, Vlad I. The need to look at antibiotic resistance from a health systems perspective. Ups J Med Sci. 2014;119(2):117-124. doi:10.3109/03009734.2014.902879

21 World Health Organization. Global Surveillance and Monitoring System for Substandard and Falsified Medical Products. Geneva; 2017.

22 Pauwels K, Simoens S, Casteels M, Huys I. Insights into European Drug Shortages: A Survey of Hospital Pharmacists. Conly J, ed. PLoS One. 2015;10(3):e0119322. doi:10.1371/journal.pone.0119322

23 Cogan D, Karrar K, Iyer JK. Shortages, stockouts and scarcity. 2018. Access to Medicine Foundation

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