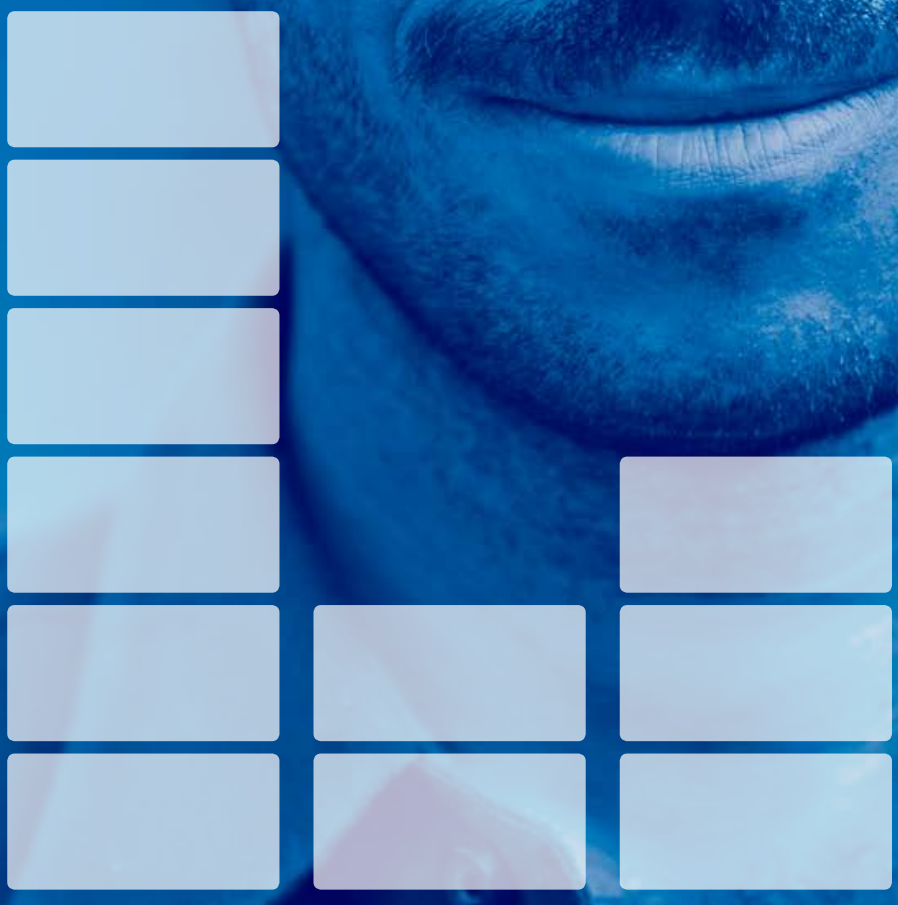
First independent framework for assessing pharmaceutical company action

Antimicrobial Resistance Benchmark 2018

METHODOLOGY 2017



access to medicine FOUNDATION

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 to medicine.

ADDRESS

Naritaweg 227 A
NL-1043 CB Amsterdam
The Netherlands

CONTACT

For more information about this publication, please contact
Gowri Gopalakrishna, Research Programme Manager
E gkrishna@accesstomedicinefoundation.org
T +31 (0)20 21 53 535
W www.accesstomedicinefoundation.org

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Antimicrobial Resistance Benchmark 2018

Methodology Report

ACCESS TO MEDICINE FOUNDATION

August 2017

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Expert Committee

Hans Hogerzeil (Chair)
Greg Frank
Nina Grundmann
Magdalena Kettis
Jeremy Knox
Joakim Larsson
Marc Mendelson
Katarina Nedog
Evelina Tacconelli
Evelyn Wesangula

Research team

Gowri Gopalakrishna
Josefien Knoeff
Marijn Verhoef
Tara Prasad

Editorial team

Anna Massey
Emma Ross

This acknowledgement is not intended to imply that the individuals and institutions referred to above endorse the Antimicrobial Resistance Benchmark methodology, analyses or results. Decisions regarding inclusion of all feedback were ultimately made by the Access to Medicine Foundation.

A framework for action on AMR

The global healthcare system depends on appropriate and timely access to antimicrobials. Without antibiotics, there is no direct treatment for infections, no safe surgery, no emergency medicine. The unchecked rise of Antimicrobial Resistance (AMR) puts this at risk for us all. While AMR results from natural selection, the ways we make, use and dispose of antimicrobials are undoubtedly accelerating its spread. To address AMR, a fine balance must be struck – between appropriate access to antimicrobials and efforts to curb overuse and misuse. Novel antimicrobials and vaccines are also urgently needed.

These past years have seen growing attention being paid to public health, paving the way toward a global strategy on AMR. AMR has topped agendas at G7 and G20 Summits, the UN General Assembly, the World Health Assembly and World Economic Forum. Governments and the pharmaceutical industry have come forward to address the AMR threat. A group of companies has published a roadmap for how they plan to play their part. This commitment, action and willingness to share and collaborate is unique from the pharmaceutical industry.

At the Access to Medicine Foundation, we have 10 years of experience in publicly mapping how pharmaceutical companies are responding to global health priorities. The idea of benchmarking company action to combat AMR came from discussions with the UK and Dutch governments. The proposal of a benchmark was also endorsed by the AMR Review Team. In this report, we publish the first independent analytical framework dedicated to assessing the industry's engagement in curbing AMR. It has been developed with close reference to the detailed research and initiatives underway on AMR, and in consultation with many experts and stakeholders working in the AMR field.

The Benchmark is intended to complement and maximise the impact of these important initiatives on AMR.

In the coming months, we will apply this framework to a cross-section of the pharmaceutical industry, in order to report publicly on individual companies' actions along with their collaborative efforts. We will examine the evidence, compare different approaches, recognise good practice, and shine a light on where more action or coordination is vital. Our aim is to incentivise and guide positive change, spur deeper company engagement and challenge the barriers to progress.

Now is the time to tackle AMR. When antimicrobial resistance becomes widespread, it compromises the very foundation of healthcare. No single stakeholder can bring AMR under control. Global solidarity and collaboration between governments, industry, NGOs and others is critical. This Benchmark methodology can be seen as a framework for action for companies seeking to join the global coalition of forces curbing AMR.

Jayasree K. Iyer
Executive Director
Access to Medicine Foundation

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Executive Summary

Antimicrobial resistance (AMR) is a widely recognised and growing problem. Without effective antimicrobials, infections become more difficult to treat, while medical and surgical procedures can become high-risk interventions, leading to prolonged sickness, disability and death. AMR already causes more than 700,000 deaths each year worldwide. The push to limit AMR requires a consolidated, concerted effort by multiple stakeholders, including governments, public health authorities, international health organisations, academic institutions and pharmaceutical companies.

Although AMR is a natural phenomenon, its development is accelerated by the misuse and overuse of antimicrobials. More rational use of antimicrobials is a cornerstone of strategies aimed at ensuring existing drugs remain useful for longer by decelerating the pace at which pathogens develop resistance. Successful stewardship involves a 'One Health' approach – an integrated approach addressing how antimicrobials are used in humans and in animals, as well as the antimicrobial load in the environment.

At the same time, millions of people do not have access to the antibiotics and other antimicrobials they need, despite having curable infections. Many of the global initiatives to address AMR aim to balance the need for better stewardship with the need to enhance access where necessary. The need for new strategies and programmes to appropriately increase access to antimicrobials remains particularly acute in low- and middle-income countries, where weaknesses in healthcare delivery systems are often present. Such weaknesses can limit access to antimicrobials while also promoting their inappropriate overuse. These two issues are closely interlinked and must be addressed in tandem.

In addition to stewardship and access, many global strategies for addressing AMR focus on pharmaceutical innovation and the pipeline of antimicrobial products, to counter resistance to existing medicines.

The role of the pharmaceutical industry

As AMR grows, there is a pressing need for novel products to be developed to treat life-threatening infections. Yet there is little incentive for pharmaceutical companies to invest in antimicrobial R&D, not least because of the major technical challenges involved in discovering and developing new antimicrobial classes. There is also little promise of a swift return on investment. New antibiotics are particularly highly sought after, yet must be used conservatively to limit the risk of resistance emerging. This makes high-volume, high-return markets less likely to develop. Nevertheless, a core group of companies remain committed and have dedicated antimicrobial R&D divisions. To stimulate pharmaceutical company investment in R&D for new antimicrobials, the global AMR community has established a range of both "push" and "pull" incentives; these either lower the cost of developing a new antimicrobial medicine or reward its successful development.

Numerous pharmaceutical companies have publicly committed to tackling AMR, with many signing the "Declaration by the Pharmaceutical, Biotechnology and Diagnostics Industries on Combating Antimicrobial Resistance" (The Davos Declaration), which was made in 2016. This was followed by the publication by a core group of manufacturers of an "Industry Roadmap for Progress on Combating Antimicrobial Resistance" (Industry Roadmap). Both documents signal that several pharmaceutical and biotechnology companies are poised to play their part in addressing AMR.

The Antimicrobial Resistance Benchmark

There is growing recognition of the need for consensus on the responsibilities of each stakeholder engaged in addressing AMR, as well as the need for new, independent tools for tracking progress. The Access to Medicine Foundation has responded to this need, drawing on its expertise in developing industry metrics related to public health. The Foundation has developed the Antimicrobial Resistance Benchmark, the first independent and public tool for measuring how pharmaceutical companies are responding to AMR.

The goal of the Benchmark is to incentivise pharmaceutical companies to implement effective actions for tackling the problem of AMR. It will map the responses of a cross-section of the pharmaceutical industry to AMR, benchmarked against the consensus view on where they can and should be making progress. It will show where action is being taken in R&D, access and stewardship, as well as where deeper engagement

by the industry needs further incentivisation. The Benchmark will be a tool for companies, governments, investors, NGOs and others seeking to deepen industry engagement in efforts to curb AMR. Its analyses will identify innovative approaches and best practices, and highlight where progress is being made and where companies and other stakeholders can take action together, while pointing toward where new ideas are needed.

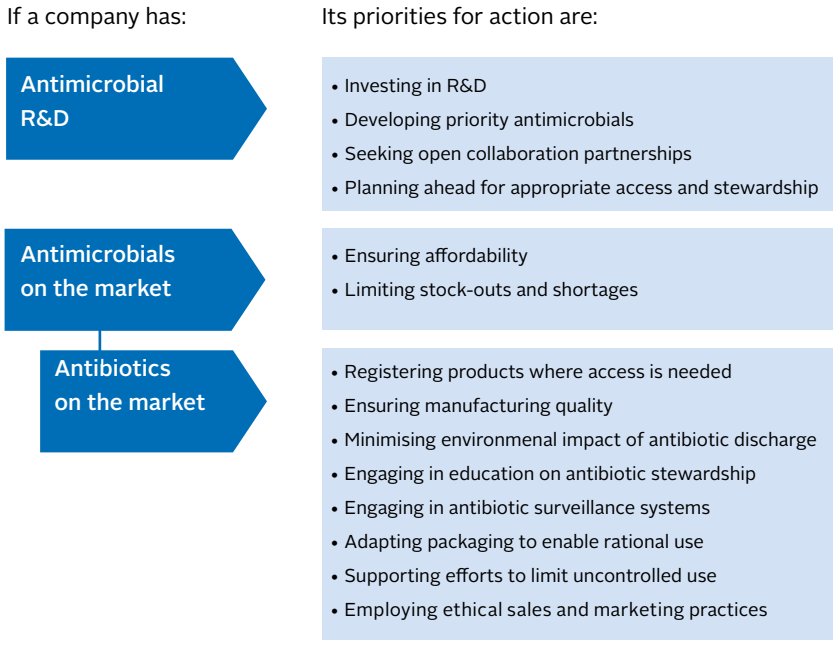
How the Benchmark was developed

To develop the Benchmark's methodology, the Foundation's research team sought input and gathered feedback from reports and a variety of stakeholders, such as governments, non-governmental organisations (NGOs), pharmaceutical companies and industry associations, investors, academia, public-private partnerships and relevant international organisations. The aim was to identify where stakeholders agree that pharmaceutical companies can and should be taking action to curb AMR (see Figure 1). These opportunities for action have been distilled into the Benchmark's analytical framework. Methodology development began with the drafting of a concept methodology after a review of reports and publications analysing the scope, scale and potential solutions to AMR. The review included policy reports by the AMR Review Team, Center for Disease Dynamics, Economics & Policy (CDDEP), Chatham House, DRIVE-AB, German Global Union for Antibiotics Research and Development (GUARD), Pew Charitable Trust, ReAct and WHO. The Foundation team also reviewed companies' public commitments to addressing AMR, as stated in the Davos Declaration and the subsequent Industry Roadmap. The review was guided by the principle that the Antimicrobial Resistance Benchmark complements existing processes for tackling AMR and builds on where consensus already exists between companies and stakeholders.

The review was followed by targeted engagement with key stakeholders working on AMR, who were invited to challenge the concept methodology. Their views were then balanced to

Figure 1. How pharmaceutical companies can curb AMR

The Antimicrobial Resistance Benchmark maps pharmaceutical companies' actions against priorities for limiting AMR. A company's opportunities to act are linked to its R&D pipeline and portfolio.



identify the areas in which pharmaceutical companies can be expected to take action. Industry views on the concept methodology were gathered in parallel. Strategic guidance was provided by an Expert Committee of specialists in AMR. The resulting methodology distributes the performance indicators across three areas where companies can be expected to contribute to the effort against AMR, described below as the Benchmark's Research Areas.

What the Benchmark covers

The Benchmark will evaluate pharmaceutical companies with antimicrobial products and the ability and a commitment to address AMR. A total of 30 companies are in scope – across multinational research-based pharmaceutical companies, generic medicine manufacturers and clinical-stage biopharmaceutical companies with antimicrobial pipelines. The opportunities for a company to act on AMR depends on its antimicrobial pipeline and portfolio. The Antimicrobial Resistance Benchmark will evaluate companies in three Research areas. Whether a company is measured in a specific Research Area depends on its antimicrobial portfolio and R&D.

Table 1. Analysis scopes for the AMR Benchmark

Company scope	30 companies
	• 8 large research-based pharmaceutical companies
	• 10 generic medicine manufacturers
	• 12 clinical-stage biopharmaceutical companies
Disease scope	Infectious diseases/pathogens
	• Bacteria, viruses, protozoa, fungi, helminths
Product scope	Antimicrobial medicines and vaccines
	• Medicines and vaccines in development
	• Antimicrobial medicines on WHO Model List of Essential Medicines 2017
	• Antibiotics
Geographic scope	Global, with access indicators focusing on 106 low- and middle-income countries

The Benchmark's analysis will be presented around the following three Research Areas:

A. Research & Development: This will assess company efforts to develop new medicines and vaccines for infectious diseases. It will map their R&D pipelines, highlighting where efforts are being concentrated and whether gaps remain. It will also identify the proportion of company revenue invested in antimicrobial R&D and recognise efforts to target pathogens whose distribution and drug resistance makes them a priority target for R&D. This Research Area will also examine whether companies seek collaborative R&D partnerships to target priority pathogens, and whether they put plans in place during development for ensuring successful candidate products are made available rapidly, appropriately and affordably in low- and middle-income countries.

B. Manufacturing & Production: This includes an examination of how companies maintain the quality of their antibiotics, the degree to which they make provisions in their manufacturing and environmental risk-management strategies for minimising the impact of antibiotic discharge, and how transparent they are about these strategies, the results of audits and the levels of antibiotic discharge.

C. Appropriate Access & Stewardship: This area will assess company engagement in educating healthcare professionals on antibiotic stewardship, use of innovative models to reduce uncontrolled antibiotic purchases, practices related to ethical marketing, the degree to which companies adapt their brochures and packaging to facilitate appropriate use of antibiotics, and their contributions to AMR surveillance. This Research Area also covers access to antimicrobial medicines in 106 low- and middle-income countries. Indicators evaluating access plans include company efforts to register their antibiotics in low- and middle-income countries, the evidence basis for company pricing strategies, and mechanisms for preventing stock-outs and improving demand forecasting for their highest-volume antimicrobial medicines. The aim is to understand how companies approach these two challenges of appropriate access and stewardship, and whether they integrate their approaches.

INTRODUCTION

The rise of AMR and the role of the pharmaceutical industry

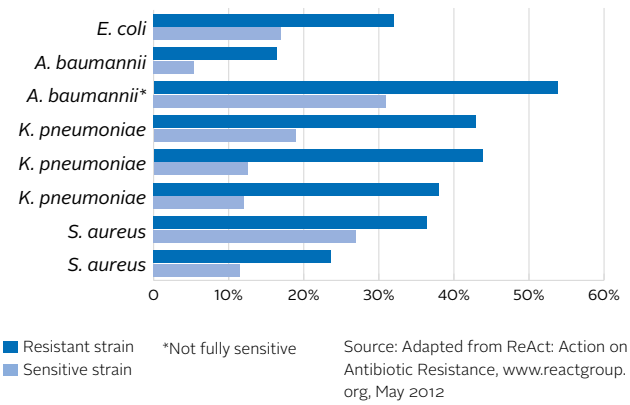
Antimicrobial resistance (AMR) is a widely recognised and growing problem that causes over 700,000 deaths each year worldwide.[1] At the same time, millions of people cannot access the antimicrobial medicines they need, despite having curable infections.[2] These situations must be addressed in tandem. Steps to increase access must include measures to prevent resistance; steps to curb resistance must include measures to enable appropriate access. Progress depends on coordinated, disciplined efforts from many different players, not least in government, but also across the healthcare and farming industries and the development and global health communities.

AMR threatens all countries

In recent decades, AMR has become widespread, irrespective of countries' level of income. In Europe, it has been estimated that 25,000 people die every year from antibiotic-resistant bacteria[3] (see Figure 2). A recent report by the US Centers for Disease Control and Prevention (CDC) conservatively estimated that at least 2 million illnesses and 23,000 deaths a year in the USA could be attributed to antibiotic resistance.[4] Such estimates are useful for giving an indication of the scale of the problem, yet it is difficult to determine whether resistance is the cause of death or it is a correlate of long antibiotic treatment, hospitalisation and underlying sickness.

Figure 2. Antibiotic resistance and increased risk of death

The figure compares death rates (mortality) in patients with resistant and sensitive strains of selected bacteria. Some pathogens are shown more than once, representing available data sets.



Source: Adapted from ReAct: Action on Antibiotic Resistance, www.reactgroup.org, May 2012

The true extent of the burden of resistant pathogens is even less well characterised for low- and middle-income countries. In part, this is due to an absence of local disease surveillance systems, which are critical for monitoring and preventing the rise and spread of diseases. The ability of different stakeholders to understand and respond to the challenges raised by AMR is affected by significant data limitations. For instance, information about antibiotic use, resistance levels and transmission patterns is still scarce in many countries. Nevertheless, we know that mortality rates due to bacterial infections such as untreated pneumonia and sepsis continue to be a public health problem in low- and middle-income countries, due to poor and/or limited access to relevant medicines, especially in children.[5] Many community-based infectious diseases, such as tuberculosis, remain more common in low- and middle-income countries than in wealthier countries.

How does the problem vary globally?

AMR affects human health when infections become difficult to treat or life-threatening, and the appropriate antimicrobial mediciness 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 individuals and communities depends on an interplay of factors, including the distribution of pathogens, 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 existing antimicrobial medicines while also promoting their overuse. These issues are closely interlinked and can contribute to resistance; attempts to increase access can lead to overuse, which leads in turn to greater resistance. This then increases the need for second- and third-line products that are more expensive, and thus harder to access. The need for new strategies and programmes to appropriately increase access to antimicrobial medicines remains particularly acute in low- and middle-income countries.[2]

In the hospital setting, particularly in high-income countries, the public health focus and most clinical intervention is shift-

The need to increase appropriate access to antimicrobials is particularly acute in many low- and middle-income countries.

ing to the increasing burden of chronic diseases including cancers, relative to infectious diseases. Where this shift has taken place, the infections that persist now tend to occur in sicker patients and in challenging settings such as hospital intensive care units. The resistant pathogens that have emerged here 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 chance exists for a dramatic increase in high-risk infections.

Growing demand

Infectious disease products may broadly be broken down into three categories: vaccines, diagnostics and antimicrobial medicines. The global market for such products reached USD 108.4 billion in 2015, and is forecast to reach USD 183.2 billion in 2021.[6] The antibiotic market is expected to grow from USD 27.1 billion in 2015 to USD 35.6 billion in 2022, in step with growing demand for generic antibiotics from emerging markets.[7] Human consumption of antibiotics is mainly growing in low- and middle-income countries, where they are often accessed over the counter rather than by prescription. Growing demand coupled with poor surveillance and stewardship is likely to drive the emergence of resistant strains.

The majority of antibiotics are generic; only a small number remains on patent.[8] In general, new antibiotics, antimicrobial medicines and vaccines are developed by either large research-based pharmaceutical companies or smaller biopharmaceutical companies. However, 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

As AMR grows, there is a pressing need for novel products to be developed to treat life-threatening infections. Yet there is little incentive for pharmaceutical companies to invest in antimicrobial research & development (R&D), not least because of the major technical challenges involved in discovering and developing new antimicrobial classes. There is little promise of a swift return on investment, as well as questions around pricing and affordability. New antibiotics in particular are highly sought after, yet must be used conservatively to limit the risk of resistance emerging. This makes high-volume, high-return markets less likely to develop. Since 2000, several pharmaceutical companies have left the antibiotics market, stopping production and engagement in R&D. The number of antibiotics in development also fell sharply.[9] Nevertheless, a core group of companies remain committed and have dedicated antimicrobial R&D divisions. A growing number of smaller biopharmaceutical companies demonstrate a strong focus on antimicrobial R&D.

To incentivise pharmaceutical companies to invest in R&D for new antimicrobial medicines and vaccines, the global AMR community has established “push” incentives that reduce the costs of necessary inputs for developers. For instance, the European Commission partners with the European Federation of Pharmaceutical Industries and Associations (EFPIA) in the Innovative Medicines Initiative (IMI); World Health Organization (WHO) and the Drugs for Neglected Diseases initiative (DNDi) have created the Global Antibiotic Research and Development Partnership (GARDP), which is supported by the Federal Ministry of Health of Germany, the Netherlands’ Ministry of Health, Welfare and Sports, the South African Medical Research Council, and UKAID; the US government’s Biomedical Advanced Research and Development Authority (BARDA) and the Wellcome Trust provide funding to CARB-X.

"Pull" incentives are also being developed. They involve the promise of a reward for the development of new antimicrobials targeting priority pathogens. For instance, the United States' Generating Antibiotic Incentives Now (GAIN) Act grants an additional five years of market exclusivity for companies developing antibiotics that target a selected group of qualifying pathogens. Numerous initiatives, such as DRIVE-AB and the German Global Union for Antibiotics Research and Development (GUARD), have produced policy recommendations on how to best to structure pull incentives. Novel as well as existing antimicrobial medicines need to be affordably priced and prudently used. The challenge is to ensure affordable, sufficient and appropriate access, while advancing antimicrobial stewardship, within a viable business model.[10]

Multiplayer solution

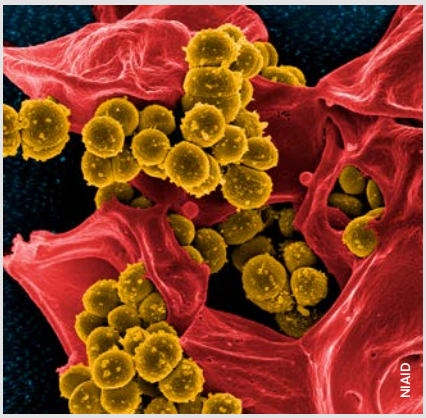
In 2016, UN Member States committed to addressing the growing problem of antimicrobial resistance in the 2030 Agenda for Sustainable Development. Indeed, AMR is expected to affect the potential achievement of Sustainable Development Goal 3 (Good Health & Wellbeing), among others. That AMR has risen up the global agenda is due at

PATHOGENS AND RESISTANCE

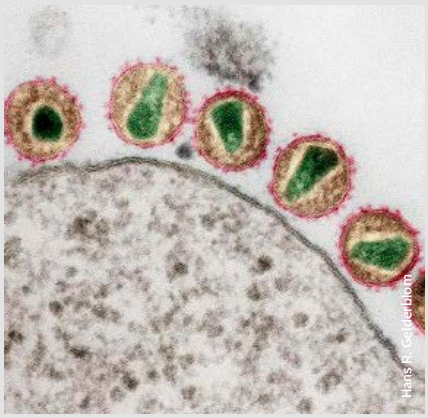
Four main groups of pathogenic microorganisms are relevant to current efforts to curb AMR: bacteria (such as those causing pneumonia and meningitis), viruses (such as HIV), fungi (such as *Candida*) and parasites (such as *Plasmodium falciparum*, which causes malaria). There is large variation among these groups in how resistance emerges and is transferred.

Certain pathogens are already resistant to most antimicrobials on the market. Resistance emerges due to a variety of reasons such as the inappropriate use of medicines, low-quality medicines, incorrect prescriptions and issues with infection prevention and control.

New and adapted medicines targeting different pathogens must take into account their modes of resistance. Resistance mechanisms can comprise, for example, structural changes in or around a medicine's target molecule; reduced permeability of the cell membrane to the medicine; and the production of enzymes that inactivate the medicine.

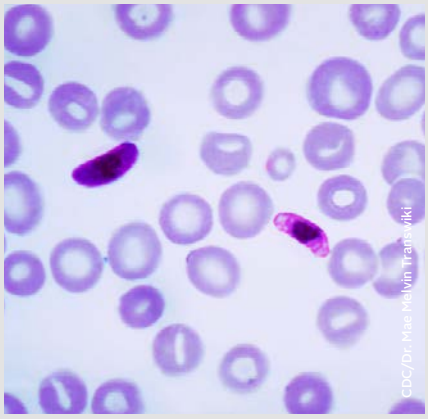


Most infections with Methicillin-resistant *Staphylococcus aureus* (MRSA, above) occurr in a hospital setting.



The HIV virus (above) has been identified by WHO as a priority for strategies to address AMR.

Some strains of the *Candida aurus* fungus (above) are resistant to all three major classes of antifungal drugs.



There is a limited number of drugs available to treat or prevent malaria caused by certain strains of the parasite *Plasmodium falciparum* (above).

least in part to the actions of a range of advocacy and policy-oriented organisations and initiatives, such as 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).

Limiting AMR requires a consolidated, concerted effort by multiple stakeholders, including governments, pharmaceutical companies, public health authorities, international health organisations, and academic institutions to name a few. AMR is a public health issue that impacts not only human health, but the animal and agricultural industries as well. Successfully addressing AMR requires a "One Health" approach that stimulates increased access and affordability, stewardship that limits overuse, innovative R&D in next generation medicines and a higher level of environmental care in the management of antibiotic manufacturing and discharge. Action by governments is also essential. Numerous pharmaceutical companies have publicly committed to addressing AMR, with many signing the "Declaration by the Pharmaceutical, Biotechnology and Diagnostics Industries on Combating Antimicrobial Resistance" in 2016,[11] followed by the publication of the "Industry Roadmap for Progress on Combating Antimicrobial Resistance".[12] This is a clear sign that several pharmaceutical and biotechnology companies are poised to play their part in addressing AMR.

There is growing recognition that we need consensus on the responsibilities for each stakeholder, as well as new, independent tools for publicly tracking progress.[1] The Access to Medicine Foundation has responded to this need, drawing on its expertise in developing industry metrics related to public health. The Foundation has developed the Antimicrobial Resistance Benchmark, the first independent and public tool for measuring how pharmaceutical companies are responding to AMR.

A BENCHMARK TO GUIDE DEEPER PHARMACEUTICAL INDUSTRY ENGAGEMENT IN AMR

The goal of the Antimicrobial Resistance Benchmark is to guide and incentivise pharmaceutical companies to adopt and implement effective actions for tackling the problem of AMR. It will map the responses of a cross-section of the pharmaceutical industry to AMR, benchmarked against the consensus view on where they can and should be making progress. It will show where action is being taken, in R&D, access and stewardship, as well as where deeper engagement by the industry needs further incentivisation. It will also shine a light on where more data is needed and where data collection should be prioritised.

To develop the Benchmark's methodology, the Foundation has applied its proven process for building consensus on the role of pharmaceutical companies in tackling global health priorities. The Foundation's research team sought input and gathered feedback from a variety of stakeholders, such as governments, non-governmental organisations, pharmaceutical companies and industry associations, investors, academia, public-private partnerships and relevant international organisations. The aim of this process was two-fold: to build consensus on the pharmaceutical industry's role in limiting AMR; and to ensure the Antimicrobial Resistance Benchmark is a useful tool for pharmaceutical companies and others seeking to curb AMR. The methodology has been finalised in consultation with experts on AMR.

The Benchmark has been developed to give companies, governments, investors, NGOs and others a tool for deepening industry engagement in efforts to curb AMR. The Benchmark metrics and analyses will highlight where good practice and progress can be expanded, and where companies and other stakeholders can take action together, while pointing toward where new ideas are needed.

BUILDING THE METHODOLOGY

How experts' views were distilled into a new benchmarking tool

The Antimicrobial Resistance Benchmark is an analytical framework for mapping how the pharmaceutical industry is responding to the rise of AMR. To develop it, the Foundation applied its proven process for building consensus on the role of pharmaceutical companies in tackling global health priorities. The Benchmark Methodology distills views of experts and stakeholders in the AMR field, industry, NGOs, governments and investors.

Methodology development began with a review of reports and publications analysing the scope, scale and potential solutions to AMR. This was followed by targeted engagement with key stakeholders working in antimicrobials. Strategic guidance was provided by an Expert Committee of specialists in AMR.

Toward a first concept methodology

The initial review assessed the current degree of consensus on the role and responsibilities for pharmaceutical and biotechnology companies in limiting AMR. The process included a literature review of academic papers, as well as policy reports from relevant organisations and initiatives, including the AMR Review Team, CDDEP, Chatham House, DRIVE-AB, GUARD, Pew Charitable Trust, ReAct and WHO. The Foundation team also analysed companies' public commitments to addressing AMR, as stated in the Davos Declaration on Antibiotic Resistance and the Industry Roadmap for Progress on Combating Antimicrobial Resistance.[11,12] The review was guided by the principle that the Antimicrobial Resistance Benchmark complements existing processes for tackling AMR and builds on where consensus already exists between companies and stakeholders.

The Foundation mapped its conclusions from the review against company data submitted for the Access to Medicine Index (also published by the Access to Medicine Foundation). This gave a preliminary indication of the perceived role for companies and of data that can feasibly be collected from companies and other sources. Based on these indications, the Foundation team developed the first concept for an Antimicrobial Resistance Benchmark of pharmaceutical companies. This formed the starting point for targeted stakeholder consultations.

STAKEHOLDER DIALOGUE

The Foundation invited representatives of key stakeholder groups working on AMR to challenge different aspects of the concept methodology. Aspects of the methodology were discussed with a range of international organisations, departments of multiple governments, NGOs, leading research centres and groups, and other initiatives addressing AMR. The scope of discussions ranged widely, from the Benchmark's objectives and analytical framework, to individual indicators and the feasibility of data collection. Industry views on the concept methodology were gathered in parallel. The Foundation spoke with companies individually, as well as with industry organisations and alliances, such as the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), Biotechnology Innovation Organization (BIO), Medicines for Europe and the AMR Industry Alliance.

Role of the Expert Committee

Strategic guidance was provided by the Expert Committee (EC) for the Antimicrobial Resistance Benchmark, an independent body of experts, from top-level academic centres, donor governments, local governments in low- and middle-income countries, investors and companies. The EC met in June 2017 to review proposals for the scope, structure and analytical approach of the Benchmark. Their recommendations helped identify ways forward where disagreement or uncertainty existed regarding areas of research.

The Expert Committee members:

Hans Hogerzeil (Chair)	University of Groningen
Greg Frank	Biotechnology Innovation Organization
Nina Grundmann	IFPMA
Magdalena Kettis	Nordea
Jeremy Knox	Formerly The Review on Antimicrobial Resistance
Joakim Larsson	University of Gothenburg
Marc Mendelson	University of Cape Town
Katarina Nedog	Medicines for Europe
Evelina Tacconelli	University of Tübingen
Evelyn Wesangula	Ministry of Health, Kenya

STAKEHOLDERS BY GROUP

Discussions were held with representatives of a wide range of organisations, including:

Government ministries of: The Netherlands, Germany, Japan, Kenya, UK, US.

International organisations: European Union, Organisation for Economic Co-operation and Development, World Health Organization.

Research and academic groups: Center for Disease Dynamics, Economics & Policy, Chatham House, Pew Charitable Trusts, the Review on Antimicrobial Resistance, Robert Koch Institute, University of KwaZulu-Natal.

Industry: International Federation of Pharmaceutical Manufacturers and Associations, Biotechnology Innovation Organization, Medicines for Europe and the AMR Industry Alliance, individual companies.

Investors: Aviva, Nordea, Schroders, the Farm Animal Investment Risk and Return Initiative.

NGOs: The Alliance for the Prudent Use of Antibiotics, the Alliance to Save our Antibiotics, As You Sow, Médecins Sans Frontières.

Others: The Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), the DRIVE-AB project, the Global Antibiotic Research & Development Partnership, the Global Antibiotic Resistance Partnership, the UN Foundation, the Wellcome Trust, the World Economic Forum.

Stakeholders did not align on all topics. Where differences were apparent, the Foundation balanced the views presented to identify the most appropriate way forward.

KEY DISCUSSIONS AND DECISIONS

The Foundation has engaged in targeted discussions with AMR experts on how pharmaceutical and biotechnology companies should address AMR. Below is a summary of the key topics discussed and decisions reached.

Company scope: stakeholders focus on antibiotic resistance
Among AMR stakeholder groups, there is a discernible focus on antibiotic resistance, rather than resistance to other antimicrobials. The Foundation has decided to reflect this focus in the selection of companies for the first Antimicrobial Resistance Benchmark: global antibiotic sales is one of the key criteria for bringing large research-based pharmaceutical companies and generic medicine manufacturers into scope.

Broad agreement on main areas of company responsibility
The Foundation's discussions quickly identified general alignment on critical areas of pharmaceutical industry responsibility:

- R&D for new antimicrobial medicines, with a focus on priority R&D gaps identified by WHO and/or the CDC;
- Responsible manufacturing and production process, focused on antibiotic discharge; and
- Approaches to antibiotic stewardship and, in low- and middle-income countries, accessibility and affordability of on-market antimicrobial medicines.

These areas have been translated into the Benchmark's three Research Areas:

A RESEARCH & DEVELOPMENT

B MANUFACTURING & PRODUCTION

C APPROPRIATE ACCESS & STEWARDSHIP

BUILDING THE METHODOLOGY

KEY DISCUSSIONS PER RESEARCH AREA

A RESEARCH & DEVELOPMENT

Priority pathogens for antimicrobial R&D by companies
There was strong alignment on the need to encourage R&D for anti-infectives. Experts were also generally interested in mapping whether companies target pathogens deemed a priority for R&D by WHO and the CDC. Such R&D will be captured and rewarded by the Benchmark. There was strong alignment within stakeholder discussions that emerging pathogens, such as the Zika, Ebola and MERS viruses, should not be included in this methodology as AMR priority pathogens, at this point in time.

Early planning needed for access and stewardship
Stakeholders agreed that companies should start planning during late-stage development for new products to be swiftly accessible. At the same time, stakeholders saw it as essential that companies take steps to ensure future anti-infectives are used with stewardship in mind. The Benchmark will assess and reward stewardship plans and/or access provisions that are put in place during development for products that target priority pathogens.

B MANUFACTURING & PRODUCTION

Wastewater management technicalities and transparancy
There was agreement that companies must minimise the impact of manufacturing processes on antibiotic resistance. However, the role of manufacturers was viewed by some to be limited given companies' reliance on third-party suppliers for antibiotic production. Stakeholders expect companies to monitor levels of antibiotics in manufacturing wastewaters. Some also called for transparency here; others doubted the value of such transparency given a lack of a clear scientific targets. Pharmaceutical companies have committed to establishing and standardising science-driven targets for discharge concentrations for antibiotics.[11] The Benchmark will capture company strategies and processes relating to wastwater, and will use data collected to further the discussion on the role of manufacturers on environmental impact of antibioitic production.

C APPROPRIATE ACCESS & STEWARDSHIP

Company responsibilities around stewardship
The industry's role in antibiotic stewardship generated conflicting views among stakeholders. Some felt that stewardship activities, such as the surveillance of resistance and educational initiatives, should be the sole responsibility of governments and public health authorities; it was felt that this would avoid conflicts of interest for industry. Others argued that, as long as conflicts of interest are identified and systematically managed, companies can and should contribute to the stewardship of their products, particularly considering their deep understanding of their products. The Benchmark includes indicators that will capture how companies engage in these activities and identify current best practice.

Alignment to address appropriate access and responsible stewardship in tandem
Regarding access, stakeholder discussions centered mostly on the need for improved access in low- and middle-income countries. There continues to be high mortality and morbidity due to infections such as pneumonia and sepsis in such countries. At the same time, improving access needs to be cautiously managed to prevent inappropriate use. The Foundation concluded that companies' access-related activity must be assessed and measured alongside stewardship-related actions.

What the Benchmark measures

The Antimicrobial Resistance Benchmark assesses company behaviour regarding specific diseases and product types and in 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
	• 10 generic medicine manufacturers
	• 12 clinical-stage biopharmaceutical companies
Disease scope	Infectious diseases/pathogens
	• Bacteria, viruses, protozoa, fungi, helminths
Product scope	Antimicrobial medicines and vaccines
	• Medicines and vaccines in development
	• Antimicrobial medicines on WHO Model List of Essential Medicines 2017
	• Antibiotics
Geographic scope	Global, with access indicators focusing on 106 low- and middle-income countries

WHAT WE MEASURE

Scopes of analysis

The Antimicrobial Resistance Benchmark assesses pharmaceutical company behaviour regarding specific diseases and product types and in 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.

COMPANY SCOPE

The Benchmark covers pharmaceutical companies with antimicrobial products and/or R&D projects and the ability and a commitment to address AMR. Thirty companies are in scope, selected based on a combination of factors, including R&D focus and experience, antibiotic market share and public commitment to AMR.

The landscape of pharmaceutical companies with antimicrobials for human health can be divided into three broad and overlapping groups: large research-based pharmaceutical companies; generic medicine manufacturers; and clinical-stage biopharmaceutical companies. There are key differences in the expertise and capacities of each type, notably in the size and nature of their product portfolios and their R&D focus and expertise. As a result, each group can address AMR in different ways.

With this in mind, the Foundation uses these broad categorisations to structure its analytical framework. The thirty companies in scope have been grouped according to their key defining characteristic (see Figure 3). The Foundation acknowledges that several companies in scope could be placed in more than one group. Where possible and appropriate, in the Benchmark report, such nuances will be used to inform the analysis of company performance. Each company will be evaluated in those areas where it has relevant products and/or activities.

Criteria for inclusion

The companies in scope have been selected based on a combination of factors. Companies with an antibiotics focus have been prioritised in this first iteration of the Benchmark. Bacteria represent the greatest number of resistant pathogens, the widest geographic scope of resistance, and the bulk of the interventions at the government, manufacturer, provider and patient levels. The final selection of companies was based on several size and opportunity criteria, including: (1) relevance of marketed portfolio, (2) relevance of antimicrobial pipeline, and (3) commitment to addressing AMR. A small number of companies were selected following clear stakeholder recommendations and on their readiness to engage with the data-collection process.

Large research-based pharmaceutical companies were selected based on their antibiotic business volume and revenue, their antimicrobial pipelines and portfolios and/or public commitments to tackling AMR (i.e., they had signed, per 29 April 2016, the Davos Declaration and Industry Roadmap on AMR).[11,12,13] Generic medicine manufacturers were selected if they ranked within the global top 10 by antibiotics volume and/or if they are signatories to the Industry Roadmap on AMR.[12,14] Clinical-stage biopharmaceutical companies were identified as having at least one drug in clinical development targeting a priority pathogen as overviewed by The Pew Charitable Trusts' report[15] on antibiotics registered at clinicaltrials.org. All of the companies selected from this list for inclusion have signed the Davos Declaration, except one (Summit Therapeutics). Industry associations representing these and other companies have signed the Davos Declaration.

Table 2. 2018 Antimicrobial Resistance Benchmark – companies in scope

LARGE RESEARCH-BASED PHARMACEUTICAL COMPANIES

	Country	Ticker	Stock exchange	Revenue (bn USD)[1]	Global antibiotic sales Kgs[2]	Signatory to the Davos Decl.[3]	Signatory to the Industry Roadmap[4]
GlaxoSmithKline plc	GBR	GSK	London	34.4	28,810.0	●	●
Johnson & Johnson	USA	JNJ	New York	71.9	2,053.6	●	●
Merck & Co., Inc.	USA	MRK	New York	39.8	12,273.1	●	●
Novartis AG	CHE	NIVN	Six Swiss Exchange	47.6	3,000.0	●	●
Pfizer Inc.	USA	PFZE	New York	52.8	9,028.9	●	●
Roche Holding AG	CHE	RO; ROG	Six Swiss Exchange	49.6	349.5	●	●
Sanofi	FRA	SAN	EURONEXT Paris	35.6	–	●	●
Shionogi & Co., Ltd.	JPN	4507	Tokyo	3.0	–	●	●

GENERIC MEDICINE MANUFACTURERS

	Country	Ticker	Stock exchange	Revenue (bn USD)[1]	Global antibiotic sales International Units[5]	Signatory to the Davos Decl.[3]	Signatory to the Industry Roadmap[4]
Aspen Pharmacare Holdings Limited	ZAF	APN	Johannesburg	2.4	3.2		
Aurobindo Pharma Ltd.*	IND	ARBP	NSE	2.3	–		
Cipla Inc.	IND	CIPLA	NSE	2.3	–	●	●
Dr. Reddy's Laboratories Ltd.	IND	DRRD / RDY	NSE / New York	2.2	2.1		
Fresenius Kabi AG	DEU	FRE	Frankfurt	6.3	8.3		
Lupin Limited	IND	LPC	NSE	2.6	2.7		
Macleods Pharmaceuticals Ltd.*	IND	–	–	–	–		
Mylan NV	USA	MYL	NASDAQ	11.0	11.5		
Sun Pharmaceutical Industries Ltd.	IND	SUNP	NSE	4.7	5.5		
Teva Pharmaceutical Industries Ltd.	ISR	TEVA	New York / Tel Aviv	21.9	13.3		

BIOPHARMACEUTICAL COMPANIES WITH PRIORITY R&D PROJECTS

	Country	Ticker	Stock exchange	Revenue (mn USD)[1]	Priority R&D projects	Signatory to the Davos Decl.[3]	Signatory to the Industry Roadmap[4]
Achaogen Inc.	USA	AKAO	NASDAQ	41.8	1	●	
Cempra Inc.	USA	CEMP	NASDAQ	18.0	2	●	
Entasis Therapeutics Inc.	USA	–	–	–	2	●	
Melinta Therapeutics Inc.	USA	–	–	–	1	●	
MGB Biopharma	GBR	–	–	–	1	●	
Motif Bio plc	GBR /USA	MTFB	London / NASDAQ	0.0	1	●	
Nabriva Therapeutics plc	IRL	NBRV	NASDAQ	6.5	1	●	
Polyphor Ltd.	CHE	–	–	–	1	●	
Summit Therapeutics*	GBR	SMMT	London / NASDAQ	3.0	1		
Tetraphase Pharmaceuticals Inc.	USA	TTPH	NASDAQ	5.1	3	●	
The Medicines Company	USA	MDCO	NASDAQ	167.8	1	●	
Wockhardt Ltd.	IND	WPL	NSE	619.0	4	●	●

*Company included on basis of stakeholder recommendations and willingness to participate.

1 Revenue = fiscal year 2016/17 (Exchange rates from www.x-rates.com, the exchange rate of the last day of the fiscal year was used)
2 Mordor Intelligence. (2016). Global Antibiotics Market Leaders – Top 10 by value, volume and company profiles.
3 Declaration by the Pharmaceutical, Biotechnology and Diagnostics Industries on Combating Antimicrobial Resistance. Signatories as at April 29, 2016.
4 Industry Roadmap for Progress on Combating Antimicrobial Resistance. September 2016.
5 Mordor intelligence (2016). Top 10 Generic Antibiotic Manufacturers by Volume – Custom Study.
6 The PEW Charitable Trusts. (March, 2016). Antibiotics Currently in Clinical Development.

DISEASE SCOPE

The disease scope is deliberately broad. This is to ensure the Benchmark can capture the full range of companies' AMR-related policies and practices. All infectious diseases are in scope for analysis. Certain pathogens have been deemed by stakeholders to be a priority for efforts to curb AMR, particularly for R&D. Priority pathogens identified by the Benchmark are listed in Appendix I. These are drug-resistant pathogens as defined by WHO's R&D Priority List and by CDC's Biggest Threat List.

The Benchmark applies a wide definition of infectious disease: as occurring when microbial pathogens invade a host and harm tissues, and can be transmitted to other individuals. It encapsulates diseases caused by the four main groups of infectious microorganisms relevant to AMR: bacteria, viruses, fungi, and protozoa.

PRODUCT SCOPE

The product scope covers antimicrobial medicines on the market and in development, and vaccines in development. Vaccines are undoubtedly critical for limiting AMR. See the 2017 Access to Vaccines Index for an assessment of vaccine companies' practices for improving vaccination coverage. Each of the Benchmark's three Research Areas has a tailored product scope:

Research & Development: antimicrobial medicines and vaccines in discovery, preclinical and clinical phases 1-3, or approved in 2016–17.

Manufacturing & Production: marketed antibiotics; the potential impact of companies' manufacturing processes on AMR mainly relate to antibiotic discharge into the environment and parameters that promote antibacterial resistance.

Access & Stewardship:

- **For Access indicators (C.1 – C.3)**: antibiotics for indicator C.1; antimicrobial medicines on the WHO Model List of Essential Medicines 2017 (EML), Chapter 6, for indicators C2, C.3 (see Appendix III). These medicines are deemed essential to the basic functioning of any health system. Access to these medicines, particularly in low- and middle-income countries, is a continued priority that must be considered alongside efforts to curb AMR.
- **For Stewardship indicators (C.4 - C.8):** marketed antibiotics. Stewardship practices to prevent overuse can limit the emergence and spread of resistance.

Table 3. How products will be assessed per Research Area

The table shows which products are relevant to each Research Area. Whether a particular product group is relevant has been determined through stakeholder consultation.

	AMR Benchmark Research Areas			
	Research & Development	Manufacturing & Production	Appropriate Access & Stewardship	
Products			Access	Stewardship
Innovative and adaptive antimicrobial medicines and vaccines in development	●			
Antimicrobial medicines on WHO Model List of Essential Medicines 2017			●	
Antibiotics		●	●	●

GEOGRAPHIC SCOPE

The geographic scope is global. Access indicators have an exclusive focus on low- and middle-income countries. Antimicrobial resistance is emerging across the globe. The need for new antimicrobials and sustainable antibiotic production are global priorities. The rational use of antibiotics in particular is needed wherever antibiotics are available.

Access metrics focus on low- and middle-income countries
The challenges of sufficient access and affordability are significantly higher in poorer countries. A group of indicators (A.4, C.1, C.2 , C.3) measure how companies either plan for or already address access to prioritised antimicrobial medicines in 106 low- and middle-income countries.[16] This group of countries is defined based on: (1) countries' level of income (gross national income [GNI] per capita); (2) their levels of development; and (3) the scope and scale of inequality in each country (see Appendix II). These assessments are based on data from the World Bank, the United Nations Development Programme (UNDP), and the United Nations Economic and Social Council (ECOSOC).[17,18,19]

How the Benchmark measures

The Antimicrobial Resistance Benchmark will map how 30 pharmaceutical, generic and biopharmaceutical companies are responding to the rise of AMR. It will assess their policies and practices for addressing antimicrobial resistance and for improving appropriate access to antimicrobial medicines and vaccines for people living in low- and middle-income countries. The Benchmark will compare companies' approaches, where relevant and appropriate, with reference to their antimicrobial pipelines and portfolios.

The analytical framework is structured along three Research Areas:

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

HOW WE MEASURE

Overview of the analytical framework

The Antimicrobial Resistance Benchmark analyses company actions using an analytical framework of three Research Areas and 15 metrics. Whether a company is assessed in a Research Area depends on its pipeine and portfolio. Each Research Area has a specific product and geographic scope.

A RESEARCH & DEVELOPMENT

ANALYSIS SCOPES

- Companies engaged in antimicrobial R&D
- All countries globally
- Antimicrobial medicines and vaccines in development

WHAT THIS AREA COVERS

The Benchmark will capture companies' R&D activities targetting infectious diseases. It will map R&D and reward efforts to target pathogens whose distribution and drug resistance makes them a priority target for R&D. It will also recognise companies that plan for the stewardship and accessibility of new products that target priority pathogens, following market entry.

B MANUFACTURING & PRODUCTION

ANALYSIS SCOPES

- Companies with antibiotics on the market
- All countries globally
- Antibiotics

WHAT THIS AREA COVERS

The Benchmark will compare company strategies for limiting the impact of antibiotic manufacturing on resistance. It will assess how companies take antibiotic discharge into account in their manufacturing and environmental risk-management strategies. It will also ask how companies maintain the quality of their antibiotics.

C APPROPRIATE ACCESS & STEWARDSHIP

ANALYSIS SCOPES

- Companies with antimicrobial medicines on the market

Access indicators
- 106 low- and middle-income countries
- Antimicrobial medicines on the WHO Model List of Essential Medicines 2017; Antibiotics

Stewardship indicators
- All countries globally
- Antibiotics

WHAT THIS AREA COVERS

The Benchmark will assess companies' access strategies for antimicrobial medicines in low- and middle-income countries, alongside their global stewardship strategies for antibiotics. The aim is to understand how companies approach these twin challenges, including whether and how each company integrates these approaches.

A RESEARCH & DEVELOPMENT INDICATORS

A.1	R&D investments	Financial R&D investments dedicated to the development of antimicrobial medicines and vaccines. The denominator is a company's (i.e. research-based or generic) total revenue of its pharmaceutical and vaccine products. For clinical-stage biopharmaceutical companies this, is an absolute measurement.
A.2	R&D projects	Size of pipeline and public health value of investigational antimicrobials and vaccines under development. Public health value is evaluated based on criteria such as targeting a priority pathogen and/or new mode of action.
A.3	R&D collaborations	The company engages in open collaborations to overcome the scientific challenges of creating new antimicrobial medicines and vaccines targeting priority pathogens.
A.4	Facilitating access and stewardship	The proportion of late-stage antimicrobial R&D projects targeting priority pathogens for which the company provides evidence of having: 1) access-to-medicine provisions for the countries in scope; and 2) global stewardship provisions in place. Late-stage R&D includes projects in phase II and III of clinical development (developed in-house or through collaborative R&D). Access-to-medicine provisions refer to plans for ensuring the future appropriate availability and affordability of novel products in countries in scope.

B MANUFACTURING & PRODUCTION INDICATORS

B.1	Environmental risk management strategy	The company has an environmental risk management strategy to minimise environmental impact of manufacturing discharge of antibiotics that: 1) applies to its own facilities, to third-party manufacturers of antibiotic API and drug products and to waste treatment plants; 2) includes auditing; and 3) includes discharge limits.
B.2	Disclosure on environmental risk management	The company publicly discloses: 1) its environmental risk management strategy to minimise environmental impact of manufacturing discharge of antibiotics; 2) results of audits on this strategy of the company's manufacturing sites; 3) results of audits on this strategy of third parties' manufacturing sites of antibiotic Active Pharmaceutical Ingredient (API) and drug products and of wastewater treatment plants; 4) the identities of their third parties manufacturing antibiotic API and drug products, and antibiotic waste treatment plants; and 5) the levels of antibiotic discharge.
B.3	Manufacturing high-quality antibiotics	The company has mechanisms in place to ensure that its own and third-party production facilities manufacturing antibiotic drug products maintain high quality of antibiotic production consistent with international standards developed and accepted by recognised national and international authorities.

C APPROPRIATE ACCESS & STEWARDSHIP INDICATORS

C.1	Registration of antibiotics	The company files to register its newest antibiotics in the highest number of countries in scope.
C.2	Pricing of antimicrobials	The company implements an appropriate access strategy that includes affordability considerations of its highest volume antibiotics and non-antibiotic antimicrobial medicines for countries in scope.
C.3	Ensuring sustainable delivery	The company has mechanisms in place to improve supply chain efficiency aimed at preventing stock-outs and improving demand forecasting of its highest volume antibiotics and non-antibiotic antimicrobial medicines, so as to ensure sustainable delivery to countries in scope.
C.4	Supporting educational stewardship activities	The company engages and/or supports educational activities that are non-product specific to educate healthcare professionals (HCP) on antibiotic stewardship.
C.5	Ethical promotional activities	The company adopts ethical marketing practices that advance appropriate use of antibiotics in its promotional activities and has mechanisms in place to incentivise ethical marketing practices by its in-house and/or third-party sales representatives.
C.6	Brochure and packaging	The company implements brochure and packaging adaptation to facilitate appropriate use of antibiotics by patients, beyond local regulatory requirements, for its highest volume antibiotics. The company considers needs – literacy, language, cultural, demographic and environmental considerations – when adapting brochure and packaging.
C.7	AMR surveillance	The company has/supports/contributes to local and/or global antibiotic resistance surveillance systems
C.8	Reducing uncontrolled use	The company has innovative models and mechanisms in place with relevant stakeholders to reduce uncontrolled antibiotic purchase, such as over-the-counter (OTC) and non-prescription sales.

RESEARCH AREAS

A Research & Development

New and improved medicines and vaccines are critical to curb AMR, particularly new antibiotics that target resistant pathogens. Antibiotics mitigate against the effects of pathogen exposure during invasive procedures, underpinning modern medicine. Vaccines are also crucial; by preventing disease, they limit the risk that antimicrobial medicines are used irrationally, and in turn slow the emergence of resistance.

The Antimicrobial Resistance Benchmark will capture companies' R&D activities to develop new medicines and vaccines for infectious diseases. It will map companies' R&D pipelines, highlighting where efforts are being concentrated and whether gaps remain. This map will highlight R&D efforts to target "priority pathogens" - pathogens whose distribution and drug resistance makes them a priority target for R&D (see Appendix I). For projects targeting these pathogens, the Benchmark will capture companies' plans for ensuring new products can swiftly be made available and accessible following market entry. Only companies engaged in antimicrobial R&D will be assessed in this Research Area.

WHICH ACTIVITIES WILL BE ANALYSED IN R&D?

R&D investments

The Benchmark will capture the overall financial resources dedicated to antimicrobial R&D. The Benchmark assesses companies with considerably different financial resources available to invest in R&D. To recognise these differences, the Benchmark will primarily capture the proportion of revenue invested in antimicrobial R&D (rather than total investments). For biopharmaceutical companies in scope, absolute investments will be compared, as these companies are unlikely to have antimicrobials on the market. Generic medicine manufacturers can have an impact with incremental innovations, for example, improving the dosing regimen.

R&D projects

The Benchmark will map the size and distribution of compounds in development, including those targeting priority pathogens, within antimicrobial R&D. It will look at the size of companies' pipelines, and at the public health value of the investigational antimicrobial medicines and vaccines under development. A project's public health value will be evaluated based on a range of criteria, such as whether it targets a priority pathogen identified by WHO or CDC (see Appendix I) and/or has a new mode of action.

R&D collaborations

The Benchmark examines whether companies work in partnerships toward the development of new drugs that target priority pathogens. There is a widespread consensus that such partnerships (most often called Product Development Partnerships or PDPs) can accelerate drug development and to ensure accessibility is approached systematically and more fairly. PDPs pool multi-stakeholder expertise, promote the open and collaborative sharing of intellectual property, and ensure resources can be rapidly deployed.

Access and stewardship plans during late stage development

The Benchmark assesses whether companies create and disclose strategies for ensuring new products targeting priorioty pathogens can swiftly be made accessible upon market entry, and for facilitating their appropriate use. After a new medicine or vaccine has demonstrated its safety and efficacy in clinical trials, it must be registered with local authorities prior to marketing. The cost in terms of both money and time involved in this process means most medicines reach high-income markets first and reaches other markets only if sufficient revenue is generated to justify the additional expense. There are mechanisms, such as licensing and price commitments, that can enhance access to newer medicines and vaccines in a large number of low- and middle-income countries. For antimicrobial medicines, such mechanisms must be accompanied by plans to ensure novel products are used appropriately.

	Indicator	Rationale
A.1	**R&D investments** Financial R&D investments dedicated to the development of antimicrobial medicines and vaccines. The denominator is a company's (i.e. research-based or generic) total revenue of its pharmaceutical and vaccine products. For clinical-stage biopharmaceutical companies this is an absolute measurement.	To characterise the overall financial resources dedicated to antimicrobial R&D.
A.2	**R&D projects** Size of pipeline and public health value of its investigational antimicrobials and vaccines under development. Public health value is evaluated based on criteria such as targeting a priority pathogen and/or new mode of action.	To characterise the size and distribution of compounds in development by externally identified priorities.
A.3	**R&D collaborations** The company engages in open collaborations to overcome the scientific challenges of creating new antimicrobial medicines and vaccines targeting priority pathogens.	To evaluate the types of collaborative partnerships and the extent to which they are utilized to facilitate and streamline the R&D process.
A.4	**Facilitating access and stewardship** The proportion of late-stage antimicrobial R&D projects targeting priority pathogens for which the company provides evidence of having 1) access-to-medicine provisions for the countries in scope and 2) global stewardship provisions in place. Late-stage R&D includes projects in phase II and III of clinical development (developed in-house or through collaborative R&D). Access-to-medicine provisions refer to plans for ensuring the future appropriate availability and affordability of novel products in countries in scope.	To describe efforts currently being made to ensure that successful antimicrobial and vaccine candidates targeting priority pathogens are available rapidly and affordably and are used appropriately where needed.

RESEARCH AREAS

B Manufacturing & Production

Pharmaceutical manufacturing and production processes can contribute to antimicrobial resistance through two key routes: by releasing waste that includes antibiotics into the environment; and by manufacturing antibiotics with sub-therapeutic levels of the active antibiotic ingredient.

The Antimicrobial Resistance Benchmark will capture companies' strategies for upholding manufacturing standards in these two areas, thus limiting the impact on antimicrobial resistance. Because both of these routes relate to antibiotic manufacturing, only companies with antibiotics on the market will be assessed in this Research Area.

WHICH ACTIVITIES WILL BE ANALYSED IN MANUFACTURING & PRODUCTION?

Environmental risk-management strategy
During manufacturing, antibiotics can be washed into the environment as wastewaters are released, which risks promoting the development of antibiotic-resistant bacteria. The Benchmark will assess how companies take antibiotic discharge into account in their environmental risk management strategies, and how these are applied to third-party suppliers.

Disclosure on environmental risk management
The impact of environmental discharge on antibiotic resistance in humans is currently not well understood. For those working to better understand the mechanisms involved, greater insight into antibiotic levels in the environment is needed. The Benchmark will assess companies' transparency regarding risk-management strategies, audit results and discharge levels, and regarding first-tier suppliers that manage manufacturing and waste-treatment plants.

Manufacturing high-quality antibiotics
Sub-therapeutic doses can accelerate the development of antibiotic-resistance in bacteria. The most important action a company can take to help limit this is to manufacture high-quality antibiotics with the correct therapeutic dosages. The Benchmark will assess the mechanisms companies have put in place to maintain high-quality antibiotic production at its own and at third-party production facilities.

Indicator	Rationale
B.1 Environmental risk management strategy The company has an environmental risk management strategy to minimise environmental impact of manufacturing discharge of antibiotics that: 1) applies to its own facilities, to third-party manufacturers of antibiotic API and drug products and to waste treatment plants; 2) includes auditing; and 3) includes discharge limits.	To assess the incorporation of auditing and discharge limits in an environmental risk strategy within each phase of manufacturing and production, to minimise impact of antibiotic production on antibiotic resistance.
B.2 Disclosure on environmental risk management The company publicly discloses: 1) its environmental risk management strategy to minimise environmental impact of manufacturing discharge of antibiotics; 2) results of audits on this strategy of the company's manufacturing sites; 3) results of audits on this strategy of third parties' manufacturing sites of antibiotic API and drug products and of wastewater treatment plants; 4) the identities of their third parties manufacturing antibiotic API and drug products, and antibiotic waste treatment plants; and 5) the levels of antibiotic discharge.	To assess public availability of information to allow independent third parties to analyse and compare processes and performance.
B.3 Manufacturing high-quality antibiotics The company has mechanisms in place to ensure that its own and third-party production facilities manufacturing antibiotic drug products maintain high quality of antibiotic production consistent with international standards developed and accepted by recognized national and international authorities.	To assess areas at risk for producing medicines below therapeutic dose levels and/or of sub-optimal quality which can be a source of resistance.

RESEARCH AREAS

C Appropriate Access & Stewardship

Mortality rates due to bacterial infections are a public health problem in low- and middle-income countries due to poor and/or limited access to antibiotics. Plus, the effectiveness of these medicines is declining as increased use in other regions drives up rates of resistance. The twin challenges of ensuring good stewardship and improving access must be tackled in tandem. As the developers and manufacturers of antibiotics, pharmaceutical companies have the ability to positively influence both access and stewardship practices.

The Antimicrobial Resistance Benchmark will assess companies' access strategies regarding antimicrobial medicines in low- and middle-income countries, alongside their global stewardship of antibiotics. Companies will be assessed across a number of aspects ranging from education, to surveillance, to ethical and responsible marketing practices. Their practices must be seen in the broader context of antibiotic stewardship, which requires nuanced and multi-stakeholder collaborations between antibiotic manufacturers, governments, international health organisations and the animal and agricultural sectors. Access indicators examine company practices in 106 low- and middle-income countries; Stewardship indicators examine practices specifically related to antibiotics, with a global scope.

WHICH ACTIVITIES WILL BE ANALYSED IN APPROPRIATE ACCESS & STEWARDSHIP?

▸ ACCESS

Registration of antibiotics
Registration is the first step to enabling access. As such, the Benchmark will assess the efforts companies undertake to register their antibiotics in low-and middle-income countries.

Pricing of antimicrobials
Issues surrounding affordability influence access to almost all pharmaceutical products, including antimicrobial medicines, in many low- and middle-income countries. On affordability, the Benchmark will assess the evidence basis for companies' pricing strategies for these countries.

Ensuring sustainable delivery
Stock-outs of antimicrobial medicines can have a profound impact on access in low- and middle-income countries. The Benchmark will examine companies' mechanisms for preventing stock-outs and improving demand forecasting for their highest-volume antimicrobial medicines.

▸ STEWARDSHIP

Supporting educational stewardship activities
Awareness of AMR and how to prevent it is the first step in changing prescribing behaviour. Companies have expertise in this area and an opportunity to contribute. The Benchmark asks whether companies are educating healthcare professionals on antibiotic stewardship.

Ethical promotional activities
Companies have a clear responsibility to market their antibiotics ethically, not only with regard to the health of the patient but also to limit the risk of resistance. The Benchmark assesses whether companies are adopting and incentivising ethical marketing practices by their own and by third-party sales representatives.

Brochure and packaging
The information provided with antibiotics can improve the likelihood of their being used appropriately. The Benchmark captures whether companies adapt their brochures and packaging to facilitate the appropriate use of its antibiotics.

AMR surveillance
Surveillance systems are critical for monitoring, controlling and preventing the rise and spread of diseases and resistance. The Benchmark tracks companies' contributions to local and global systems for tracking antibiotic resistance.

Reducing uncontrolled use
Non-prescription sales of antibiotics represent a risk for increasing AMR. The Benchmark asks whether companies have innovative models and mechanisms in place to reduce uncontrolled antibiotic purchases.

	Indicator	Rationale
C.1	**Registration of antibiotics** The company files to register its newest antibiotics in the highest number of countries in scope.	To evaluate the geographic scope of registration filings of new antibiotics, particularly in the countries with the highest perceived need for greater access.
C.2	**Pricing of antimicrobials** The company implements an appropriate access strategy that includes affordability considerations of its highest volume antibiotics and non-antibiotic antimicrobial medicines for countries in scope.	To assess efforts to consider various affordability factors when developing and implementing pricing strategies for antimicrobial medicines.
C.3	**Ensuring continuous supply** The company has mechanisms in place to improve supply chain efficiency aimed at preventing stock-outs and improving demand forecasting of its highest volume antibiotics and non-antibiotic antimicrobial medicines so as to ensure sustainable delivery to countries in scope.	To evaluate measures taken by companies in their supply and manufacturing processes that may reduce the time between identification of a local shortage and re-stocking.
C.4	**Supporting educational stewardship activities** The company engages and/or supports educational activities that are non-product specific to educate healthcare professionals (HCP) on antibiotic stewardship.	To assess the types of educational activities a company engages in and/or supports that are non-promotional in nature and which contribute to improving knowledge and awareness around stewardship of antibiotics.
C.5	**Ethical promotional activities** The company adopts ethical marketing practices that advance appropriate use of antibiotics in its promotional activities and has mechanisms in place to incentivise ethical marketing practices by its in-house and/or third-party sales representatives.	To evaluate the extent to which antibiotic promotion materials reflect emerging resistance issues to enhance awareness around appropriate use, and the extent to which ethical marketing practices may support antibiotic stewardship.
C.6	**Brochure and packaging** The company implements brochure and packaging adaptation to facilitate appropriate use of antibiotics by patients, beyond local regulatory requirements, for its highest volume antibiotics. The company considers needs – literacy, language, cultural, demographic and environmental considerations – when adapting brochure and packaging.	To assess efforts to take a needs-based approach in adapting brochures and packaging to facilitate appropriate use of antibiotics.
C.7	**AMR surveillance** The company has/supports/contributes to local and/or global antibiotic resistance surveillance systems.	To review what companies are doing and can do to support collection and public use of surveillance data, particularly where public health infrastructure and resources may be lacking.
C.8	**Reducing uncontrolled use** The company has innovative models and mechanisms in place with relevant stakeholders to reduce uncontrolled antibiotic purchase, such as over-the-counter (OTC) and non-prescription sales.	To assess efforts being made, either individually or in collaboration with other stakeholders, to minimise non-prescription sales of antibiotics.

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 antimicrobial medicines and vaccines. Public health value is evaluated based on criteria such as: targeting a priority pathogen and/or new mode of action. The pathogens deemed priority by the Benchmark are listed here, and comprises (emerging) drug-resistant pathogens as defined by WHO's R&D Priority List and by the Centers for Disease Control's Biggest Threat List.

	Stakeholder prioritisation	
Pathogen	WHO Priority List[20]	CDC Biggest Threat[4]
BACTERIA		
Clostridium difficile		Urgent
Carbapenem-resistant *Enterobacteriaceae* (CRE)	Critical	Urgent
Extended-spectrum beta-lactamase *Enterobacteriaceae* (ESBL)	Critical	Serious
Neisseria gonorrhoeae	High	Urgent
Multidrug-resistant *Acinetobacteria* (including *A. baumannii*)	Critical	Serious
Drug-resistant *Campylobacteria*	High	Serious
Vancomycin-resistant *Enterococcus* (VRE) (*Enterobacteria. faecalis* & *Enterobacteria faecium*)	High	Serious
Multidrug-resistant *Pseudomonas aeruginosa*	Critical	Serious
Drug-resistant *salmonella* (including non-*typhoidella Salmonella* & *Salmonella serotype typhi*)	High	Serious
Drug-resistant *Shigella*	Medium	Serious
Drug-resistant *Staphylococcus aureus* (Methicillin-resistant *S. aureus* & Vancomycin-resistant *S. aureus*)	High	Serious
Drug-resistant *Streptococcus pneumoniae*	Medium	Serious
Drug-resistant *Mycobacterium tuberculosis*		Serious
Erythromycin-resistant group *A Streptococcus*		Concerning
Clindamycin-resistant group *B Streptococcus*		Concerning
Clarithromycin-resistant *Helicobacter pylori*	High	
Ampicillin-resistant *Haemophilus influenza* (Hib)	Medium	
PROTOZOA		
Multi-drug resistant *Plasmodium falciparum*	Identified as WHO AMR priority area	
FUNGI		
Fluconazole-resistant *Candida*		Serious
VIRUSES		
Human immunodeficiency virus (HIV)	Identified as WHO AMR priority area	

APPENDIX II. COUNTRIES IN SCOPE FOR INDICATORS A.4, C.1, C.2, C.3

The challenges of sufficient access and affordability are significantly higher in poorer countries. Access indicators (A.4, C.1, C.2, C.3) measure how companies address access in 106 low- and middle-income countries. The country scope was defined by following these four steps in sequence: (1) include countries defined as low-income countries or lower middle-income countries by the World Bank; (2) include countries defined as having low or medium levels of human development by UNDP; (3) include countries with a value of less than 0.6 on the UNDP's Inequality-adjusted Human Development Index; and lastly (4) include countries defined as least developed countries by the Committee for Development Policy of ECOSOC.[17,18,19] This is the same geographic scope as used by the 2018 Access to Medicine Index.

EAST ASIA & PACIFIC	
Cambodia	LMIC
China	HiHDI
Indonesia	LMIC
Kiribati	LMIC
Korea, Dem. Rep.	LIC
Lao PDR	LMIC
Micronesia, Fed. Sts.	LMIC
Mongolia	LMIC
Myanmar	LMIC
Papua New Guinea	LMIC
Philippines	LMIC
Samoa	LMIC
Solomon Islands	LMIC
Thailand	HiHDI
Timor-Leste	LMIC
Tonga	LMIC
Tuvalu	LDC
Vanuatu	LMIC
Vietnam	LMIC

EUROPE & CENTRAL ASIA	
Armenia	LMIC
Kosovo	LMIC
Kyrgyz Rep.	LMIC
Moldova	LMIC
Tajikistan	LMIC
Turkmenistan	MHDC
Ukraine	LMIC
Uzbekistan	LMIC

LATIN AMERICA & CARIBBEAN	
Belize	HiHDI
Bolivia	LMIC
Brazil	HiHDI
Colombia	HiHDI
Dominican Rep.	HiHDI
Ecuador	HiHDI
El Salvador	LMIC
Guatemala	LMIC
Guyana	MHDC
Haiti	LIC
Honduras	LMIC
Mexico	HiHDI
Nicaragua	LMIC
Paraguay	MHDC
Peru	HiHDI
Suriname	HiHDI

MIDDLE EAST & NORTH AFRICA	
Djibouti	LMIC
Egypt, Arab Rep.	LMIC
Iran, Islamic Rep.	HiHDI
Iraq	MHDC
Morocco	LMIC
Palestine, State	LMIC
Syrian Arab Rep.	LMIC
Tunisia	LMIC
Yemen, Rep.	LMIC

SOUTH ASIA	
Afghanistan	LIC
Bangladesh	LMIC
Bhutan	LMIC
India	LMIC
Maldives	HiHDI
Nepal	LIC
Pakistan	LMIC
Sri Lanka	LMIC

SUB-SAHARAN AFRICA	
Angola	LHDC
Benin	LIC
Botswana	MHDC
Burkina Faso	LIC
Burundi	LIC
Cameroon	LMIC
Cape Verde	LMIC
Central African Rep.	LIC
Chad	LIC
Comoros	LIC
Congo, Dem. Rep.	LIC
Congo, Rep.	LMIC
Côte d'Ivoire	LMIC
Equatorial Guinea	MHDC
Eritrea	LIC
Ethiopia	LIC
Gabon	MHDC
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 Principe	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

Table legend

LIC: Low-income country (*World Bank income classifications)*

LMIC: Lower middle-income Country (*World Bank income classifications)*

LDC: Least Developed Country (*UN Human Development Index)*

LHDC: Low Human Development Country (*UN Human Development Index)*

MHDC: Medium Human Development (*Country UN Human Development Index)*

HiHDI: High Human Development Country with high inequality *(UN Inequality-adjusted Human Development Index)*

APPENDIX III. PRODUCTS IN SCOPE FOR INDICATORS C.2, C.3

Only anti-infective medicines on the WHO Model List of Essential Medicines 2017 (EML), Chapter 6, are in scope for indicators C.2 and C.3. They 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.

WHO Model List of Essential Medicines (March 2017). Chapter 6. Anti-Infective Medicines.

6.1 ANTHELMINTHICS

albendazole	Tablet: (chewable): 400 mg
ivermectin	Tablet: (scored): 3 mg
levamisole	Tablet: 50 mg; 150 mg (as hydrochloride)
mebendazole	Tablet (chewable): 100 mg; 500 mg
niclosamide	Tablet (chewable): 500 mg
praziquantel	Tablet: 150 mg; 600 mg
pyrantel	Oral liquid: 50 mg (as embonate or pamoate)/ mL Tablet (chewable): 250 mg (as embonate or pamoate)
diethylcarbamazine	Tablet: 50 mg; 100 mg (dihydrogen citrate)
triclabendazole	Tablet: 250 mg
oxamniquine	Capsule: 250 mg Oral liquid: 250 mg/5 mL

6.2 ANTIBACTERIAL MEDICINES

amikacin	Injection: 250 mg (as sulfate)/mL in 2- mL vial Powder for injection: 100 mg; 500 mg; 1 g (as sulfate) in vial
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
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
ampicillin	Powder for injection: 500 mg; 1 g (as sodium salt) in vial
azithromycin	Capsule: 250 mg; 500 mg (anhydrous) Oral liquid: 200 mg/5 mL
aztreonam	Powder for injection: 1 g; 2 g in vial
bedaquiline	Tablet: 100 mg
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
benzylpenicillin	Powder for injection: 600 mg (= 1 million IU); 3 g (= 5 million IU) (sodium or potassium salt) in vial
capreomycin	Powder for injection: 1 g (as sulfate) in vial
cefazolin	Powder for injection: 1 g (as sodium salt) in vial
cefixime	Capsule or tablet: 200 mg; 400 mg (as trihydrate) Powder for oral liquid: 100 mg /5 mL
cefotaxime	Powder for injection: 250 mg per vial (as sodium salt)
ceftazidime	Powder for injection: 250 mg or 1 g (as pentahydrate) in vial
ceftriaxone	Powder for injection: 250 mg; 1 g (as sodium salt) in vial
cefalexin	Powder for reconstitution with water: 125 mg/5 mL; 250 mg/5 mL (anhydrous) Solid oral dosage form: 250 mg (as monohydrate)
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
ciprofloxacin	Oral liquid: 250 mg/5 mL (anhydrous) Solution for IV infusion: 2 mg/ mL (as hyclate) Tablet: 250 mg (as hydrochloride)

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
clindamycin	Capsule: 150 mg (as hydrochloride) Injection: 150 mg (as phosphate)/ mL Oral liquid: 75 mg/5 mL (as palmitate)
clofazimine	Capsule: 50 mg; 100 mg.
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
cycloserine	Solid oral dosage form: 250 mg
dapsone	Tablet: 25 mg; 50 mg; 100 mg
daptomycin	Powder for injection: 350 mg; 500 mg in vial
delamanid	Tablet: 50 mg
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 Tablet (dispersible): 100 mg (as monohydrate)
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
ethionamide	Tablet: 125 mg; 250 mg
fifth generation **cephalosporins** (with or without beta-lactamase inhibitor) e.g., ceftaroline	Powder for injection: 400 mg; 600 mg (as fosamil) in vial
fosfomycin	Powder for injection: 2 g; 4 g (as sodium) in vial
fourth generation **cephalosporins** (with or without beta-lactamase inhibitor) e.g., cefepime	Powder for injection: 500 mg; 1g; 2g (as hydrochloride) in vial
gentamicin	Injection: 10 mg; 40 mg (as sulfate)/ mL in 2- mL vial
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 Tablet (dispersible): 50 mg + 150 mg + 75 mg
isoniazid + rifampicin	Tablet: 75 mg + 150 mg; 150 mg + 300 mg; 60 mg + 60 mg; 150 mg + 150 mg Tablet (dispersible): 50 mg + 75 mg
kanamycin	Powder for injection: 1 g (as sulfate) in vial
levofloxacin	Tablet: 250mg; 500 mg; 750 mg
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
meropenem	Powder for injection: 500 mg (as trihydrate); 1 g (as trihydrate) in vial
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
moxifloxacin	Tablet: 400 mg
nitrofurantoin	Oral liquid: 25 mg/5 mL Tablet: 100 mg
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
p-aminosalicylic acid	Granules: 4 g in sachet Tablet: 500 mg

☐ Primarily intended to indicate similar clinical performance within a pharmacological class.

phenoxymethylpenicillin	Powder for oral liquid: 250 mg (as potassium salt)/5 mL Tablet: 250 mg (as potassium salt)
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
polymyxins **e.g., colistin**	Powder for injection: 1 million I.U. (as colistemethate sodium) in vial
procaine benzylpenicillin	Powder for injection: 1 g (=1 million IU); 3 g (=3 million IU) in vial
pyrazinamide	Oral liquid: 30 mg/ mL Tablet: 400 mg Tablet (dispersible): 150 mg Tablet (scored): 150 mg
rifabutin	Capsule: 150 mg
rifampicin	Solid oral dosage form: 150 mg; 300 mg Oral liquid: 20 mg/ mL
rifapentine	Tablet: 150 mg
spectinomycin	Powder for injection: 2 g (as hydrochloride) in vial
streptomycin	Powder for injection: 1 g (as sulfate) in vial
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
tigecycline	Powder for injection: 50 mg in vial
vancomycin	Capsule: 125 mg; 250 mg (as hydrochloride) Powder for injection: 250 mg (as hydrochloride) 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
potassium iodide	Saturated solution
voriconazole	Tablet: 50 mg; 200 mg Powder for injection: 200 mg in vial Powder for oral liquid: 40 mg/mL

6.4 ANTIVIRAL MEDICINES

abacavir	Tablet: 300 mg (as sulfate) Tablet (dispersible, scored): 60 mg (as sulfate)
abacavir + lamivudine	Tablet (dispersible, scored): 600 mg (as sulfate) + 300 mg*; 60 mg (as sulfate) + 30 mg; 120 mg (as sulfate) + 60 mg
aciclovir □	Oral liquid: 200 mg/5 mL Powder for injection: 250 mg (as sodium salt) in vial Tablet: 200 mg
atazanavir	Solid oral dosage form: 100 mg; 300 mg (as sulfate)
atazanavir + ritonavir	Tablet (heat stable): 300 mg (as sulfate) + 100 mg
daclatasvir	Tablet: 30 mg; 60 mg (as hydrochloride)

□ Primarily intended to indicate similar clinical performance within a pharmacological class.

* Corrected based on page 153 of 'Antiretroviral Therapy for HIV Infection in Infants and Children: Towards Universal Access Recommendations for a public health approach' 2010 revision and page 15 of 'The Selection and Use of Essential Medicines' Report of the WHO Expert Committee, 2013.

darunavir	Tablet: 75 mg; 400 mg; 600 mg; 800 mg
dasabuvir	Tablet: 250 mg
dolutegravir	Tablet: 50 mg
efavirenz	Tablet: 200 mg (scored); 600 mg
efavirenz + emtricitabine + tenofovir	Tablet: 600 mg + 200 mg + 300 mg (disoproxil fumarate equivalent to 245 mg tenofovir disoproxil)
efavirenz + lamivudine + tenofovir	Tablet: 400 mg + 300 mg + 300 mg (disoproxil fumarate equivalent to 245 mg tenofovir disoproxil)
emtricitabine + tenofovir	Tablet: 200 mg + 300 mg (disoproxil fumarate equivalent to 245 mg tenofovir disoproxil)
entecavir	Oral liquid: 0.05 mg/ mL Tablet: 0.5 mg; 1 mg
isoniazid + pyridoxine + sulfamethoxazole + trimethoprim	Tablet (scored): 300 mg + 25 mg + 800 mg + 160 mg
lamivudine	Oral liquid: 50 mg/5 mL Tablet: 150 mg
lamivudine + nevirapine + zidovudine	Tablet: 30 mg + 50 mg + 60 mg; 150 mg + 200 mg + 300 mg
lamivudine + zidovudine	Tablet: 30 mg + 60 mg; 150 mg + 300 mg
ledipasvir + sofosbuvir	Tablet: 90 mg + 400 mg
lopinavir + ritonavir“	Oral liquid: 400 mg + 100 mg/5 mL Tablet (heat stable): 100 mg + 25 mg; 200 mg + 50 mg Capsule containing oral pellets: 40 mg + 10 mg
nevirapine	Oral liquid: 50 mg/5 mL Tablet: 50 mg (dispersible); 200 mg
ombitasvir + paritaprevir + ritonavir	Tablet: 12.5 mg + 75 mg + 50 mg
oseltamivir	Capsule: 30 mg; 45 mg; 75 mg (as phosphate) Oral powder: 12 mg/ mL
pegylated interferon alfa (2a or 2b)	Vial or prefilled syringe: 180 micrograms (peginterferon alfa-2a); 80 microgram, 100 microgram (peginterferon alfa-2b)
raltegravir	Tablet (chewable): 25 mg; 100 mg Tablet: 400 mg
ribavirin	Injection for intravenous administration: 800 mg and 1 g in 10-mL phosphate buffer solution Solid oral dosage form: 200 mg; 400 mg; 600 mg
ritonavir	Oral liquid: 400 mg/5 mL Tablet (heat stable): 25 mg; 100 mg
simeprevir	Capsule: 150 mg
sofosbuvir	Tablet: 400 mg
sofosbuvir + velpatasvir	Tablet: 400 mg + 100 mg
tenofovir disoproxil fumarate	Tablet: 300 mg (tenofovir disoproxil fumarate – equivalent to 245 mg tenofovir disoproxil)
valganciclovir	Tablet: 450 mg Powder for oral solution: 50 mg/mL
zidovudine	Capsule: 250 mg Oral liquid: 50 mg/5 mL Solution for IV infusion injection: 10 mg/ mL in 20- mL vial Tablet: 300 mg Tablet (dispersible, scored): 60 mg (as sulfate)

6.5 ANTIPROTOZOAL MEDICINES

amodiaquine	Tablet: 153 mg or 200 mg (as hydrochloride)
amphotericin B	Powder for injection: 50 mg in vial (as sodium deoxycholate or liposomal complex)
artemether	Oily injection: 80 mg/ mL in 1- mL ampoule
artemether + lumefantrine	Tablet: 20 mg + 120 mg Tablet (dispersible): 20 mg + 120 mg

artesunate	Injection: ampoules, containing 60 mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution. For use in the management of severe malaria Rectal dosage form: 50 mg; 100 mg; 200 mg capsules (for pre-referral treatment of severe malaria only; patients should be taken to an appropriate health facility for follow-up care) Tablet: 50 mg
artesunate + amodiaquine	Tablet: 25 mg + 67.5 mg; 50 mg + 135 mg; 100 mg + 270 mg
artesunate + mefloquine	Tablet: 25 mg + 55 mg; 100 mg + 220 mg
artesunate + pyronaridine tetraphosphate	Tablet: 60 mg + 180 mg Granules: 20 mg + 60 mg
benznidazole	Tablet: 12.5 mg; 100 mg Tablet (scored): 50 mg
chloroquine	Oral liquid: 50 mg (as phosphate or sulfate)/5 mL Tablet: 100 mg; 150 mg (as phosphate or sulfate)
dihydroartemisinin + piperaquine phosphate	Tablet: 20 mg + 160 mg; 40 mg + 320 mg
diloxanide	Tablet: 500 mg (furoate)
doxycycline	Capsule: 100 mg (as hydrochloride or hyclate) Tablet (dispersible): 100 mg (as monohydrate)
eflornithine	Injection: 200 mg (hydrochloride)/ mL in 100- mL bottle
mefloquine	Tablet: 250 mg (as hydrochloride)
melarsoprol	Injection: 3.6% solution, 5- mL ampoule (180 mg of active compound)
metronidazole ☐	Injection: 500 mg in 100- mL vial Oral liquid: 200 mg (as benzoate)/5 mL Tablet: 200 mg to 500 mg
miltefosine	Solid oral dosage form: 10 mg; 50 mg
nifurtimox	Tablet: 30 mg; 120 mg; 250 mg
paromomycin	Solution for intramuscular injection: 750 mg of paromomycin base (as the sulfate)
pentamidine	Tablet: 200 mg; 300 mg (as isethionate) Powder for injection: 200 mg (as isetionate) in vial
primaquine	Tablet: 7.5 mg; 15 mg (as diphosphate)
proguanil	Tablet: 100 mg (as hydrochloride)
pyrimethamine	Tablet: 25 mg
quinine	Injection: 300 mg quinine hydrochloride/ mL in 2- mL ampoule Tablet: 300 mg (quinine sulfate) or 300 mg (quinine bisulfate)
sodium stibogluconate or meglumine antimoniate	Injection: 100 mg/ mL, 1 vial = 30 mL or 30%, equivalent to approximately 8.1% antimony (pentavalent) in 5- mL ampoule
sulfadiazine	Tablet: 500 mg
sulfadoxine + pyrimethamine	Tablet: 500 mg + 25 mg
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
suramin sodium	Powder for injection: 1 g in vial

☐ Primarily intended to indicate similar clinical performance within a pharmacological class.

MEDICINES IN SCOPE, IN ADDITION TO 2017 WHO MODEL LIST OF ESSENTIAL MEDICINES[21,22]

i. The WHO Model List of Essential Medicines incorporates 'fourth generation cephalosporins (with or without beta-lactamase inhibitor)' and 'fifth generation cephalosporins (with or without beta-lactamase inhibitor)'. Based on the examples listed on the 2017 Model List of Essential Medicines, ceftaroline and cefepime, and using the Anatomical Therapeutic Chemical (ATC) Classification system by WHO the following cephalosporins will be evaluated as if on the WHO Model List of Essential Medicines:

Product	ATC class
ceftaroline	J01DI
ceftobiprole	J01DI
ceftolozane + tazobactam	J01DI
cefepime	J01DE
cefpirome	J01DE
cefozopran	J01DE

ii. The WHO Model List of Essential Medicines incorporates square box symbols (□) to indicate similar clinical performance within a pharmacological class. The listed medicine should be the example of the class for which there is the best evidence for effectiveness and safety. Based on the examples listed on the Model List of Essential Medicines and using the Anatomical Therapeutic Chemical (ATC) Classification system by WHO, the following antimicrobial medicines, that are not specifically mentioned on the Model List of Essential Medicines, will be evaluated as if on the WHO Model List of Essential Medicines.

Product	ATC class	Corresponding product with □
idoxuridine	J05AB	aciclovir
vidarabine	J05AB	aciclovir
ribavirin	J05AB	aciclovir
ganciclovir	J05AB	aciclovir
famciclovir	J05AB	aciclovir
valaciclovir	J05AB	aciclovir
cidofovir	J05AB	aciclovir
penciclovir	J05AB	aciclovir
valganciclovir	J05AB	aciclovir
brivudine	J05AB	aciclovir
dicloxacillin	J01CF	cloxacillin
meticillin	J01CF	cloxacillin
oxacillin	J01CF	cloxacillin
flucloxacillin	J01CF	cloxacillin
nafcillin	J01CF	cloxacillin
tinidazole	P01AB	metronidazole
ornidazole	P01AB	metronidazole
azanidazole	P01AB	metronidazole
propenidazole	P01AB	metronidazole
nimorazole	P01AB	metronidazole
secnidazole	P01AB	metronidazole

DEFINITIONS

Antimicrobial resistance
Resistance in different types of microorganisms; encompasses resistance to antibacterial, antiviral, antiparasitic and antifungal drugs.

Antibiotic resistance
Resistance that occurs when bacteria change in response to the use of antibiotics used to treat bacterial infections (such as urinary tract infections, pneumonia, bloodstream infections) making them ineffective.

Pull incentives
Pull incentives reward a successful result or research and development of a new antimicrobial medicine and provides known return on investment. Examples of pull incentives are extended exclusivity periods, higher reimbursement or market entry rewards.

Push incentives
Push incentives lower the cost of and de-risks research and development of a new antimicrobial medicine. Examples of push incentives are grants, partnerships or tax credits.

Appropriate access strategy
A strategy to provide access to medicine in low- and middle-income countries that takes affordability into account.

Affordability
A measure of the payer's ability to pay for a product (whether or not they are the end user). The Benchmark takes this into account when assessing pricing strategies for relevant products in scope.

Antibiotic stewardship
Antibiotic stewardship can be an individual, multidisciplinary, hospital or community-level commitment to ensuring appropriate antibiotic use for those patients or animals that have a bacterial infection that requires treatment, and ensuring that all aspects of the prescription (such as dose, duration) are as they should be.

Open collaborations
A multi-stakeholder partnership that focuses on pharmaceutical R&D, such as a Product Development Partnership (PDP), with an open approach to pooling and sharing resources such as data and expertise between partners.

ABBREVIATIONS

A&S: Access and Stewardship
AIDS: Acquired immune deficiency syndrome
AMR: Antimicrobial resistance
API: Active Pharmaceutical Ingredient
ATC: Anatomical Therapeutic Chemical classification
BARDA: Biomedical Advanced Research and Development Authority
BIO: Biotechnology Innovation Organization
CARB-X: Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator
CDC: US Centers for Disease Control and Prevention
CDDEP: Center for Disease Dynamics, Economics and Policy
DNA: Deoxyribonucleic acid
DNDi: Drugs for Neglected Disease initiative
DRIVE-AB: Driving reinvestment in research and development and responsible antibiotic use
EC: Expert Committee
ECOSOC: United Nations Economic and Social Council
EFPIA: European Federation of Pharmaceutical Industrial Associations
EML: WHO Model List of Essential Medicine, March 2017
FAIRR: Farm Animal Investment Risk and Return
GARDP: Global Antibiotic Research and Development Partnership
GUARD: Global Union for Antibiotics Research and Development
HCP: Healthcare Professional
HiHDI: High Human Development Country with High Inequality
HIV: Human immunodeficiency virus
IFPMA: International Federation of Pharmaceutical Manufacturers and Associations
IMI: Innovative Medicines Initiative
LDC: Least Developed Country
LHDC: Low Human Development Country
LIC: Low-Income Country
LMIC: Lower-Middle Income Country
M&P: Manufacturing and Production
MHDC: Medium Human Development Country
MSF: Médicins Sans Frontières
NGO: Non-governmental organisation
OECD: Organisation for Economic Co-operation and Development
OTC: Over-the-counter
PDP: Product Development Partnership
R&D: Research and Development
RNA: Ribonucleic acid
SARS: Severe Acute Respiratory Syndrome
UN: United Nations
UNDP: United Nations Development Programme
USD: United States Dollar
WHO: World Health Organization

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