Antimicrobial Resistance Benchmark 2021

METHODOLOGY

access to medicine FOUNDATION

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The Access to Medicine Foundation would like to thank all of the representatives of the many different stakeholders working to curb antimicrobial resistance who contributed their views to the development of this methodology.

ACCESS TO MEDICINE FOUNDATION

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

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On the cover is a young boy from Tanzania, a country where the presence of resistant bacteria is widespread as are many of the issues in access and stewardship, as covered in the Benchmark. The young boy represents these underserved populations that were the focus during the refinement of the methodology.

Antimicrobial Resistance Benchmark 2021

METHODOLOGY REPORT 2020

ACCESS TO MEDICINE FOUNDATION

October 2020

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Halting the next pandemic

COVID-19 is not the only pandemic that the world is currently battling. We have seen great progress against malaria, HIV/AIDS and TB, and to improve maternal health, while working to deliver the SDGs. However, we are also facing warnings of future pandemics of drug resistant bacterial and fungal infections. Like COVID-19, antimicrobial resistance (AMR) poses a significant risk to economies, will disrupt health systems and endanger our most vulnerable populations. Unlike COVID-19, an AMR pandemic can still be stopped if we act now; we know which actions to take and which pathogens to target. The need to invest in pandemic preparedness and R&D is clear as it is evident that it is too costly on all accounts to develop a cure at short notice. By fixing the fundamentals of healthcare systems, and by pushing for new antibiotics and vaccines, we can avert the next big superbug pandemic.

Momentum is building slowly

The key challenges are a sparse R&D pipeline of new medicines and vaccines, and discouraging economic barriers to industry engagement. Pharmaceutical companies largely pass over the antibiotics market due to a comparative lack of profitability. A viable economic environment is needed to not only spur R&D, but to ensure a sustainable market that can deliver reliable supplies once a product is commercialised. A few governments are taking steps, with the British and Swedish governments piloting new economic incentives to promote R&D and ensure availability. Several large pharmaceutical companies are also committing resources, collectively launching the AMR Action Fund to support development of novel antibiotic candidates. But there are still underserved gaps in the market and insufficient investment in commercialisation. Moreover, unless action is taken today, those low-income countries that currently bear the brunt of resistance will remain overlooked and underserved.

3rd AMR Benchmark to track progress

Despite these intermediary solutions with cash and commitments, in the end it lies to each individual company to innovate and to sustainably provide access to the vital antibiotics necessary to prevent the next pandemic. For pharmaceutical companies, the role in the global effort against AMR is clear: to develop new medicines to replace those no longer effective; to produce and promote antibiotics responsibly; and to make these available and accessible to people who need them.

This refined methodology seeks to not only further inform and assess the progress of companies, but to realistically determine our future state as a society if the most important players in the antibiotic market are not advancing and evolving at the pace required.

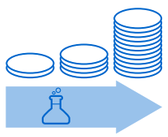
Jayasree K. Iyer
Executive Director
Access to Medicine Foundation

SUMMARY: TOWARD A 3RD AMR BENCHMARK

2021 framework will track progress on AMR by key pharma players

Each year, 5.7 million people die due to lack of access to antibiotics

Global antibiotics market predicted to grow



Late-stage clinical development costs up to 12 times more than Phase 1

AMR R&D funding

5 bn
across various sources
1.6 bn
from pharma industry (2018)
1 bn
to AMR Action Fund

Each year, around 5.7 million people die from treatable bacterial diseases due to the lack of access to antibiotics, mainly in low- and middle-income countries (LMICs). More than 700,000 die from antimicrobial resistance (AMR),[1] and the number of drug-resistant bacteria is increasing worldwide.[2] While there are signs of increased awareness and momentum to tackle AMR, there is a clear and urgent need for a viable economic environment in which the companies that develop antibiotics can survive and prosper.

An estimated USD 5 billion is being contributed by government, philanthropic and industry funders to fund research & development (R&D) for replacement antibiotics and vaccines. The dominant funder of AMR-relevant R&D is the pharmaceutical industry, investing USD 1.6 billion in 2018.[3] In a new step, in July 2020, the AMR Action Fund (a consortium of at least 20 pharmaceutical companies) committed USD 1 billion to shepherd some antibiotics through Phase II and Phase III clinical trials, aiming to bring 2-4 new antibiotics to patients by 2030. Other pharmaceutical companies are re-engaging in the field through partnerships and pacts: in early 2020, for example, Roche and Forge Therapeutics entered a development partnership, and Daiichi Sankyo released its chemical library to GARDP to enable it to be screened for novel compounds. A few national governments are stepping up, such as the United Kingdom and Sweden which are piloting new pull incentive initiatives that provide fixed compensation in return for guaranteed availability of certain medically important antibiotics. India, the world's largest producer and consumer of antibiotics, is looking at legislation to set limits on the concentrations of antibacterials found in the waste discharged by companies into the environment.

More funding is available, yet challenges remain

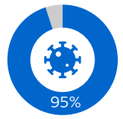
These amounts and initiatives are sizeable. While most funding targets early research, it is late-stage clinical development that is most costly, with Phase III costs at 12 times more than Phase I.[4] Moreover, the costs associated with activities beyond R&D, such as manufacturing, supply chain activities, commercialisation and regulatory requirements, are also considerable. In a recent survey, 74% of companies indicated they would increase investments in AMR if commercial models improve,[5] for example through new reimbursement models. The antibacterial market has been predicted to grow to USD 55.8 billion by 2023 (up from USD 38.3 billion in 2018).[6] This is in step with growing demand for generic antibacterials from emerging markets. Human consumption of antibacterials is growing primarily in LMICs, where antibacterials are often accessed over-the-counter rather than by prescription.

COVID-19 may accelerate AMR

Antimicrobial resistance is being impacted by the ongoing COVID-19 crisis. Studies indicate that the use of antibiotics to treat COVID-19 could drive AMR in the wider population. The current treatment can involve giving antibiotics to prevent secondary infections, with 95% of patients admitted to hospital being prescribed antibiotics.[7] Resistance rates may be positively impacted by improved infection prevention to control COVID-19 and by the decrease in travel. Conversely, resistance rates may be driven up by inappropriate use of antibiotics linked to suspected COVID-19.

AMR: the next pandemic?

Like COVID-19, AMR poses a global risk. Investors and governments alike have seen the damage of a global pandemic. Unlike with COVID-19, there is clarity on the path forward and the actions required to prevent a full-scale AMR health emergency; the next pandemic could be caused by a drug-resistant pathogen. Efforts to curb AMR are hampered by reliance on just a handful of innovators and on a few geographically spread manufacturers of active pharmaceutical ingredients (APIs), which means suppliers are limited and supply chains are fragile. Moreover, the efforts to ensure equitable access to medicine are reliant on donor funding, with the result being that a few rich countries are benefiting from innovations while low- and middle-income countries miss out.



95% of patients hospitalised with COVID-19 received antibiotics

The COVID-19 pandemic has underlined the need to invest in pandemic preparedness and antibiotic R&D, and brought into sharp focus the need for many different companies to engage in R&D, manufacturing and commercialisation. The importance of tackling AMR cannot be over-stated. Lack of preparation disrupts health systems, economies and threatens populations. Now is the time to build on the momentum with new tools, resources, and collaboration, in order to provide funding, drive robust pipelines, build capacity and supply, and ensure equitable access.

74% of surveyed companies ready to invest more in AMR if commercial models improve

Antibiotics companies need viable economic environment

VISION FOR THE PHARMACEUTICAL INDUSTRY

To limit antimicrobial resistance, the role for pharmaceutical companies is clear: to develop new medicines to replace ones that are no longer effective, make them available and accessible to those who need them, and ensure all antibiotics are produced and promoted responsibly:

- As pathogens become increasingly resistant to common antibiotics, pharmaceutical companies must remain engaged, and ramp up effective drug discovery and development operations.
- With only a few antibiotics in development, and considering the scale of unmet need, companies must protect new antibiotics at launch, and enable access in countries most at risk, by planning ahead for access and stewardship.
- Companies that are no longer active in R&D can engage once more. They nevertheless still have a role to play in sharing expertise and intellectual property, including compound libraries, contributing manufacturing capacity, securing supply and addressing affordability.
- Companies should ensure the availability of antibiotics by ensuring they are produced in sufficient volumes and registered and supplied within low- and middle-income countries.
- To prevent the overselling and subsequent over-use of antibiotics and antifungals, companies must engage in responsible sales practices, including decoupling sales bonuses from sales volumes, or stopping the use of sales teams to promote antibacterial and antifungal medicines.
- Companies must implement and audit responsible manufacturing processes that ensure medicines meet quality standards and minimise the risk of antibacterial ingredients being released into the environment.
- In sharing data and insights, companies can support AMR surveillance efforts, thereby supporting governments and hospitals in knowing where resistance is developing so they can adapt treatment guidelines used to make clinical decisions.

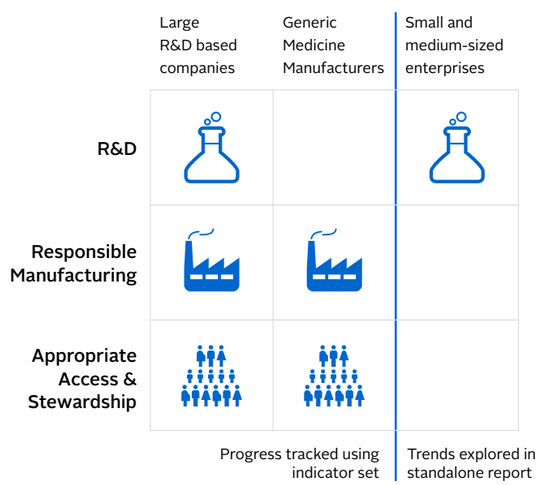
How the 2021 AMR Benchmark covers pharma companies

Figure 1

The next AMR Benchmark will evaluate the eight large research-based pharmaceutical companies and nine generic medicine manufacturers that were tracked in the previous edition of the AMR Benchmark (2020). It will analyse small and medium-sized enterprises in a standalone report.

The 2021 Benchmark covers three areas of company activity: Research & Development; Responsible Manufacturing; and Appropriate Access & Stewardship.

Changes to analysis scopes and indicators have been kept to a minimum in order to enable the longitudinal tracking of company progress, prioritising only essential changes.



HOW THE AMR BENCHMARK DRIVES CHANGE

The goal of the AMR Benchmark is to guide and incentivise pharmaceutical companies to play a full role against AMR. This industry cannot afford to overlook the AMR threat. It puts all areas of healthcare at risk, from oncology, to surgery, to universal health coverage (UHC). Tracking progress enables each company to challenge itself to improve.

The Benchmark is published every two years. It provides the consensus view on where companies can and should be responding to AMR and tracks how a cross-section of the industry is making progress against this expectation. In 2021, as in previous iterations, the Benchmark will focus on companies with a major stake in the antibiotics space, a market that has become increasingly fragile over recent decades. It covers eight large research-based pharmaceutical companies, nine generic medicine manufacturers and a cohort of small and medium-sized enterprises (SMEs) focused on R&D (SMEs will be studied in a standalone report). The Benchmark focuses on antibiotics and antifungals, as bacteria represent the greatest proportion and widest geographic spread of resistant pathogens. It will evaluate companies' actions to improve access to products and ensure their good stewardship. This part of its assessment will focus on 102 resource-limited countries with high burdens of disease.

By giving pharmaceutical companies public recognition for their actions on AMR, the Benchmark provides accountability as well as a guide and an incentive for them to do more. The Benchmark identifies good practices being implemented as templates for other companies to make further progress. Stakeholders such as investors and governments use the Benchmark to inform strategies for influencing the industry and securing their engagement in this vital sector. Its findings inform policy on incentives for industry and others to engage in infectious diseases, and identifies areas where greater investment, engagement and political weight is needed.

Companies in scope for the 2021 Antimicrobial Resistance Benchmark

Table 2

LARGE RESEARCH-BASED PHARMACEUTICAL COMPANIES

	Company	Country HQ	Revenue (bn USD)*
1	GlaxoSmithKline plc	GBR	44.8
2	Johnson & Johnson	USA	82.1
3	Merck & Co, Inc	USA	46.8
4	Novartis AG	CHE	47.4
5	Otsuka Pharmaceutical Co, Ltd**	JPN	12.8
6	Pfizer Inc	USA	51.8
7	Sanofi	FRA	40.6
8	Shionogi & Co, Ltd	JPN	3.1

GENERIC MEDICINE MANUFACTURERS

	Company	Country HQ	Revenue (bn USD)*
1	Abbott Laboratories	USA	31.9
2	Alkem Laboratories Ltd	IND	1.1
3	Aurobindo Pharma Ltd	IND	3.1
4	Cipla Ltd	IND	2.3
5	Fresenius Kabi AG	DEU	7.8
6	Hainan Hailing Chemipharma Corp Ltd***	CHN	0.7
7	Mylan NV†	GBR	11.5
8	Sun Pharmaceutical Industries Ltd	IND	4.4
9	Teva Pharmaceutical Industries Ltd	ISR	16.9

SMALL AND MEDIUM-SIZED ENTERPRISES

The 2021 Benchmark will also capture, in a separate report, the activities of clinical-stage biopharmaceutical companies that focus on antibacterial and/or antifungal R&D (termed small and medium-sized enterprises, or SMEs).

* Revenue from latest fiscal year data available (exchange rates from www.x-rates.com, the exchange rate of the last day of the fiscal year was used).
** Financial information (Revenue) is for Otsuka Holdings, the parent company of Otsuka Pharmaceutical Co, Ltd.
*** Financial information (Revenue) is for Changjiang Runfa Health Industry Co, Ltd, the parent company of Hainan Hailing Chemipharma Corp Ltd.
† Mylan is to be renamed Viatris, following closing of merger with Upjohn, a division of Pfizer, expected Q4 2020.

MAKING THE BENCHMARK METHODOLOGY

The Benchmark is developed independently by the Access to Medicine Foundation. It translates the consensus view on how pharmaceutical companies need to act on AMR into a set of ambitious but achievable expectations for action. This methodology has been refined through a targeted review of the previous methodological framework. This review aimed to ensure that the Benchmark, as a tool to evaluate pharmaceutical company activities, remains rigorous and can be extended for trend analysis between reports.

The review included checks of indicators, data sets and analytical approaches. This was followed by an external review with expert stakeholders, including individuals from international organisations, governments, industry, NGOs, research centres and other relevant groups and initiatives. It sought a consensus on specific AMR topics and the appropriate role for pharmaceutical companies, and analytical scopes.

Methodology proposals were reviewed and ratified by the Expert Committee of 10 independent experts, including from WHO, top-level academic centres and public sector entities, as well as investors and industry representatives.

DISCUSSIONS & DECISIONS

Discussions held during the methodology review covered a wide range of areas and were rich in detail and context. In many cases, there was alignment on the behaviours that the 2021 AMR Benchmark should measure and how. This section highlights some of the key decisions taken during the methodology review.

Third Benchmark will provide accountability and independent insight into progress

The stakeholder dialogue held in 2020 confirmed the need for a third Benchmark to continue tracking the pace of change. The first AMR Benchmark, published in 2018, provided a baseline analysis of pharmaceutical company action against AMR in relation to all infectious diseases, to capture a full range of companies' policies and practices. The second report provided an update, two years on. It found signs of progress, but not at the scale or pace required. The third Benchmark will provide accountability, act as a guide and incentive for companies to expand their activities, and inform policy-making on market shaping and industry engagement. Changes to analysis scopes and indicators have been kept to a minimum in order to enable the longitudinal tracking of company progress, prioritising only essential changes.

Standalone investigation into small- and medium-sized enterprises (SMEs)

The 2021 Benchmark will publish its findings in two reports. One will track the progress of large research-based pharmaceutical companies and generic medicine manufacturers since 2020. The other will examine the actions and role of SMEs. SMEs play a unique role in antibacterial and antifungal research and development, leading in novel projects, and generally have few products on the market. They are often dedicated to a small number of R&D projects. When compared to large research-based pharmaceutical companies, SMEs have limited capacity to run large clinical trials, or to produce and distribute on-market products. The SME report will provide an in-depth analysis of the unique challenges, successes, and prospects relevant to this category of companies

Refined approach to data gathering

The Benchmark has established a new standard for industry transparency in the AMR space, and looks to public and partner data sources for verification, as well as inviting companies to engage. As companies have differing capacities and commitments to data-sharing, the Benchmark team minimises the impact of this difference by collecting publicly available data, stimulating companies to publish specific information, and engaging directly with companies to clarify, verify and expand the data collected.

Evaluation of unique access strategies for medicines and for vaccines

The 2021 Benchmark will examine access strategies for medicines separately to those for vaccines. When it comes to antibacterials and antifungals, vaccines are typically more profitable than medicines, have greater international demand and global support mechanisms and infrastructure that facilitate availability. Vaccines also tend to be registered more widely across LMICs than medicines. As a result of these differences, the pharma companies that control these products have differing roles and responsibilities for improving access. To better assess current best practice, stakeholders and experts agreed that the Benchmark can best examine registration, access and affordability strategies separately in three categories: on-patent medicines, off-patent medicines and on-patent vaccines.

REVIEWING THE METHODOLOGY

How the Benchmark distills the role for pharmaceutical companies in curbing AMR

The Antimicrobial Resistance (AMR) Benchmark is an evaluation of how pharmaceutical companies are ensuring appropriate access to antimicrobial products while at the same time playing their part to curb the rise of AMR. The goal of the AMR Benchmark is to guide pharmaceutical companies to take effective action to tackle the problem of drug resistance. By giving pharmaceutical companies public recognition for their actions on AMR, the Benchmark provides accountability as well as an incentive for them to expand their activities.
The Benchmark is developed independently by the Access to Medicine Foundation, and translates the consensus view about how companies need to tackle AMR into a set of ambitious but achievable expectations for action.
The methodology framework for the next Benchmark has been the focus of a targeted review of the methodology used for the last iteration. This review aimed to confirm global health priorities regarding AMR and to define pharmaceutical companies' role in halting its rise. It drew on the Access to Medicine Foundation's experience in building consensus about where companies can take action, and how this can be translated into robust metrics. In turn, the Foundation uses the methodology review to affirm the robustness of the Benchmark analysis and to maintain its capacity for trend analysis between reports.
The primary principles of the methodology review are: (1) that the Benchmark is responsive to access and AMR needs; (2) that all metrics are relevant and actionable in terms of the appropriate role of the different types of companies that are tackling AMR, and that they stimulate change; (3) that all metrics are robust, allowing for the efficient and feasible collection of data; and (4) that each metric helps to identify best practices for companies to emulate and use to make progress.

Internal and external reviews
The review included internal checks of indicators, data sets and analytical approaches. This was followed by an external review that drew on the views of a range of expert stakeholders, and sought to establish a consensus on specific AMR topics and the appropriate role for pharmaceutical companies.

Testing the analytical framework, scopes and indicators
The framework for the methodology has been reviewed and updated with each iteration to ensure that the Benchmark (as a tool to evaluate pharmaceutical activities) remains rigorous and can be extended for trend analysis between reports.
As part of this, the Access to Medicine Foundation's research team began by conducting a targeted internal review of the analytical framework, looking at scopes and indicators to evaluate robustness, quality of response, and the potential for companies to improve performance.
The team used the following criteria during this review: (1) continued relevance for AMR and ability to add value within respective Research Areas; (2) capacity to stimulate action and create change and impact; (3) clarity about the expectations and roles set for companies; (4) assessment of the distribution of scores per indicator to evaluate overall company behaviour; (5) availability of data and resources; (6) measurability, including the quality of responses received to date, and data collected for assessment; (7) potential for additional reporting, including longitudinal comparisons both industry-wide and company-specific; and (8) expert and stakeholder feedback.

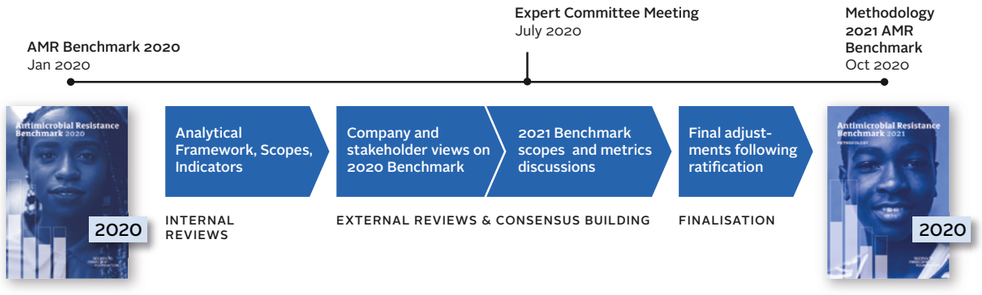
External review and consensus building
Over a period of five months, aspects of the methodology were discussed and evaluated by individuals from a range of international organisations, governments, NGOs, leading research centres and other relevant groups and initiatives addressing AMR. Our research team also gathered feedback from companies evaluated in the 2020 Benchmark, and from industry organisations and alliances including the AMR Industry Alliance, Biotechnology Innovation Organization (BIO), Indian Pharmaceutical Alliance (IPA) and Association for Accessible Medicines. The team then used feedback and insights gathered via this process to inform its proposals for modifying the methodology.

The Expert Committee
Proposals from the research team formed the basis for discussion with our Expert Committee (EC). The EC comprises 10 independent experts from organisations including WHO, top-level academic centres and public sector entities, as well as investors and pharmaceutical industry representatives.
The EC's recommendations and strategic guidance clarified a pathway, especially in areas in which it was hard to reach consensus (for example, the exact role of the industry and the details of what good practice looks like). Using recommendations from the EC, the research team adjusted its proposed methodology framework. The EC then ratified the refined framework, confirming the new methodology for a new iteration of the AMR Benchmark.

The Expert Committee members
Hans Hogerzeil (Chair), University of Groningen
Gregory Frank, Biotechnology Innovation Organization (BIO)
Sudarshan Jain, Indian Pharmaceutical Alliance (IPA)
Joakim Larsson, University of Gothenburg
Marc Mendelson, University of Cape Town
Mirfin Mpundu, ReAct Africa
Maria Larsson Ortino, Legal & General Investment Management
Sarah Paulin, World Health Organization (Observer)

Methodology Review for the 2021 Antimicrobial Resistance Benchmark

Figure 4



OUTCOME: REFINED SCOPES AND INDICATOR SET

The Access to Medicine Foundation has now finalised the methodology for the next (2021) AMR Benchmark. The key changes are summarised here and set out in more detail on the following page:

- The actions of SMEs will be explored in a standalone report, planned for publication in Q2 of 2021. Further, SMEs will not be scored in the 2021 iteration of the AMR Benchmark, reflecting the unique role that they play in antimicrobial R&D, and their limited role in improving the appropriate accessibility and stewardship of on-market products.
- As companies have differing capacities and commitments to data-sharing, the Benchmark team will take steps to reduce the impact of these differences in 2021. It will place emphasis on collecting publicly available data, while consistently pushing companies to publish more information, and continuing to engage directly with companies to clarify, verify and expand the data collected.
- Raising the bar for companies, the 2021 Benchmark will bring back into scope assessment relating to public waste- and wastewater-treatment plants, covered in the area of Responsible Manufacturing.
- In general, vaccines are more profitable than medicines for companies: there is greater international demand than for antimicrobial medicines, and agencies such as UNICEF and Gavi, the Vaccine Alliance give global support to facilitate registration and marketing. To capture this difference, the Benchmark will separately assess access strategies relating to vaccines from those relating to medicines.

The three Research Areas

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

B RESPONSIBLE MANUFACTURING
This Research Area compares companies' strategies for upholding manufacturing quality standards and limiting the environmental impact of antibacterial manufacturing on resistance.

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

What the Benchmark measures

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

Table 2. Analysis scopes for the AMR Benchmark

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

WHAT WE MEASURE

Company scope

The AMR Benchmark examines how a cross-section of the pharmaceutical industry is responding to the threat of drug-resistant infections. In 2021, as in previous iterations, its focus is on companies with a major stake in the antibiotics space, a market that has become increasingly fragile over recent decades. These companies remain major actors and can play a key role in shaping the market. The Benchmark considers the steps they are taking to address AMR through the antibacterial and antifungal medicines and vaccines to improve human health they develop and bring to market.
Pharmaceutical companies that develop and market such products can be grouped into three broad categories: (1) large research-based pharmaceutical companies; (2) generic medicine manufacturers; and (3) clinical-stage biopharmaceutical companies (referred to by the Benchmark as small and medium-sized enterprises or SMEs) that focus on R&D. Companies from all three categories are in the scope of the 2021 Benchmark research programme.
The Benchmark assesses eight large research-based pharmaceutical companies and nine generic medicine manufacturers, all of which were evaluated in the previous iteration of the Benchmark. By volume and value of sales, these are today's largest players in the global market for antibacterial medicines. The Benchmark also looks at SMEs with clinical-stage pipelines that contain relevant and mature projects. Companies are evaluated in those areas in which they possess the greatest potential and responsibility to limit antimicrobial resistance (see table 3).

Companies assessed per Research Area

Table 3

A RESEARCH & DEVELOPMENT

- Large R&D-based pharmaceutical companies
- Small & medium-sized enterprises (in standalone report)

B RESPONSIBLE MANUFACTURING

- Large R&D-based pharmaceutical companies
- Generic medicine manufacturers

C APPROPRIATE ACCESS & STEWARDSHIP

- Large R&D-based pharmaceutical companies
- Generic medicine manufacturers

Key changes for 2021
The Benchmark research programme will publish its findings in two reports. One will track the progress of large research-based pharmaceutical companies and generic medicine manufacturers since 2020, and is planned for release in Q4 of 2021. To preserve capacity for tracking progress, the companies in scope in these groups are unchanged since 2020. Thirteen of the companies in these groups in 2021 have been evaluated continuously by the Benchmark research programme since 2018.
The other report will examine the actions and role of SMEs, and is planned for release in Q2 of 2021. SMEs play a unique role in antibacterial and antifungal research and development, leading in novel projects, and generally have few products on the market. They have limited capacity, specifically when compared to large research-based pharmaceutical companies, in planning and facilitating appropriate access and stewardship of products on the market. The SME report will highlight the ways in which these companies arrange finance, develop medicines, and navigate a market that is often uncertain and volatile. Moreover, it aims to foreground examples of SMEs that, despite challenging market conditions, are striving to bring their innovations to lower- and middle-income countries (LMICs), where access to new and effective medicines is less widespread. SMEs will not be scored in the 2021 iteration of the AMR Benchmark.

Defining the scope
The company scope was held constant with the 2020 company scope, mergers and bankruptcies permitting, in order to track progress. Below, the specific criteria originally used to select the companies, based on their antibacterial market presence and pipelines,* are outlined. Table 4 lists the companies.

Large research-based pharmaceutical companies: those that rank in the top five for either the volume or value of their sales of antibacterials, as identified using IQVIA Midas intelligence data on consumption of antibiotics globally** (2017); and/or those that are active in this market and that have antibacterial pipelines with at least one antibacterial drug or vaccine candidate*** targeting a priority pathogen in scope, as identified by the Pew Charitable Trusts[8] or WHO.[9]

Generic medicine manufacturers: those that rank in the top five for volume and/or value of sales of antibacterials, based on 2017 IQVIA data; and/or market leaders that are large vendors of active pharmaceutical ingredients (APIs).[10]

SMEs: those with antibacterial and/or antifungal pipelines that are novel and/or target priority pathogens (as identified by The Pew Charitable Trusts and/or by the World Health Organization).

Companies in scope for the 2021 Antimicrobial Resistance Benchmark

Table 4

LARGE RESEARCH-BASED PHARMACEUTICAL COMPANIES

	Company	Country HQ	Ticker	Stock Exchange	Revenue (bn USD)*
1	GlaxoSmithKline plc	GBR	GSK	London	44.8
2	Johnson & Johnson	USA	JNJ	New York	82.1
3	Merck & Co, Inc	USA	MRK	New York	46.8
4	Novartis AG	CHE	NOVN	Six Swiss Exchange	47.4
5	Otsuka Pharmaceutical Co, Ltd **	JPN	4578	Tokyo	12.8
6	Pfizer Inc	USA	PFE	New York	51.8
7	Sanofi	FRA	SAN	Euronext Paris	40.6
8	Shionogi & Co, Ltd	JPN	4507	Tokyo	3.1

GENERIC MEDICINE MANUFACTURERS

	Company	Country HQ	Ticker	Stock Exchange	Revenue (bn USD)*
1	Abbott Laboratories	USA	ABT	New York	31.9
2	Alkem Laboratories Ltd	IND	ALKEM	NSE	1.1
3	Aurobindo Pharma Ltd	IND	AUROPHARMA	NSE	3.1
4	Cipla Ltd	IND	CIPLA	NSE	2.3
5	Fresenius Kabi AG	DEU	FRE***	Frankfurt	7.8
6	Hainan Hailing Chemipharma Corp Ltd †	CHN	002435	Shenzhen	0.7
7	Mylan NV ‡	GBR	MYL	NASDAQ	11.5
8	Sun Pharmaceutical Industries Ltd	IND	SUNPHARMA	NSE	4.4
9	Teva Pharmaceutical Industries Ltd	ISR	TEVA	New York/Tel Aviv	16.9

SMALL AND MEDIUM-SIZED ENTERPRISES

The 2021 AMR Benchmark will also report on the activities of clinical-stage biopharmaceutical companies (referred to by the Benchmark as small and medium-sized enterprises or SMEs) that focus on R&D. It will look at those SMEs with antibacterial and/or antifungal pipelines that are novel and/or target priority pathogens (as identified by The Pew Charitable Trusts and/or by the World Health Organization). Their actions will be explored in a standalone report. SMEs will not be scored in the 2021 iteration of the AMR Benchmark.

Data sources:
* Revenue from latest fiscal year data available (exchange rates from www.x-rates.com, the exchange rate of the last day of the fiscal year was used).
** Financial information (Ticker, Stock exchange, Revenue) is for Otsuka Holdings, the parent company of Otsuka Pharmaceutical Co, Ltd.
*** Ticker and Stock exchange information is for Fresenius SE & Co. KGaA, the parent company of Fresenius Kabi AG.
† Financial information (Ticker, Stock exchange, Revenue) is for Changjiang Runfa Health Industry Co, Ltd, the parent company of Hainan Hailing Chemipharma Corp Ltd.
‡ Mylan is to be renamed Viatris, following closing of merger with Upjohn, a division of Pfizer, expected Q4 2020.

*The selection of large research-based pharmaceutical companies and generic medicine manufacturers was done with reference to antibacterials as bacteria represent the greatest proportion and widest geographic spread of resistant pathogens. These companies will also be analysed, where appropriate, on the vaccines and antifungals they develop and market.

**Refers to aggregate sales in 75 countries.
***Candidates had to be in Phase II or more advanced stages of clinical development at the time of selection (July 2018).

WHAT WE MEASURE

Disease scope

The 2021 AMR Benchmark evaluates the actions and commitments made by pharmaceutical companies to limit the impact of AMR from bacterial and fungal pathogens.
All bacterial and fungal infections are in scope for the Benchmark's Appropriate Access & Stewardship Research Area. For R&D and Responsible Manufacturing, the Benchmark examines a narrower range, reflecting scientific evidence and stakeholder recommendations that prioritise specific pathogens or products for these areas (see table 4). Antimicrobial resistance to treatments for other pathogens, particularly HIV/AIDS and malaria, also constitutes a serious global threat. However, these diseases have R&D requirements and market structures that differ in important ways from those for bacterial and fungal diseases. Therefore, these diseases remain out of scope of the Benchmark research programme.

Key changes for 2021
Before analysis begins in 2021, the AMR Benchmark will review the application of its disease scope to reflect any changes in the published lists of priority pathogens, such as the anticipated WHO priority list for fungal pathogens.

A Research & Development
In this Research Area, the Benchmark focuses its assessment on priority pathogens (bacteria and fungi) that pose the greatest threat to human health. The pathogens in scope are limited to those included in the priority lists published by the CDC and WHO (see appendix I). The Benchmark research team will take account of any relevant updates, including the upcoming publication of a WHO priority list for fungal infections.

B Responsible Manufacturing
This Research Area will maintain its focus on antibacterial products, as in 2020. The companies in scope include some of the largest global players in terms of antibacterial product sales, and their actions to minimise the release of active antibacterial ingredients into the environment are expected to make a sizeable impact when it comes to limiting resistance. In contrast, it is not possible to achieve a comparable level of certainty regarding the management of antifungal discharge. As this is an emerging area of concern, the Benchmark will seek to identify and highlight best practices in environmental risk management, practices that also take account of antifungal discharge.

C Appropriate Access & Stewardship
It is important to ensure that people have appropriate access to antibacterials and antifungals. The disease scope of this Research Area includes all bacterial and fungal infections.

Diseases and pathogens assessed per Research Area

Table 5

A RESEARCH & DEVELOPMENT
- Priority bacteria as defined by CDC and WHO (see appendix I)
- Priority fungi as defined by CDC and WHO (see appendix I)

B RESPONSIBLE MANUFACTURING
- All bacteria

C APPROPRIATE ACCESS & STEWARDSHIP
- All bacteria
- All fungi

WHAT WE MEASURE

Product scope

The 2021 AMR Benchmark covers antimicrobial medicines and vaccines that target bacterial and fungal infections in humans, as follows:
• Medicines: all innovative and adaptive medicines, branded generics and generic medicines (regardless of formulation) used for direct treatment against bacterial and fungal pathogens, or disease processes (but not products used only for symptomatic relief); and
• Vaccines: both preventive and therapeutic vaccines that target bacteria or fungi.

Each of the Benchmark's Research Areas has its own tailored product scope, as shown in table 5.

Key changes for 2021
For the 2021 AMR Benchmark the product scope will remain the same as in the 2020 AMR Benchmark.

Products assessed per Research Area

Table 6

A RESEARCH & DEVELOPMENT
- Antibacterial medicines and vaccines that target priority pathogens (see appendix I) in discovery, pre-clinical and clinical phases I-III, or which are approved; and
- Antifungal medicines and vaccines that target priority pathogens (see appendix I) in discovery, pre-clinical and clinical phases I-III, or which are approved.

B RESPONSIBLE MANUFACTURING
- Manufactured and/or marketed antibacterial medicines; and
- Manufactured and/or marketed antibacterial active pharmaceutical ingredients (APIs).

C APPROPRIATE ACCESS & STEWARDSHIP

Appropriate Access
- Marketed on-patent antibacterial and antifungal medicines and vaccines; and
- Marketed off-patent/generic antibacterial and antifungal medicines, including products from the WHO's Essential Medicines List.

Stewardship
- All marketed antibacterial and antifungal medicines.

WHAT WE MEASURE

Geographic scope

Antibacterial and antifungal resistance is emerging and spreading across the globe. To address this, efforts to create and produce new medicines and vaccines (and establish responsible manufacturing practices) must be prioritised globally. Wherever effective antibacterial and antifungal products are marketed, efforts are needed to improve their rational use. For these reasons, the geographic scope of the 2021 Antimicrobial Resistance Benchmark remains global, comprising 218 countries and/or territories.*

Challenges around availability of products, and appropriate access, remain significantly higher in some countries, generally resource-limited countries with high burdens of disease. A group of Benchmark indicators (referred to as 'access metrics') is thus dedicated to measuring how companies plan for access to antibacterial and antifungal medicines and vaccines in such countries (referred to as 'access countries'); and/or how they are already addressing these challenges there. The access metrics are indicators A.3, C.1.1-C.1.3, C.2.1-C.2.3 and C.3.

Key changes for 2021

To enable progress to be measured, the 2021 Benchmark maintains the same subset of 102 'access countries' in scope as in 2020.

Defining the scope for access metrics

The 102 'access countries' were identified through: (1) their level of income (gross national income [GNI] per capita); (2) their levels of development; (3) their scope and scale of inequality; and (4) their infectious disease burden. Assessments of these levels drew on data published in 2018 by the World Bank,[11] United Nations Economic and Social Council (ECOSOC),[12] United Nations Development Programme (UNDP),[13] and Institute for Health Metrics and Evaluation (IHME),[14] specifically:

- Countries classified as low income or lower middle-income, according to World Bank data (June 2018);
- Countries classified as Least Developed Countries (LDCs) by ECOSOC's Committee for Development Policy (2018);
- Countries classified as low or medium human development in UNDP's Human Development Index (HDI), based on data published in September 2018;
- Countries with an Inequality-adjusted Human Development Index (IHDI) value lower than or equal to the median value of 0.583 (UNDP, 2018); and
- Countries with a high** burden of bacterial and fungal infectious diseases, as measured in disability-adjusted life years (DALYs) by IHME in its "Global Burden of Disease Study 2017" (2018).

Where countries had missing values for HDI or IHDI in UNDP's 2018 report, the Benchmark took into account past reports (to 2013).

Geographic scope assessed per Research Area

Table 7

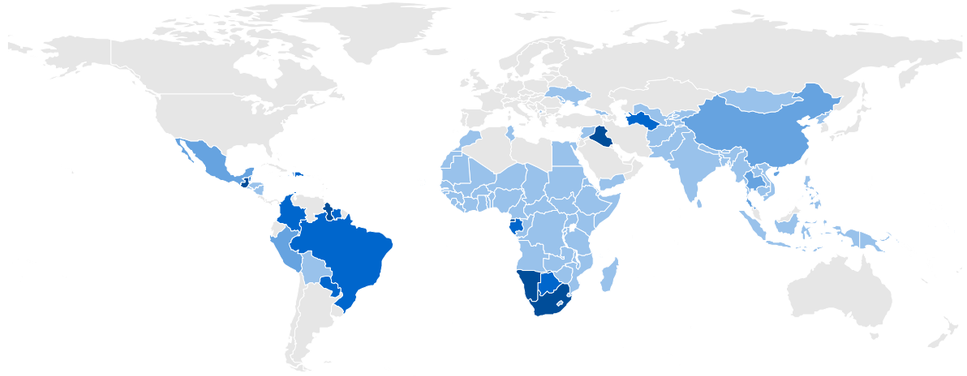
A RESEARCH & DEVELOPMENT
• R&D Pipeline: Global
• Stewardship Plans: Global
• Access Plans: 102 countries where better access is needed
B RESPONSIBLE MANUFACTURING
• Global
C APPROPRIATE ACCESS & STEWARDSHIP
• Appropriate Access: 102 countries where better access is needed
• Stewardship: Global

*The Benchmark considers all countries or territories listed in the World Bank Country and Lending Groups (June 2018). The World Bank warns that the term "country" (used interchangeably with "economy"), does not imply political independence but refers to any territory for which authorities report separate social or economic statistics.

** Calculated as the sum of the burden of disease for 24 infectious diseases included in IHME's 2017 Global Burden of Disease Study (2018). All countries above the third quartile of the data distribution were included, unless a country was classified by the World Bank as having high income or by the UNDP as having a "Very high" HDI or being above the third quartile of the IHDI distribution.

Countries in scope for access metrics in the 2021 Antimicrobial Resistance Benchmark - 102 countries

Figure 3



Basis for inclusion in scope for access metrics

- World Bank list of economies (June 2018): Income group
- ECOSOC (2018): LDC List / UNDP Human Development Indices and Indicators (2018): HDI
- UNDP Human Development Indices and Indicators (2018): IHDI
- IHME Global Burden of Disease Study 2017 Results (2018): bacterial and fungal infections
- Not in scope for access metrics

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

List of countries covered by access metrics for the 2021 Antimicrobial Resistance Benchmark – 102 countries

Table 8

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

Country classification is based on 2018 data.

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

How the Benchmark measures

The AMR Benchmark will map how a cross-section of the pharmaceutical industry is responding to the rise of antimicrobial resistance (AMR). It will assess their policies and practices for slowing drug resistance and for improving appropriate access to medicines and vaccines for people living in countries where greater access is needed. The Benchmark will compare companies' approaches, where relevant and appropriate, with reference to their pipelines and portfolios.

The analytical framework is structured along three Research Areas:

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

HOW WE MEASURE

Analytical framework

The 2021 AMR Benchmark will evaluate company action using an analytical framework of three Research Areas: Research & Development, Responsible Manufacturing and Appropriate Access & Stewardship. The three Research Areas have been confirmed by stakeholders as those areas where pharmaceutical companies have core responsibilities to limit AMR. In each Research Area, companies' policies and practices are measured by indicators that correspond to priority actions for pharmaceutical companies.

20 indicators

The framework for the 2021 AMR Benchmark comprises 20 indicators; two are new additions and one has been removed. Two new indicators were developed to examine access to on-patent vaccines separate from on-patent medicines. This split applies to both the Registration and Expanding Access and Affordability indicators (C.1.3 and C.2.3). Moreover, the Benchmark will no longer be assessing how companies share their intellectual capital (formerly the A.3 indicator) due to the inadequate data available for analysis. Other indicators have been modified or refined, to tailor the metrics or to improve data capture, to enhance comparison between companies, or to conduct additional analyses.

Analysing companies only where relevant

Whether a company is assessed in a certain Research Area depends on the size and nature of its R&D pipeline and marketed product portfolio. For example, large research-based pharmaceutical companies will be assessed across all Research Areas if they have vaccines and medicines. If they have only medicines, they will not be scored in the vaccine specific indicators (A2.3, C.1.3, C.2.3). Generic medicine manufacturers will be assessed only in the Responsible Manufacturing and Appropriate Access and Stewardship areas. Following stakeholder consensus, the unique role of small and medium-sized enterprises (SMEs) in antimicrobial R&D will be explored in a standalone report.

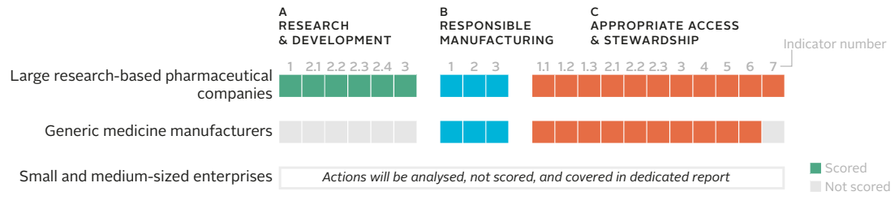
Where the data comes from

The Benchmark has established a new standard for industry transparency in the AMR space, and looks increasingly at public and partner data sources, as well as inviting companies to engage. While it is evident that companies have differing capacities and commitments to data sharing, it is an objective of the Benchmark to stimulate companies towards greater transparency and to put more data in the public domain. The next iteration of the Benchmark will continue the emphasis on collecting data primarily from the public domain as well as directly engaging with companies to clarify, verify and expand on the data collected. Public sources will include the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), ClinicalTrials.gov, annual filings and reports from companies, among others.

Analytical Framework for the 2021 AMR Benchmark

The AMR Benchmark covers three Research Areas. Large research-based pharmaceutical companies and generic medicine manufacturers are evaluated using 20 indicators. Whether a company is scored depends on its pipeline and portfolio. The role and actions of SMEs in antimicrobial R&D will be covered in a standalone report. SMEs will not be assigned scores.

Figure 4



RESEARCH AREAS

A Research & Development

Company scope: Large R&D-based companies; SMEs (separate report) • Diseases: Bacterial, fungal infections • Products: Medicines, vaccines • Geographic scope: Global/Other

As antimicrobial resistance erodes the effectiveness of the world's current arsenal of antibacterial and antifungal medicines, the need to develop new ones – to replace those losing their effectiveness – becomes ever more pressing. New vaccines also play a key role in slowing the emergence and spread of resistance, by preventing the transmission of disease and averting inappropriate use of antimicrobial medicines. The pharmaceutical industry must commit and take action to develop new medicines and vaccines for those bacteria and fungi that pose the gravest of threats to human health because of their widespread resistance against existing standard of care (see appendix I).

This research area maps and captures R&D investments and pipelines, highlighting focal points and current gaps. It also explores how companies plan ahead to ensure newly approved products are swiftly made available globally and equitably (through advance planning for access) in low- and middle-income countries (LMICs), and that new medicines are used appropriately, in ways that minimise the risk of resistance emerging and spreading (through advance planning for stewardship). The Benchmark encourages pharmaceutical companies to commit resources and engage with relevant partners to facilitate such advance planning.

In this research area, the Benchmark assesses a number of large research-based pharmaceutical companies that are engaged in: (a) R&D for new antibacterial and antifungal medicines and vaccines in preclinical and clinical stages of development; as well as (b) R&D to adapt existing medicines and vaccines. The Benchmark research programme also evaluates the R&D activities of clinical-stage biopharmaceutical companies (referred to as small and medium-sized enterprises, or SMEs), with the findings being published in a separate standalone report (see below for more information).

KEY CHANGES FOR 2021

In a change from previous iterations of the Benchmark, SMEs will be addressed in a standalone publication. As SMEs play a unique role in antibacterial and antifungal R&D, this separate report will enable a deeper exploration of the particular challenges they face in developing medicines, acquiring financing, navigating the market and surviving. It aims to highlight examples of SMEs that, despite challenging market conditions, continue to strive to bring innovations to LMICs, where access to new and effective medicines is less widespread. These companies will not be scored using the indicators presented here. In a separate change, the Benchmark will no longer be assessing how companies share their intellectual capital (formerly the A.3 indicator), due to the inadequate quality of data available for analysis. Collaboration and sharing of intellectual property remain strong tools to stimulate R&D, and the Access to Medicine Index will continue to credit relevant companies that are developing compelling initiatives in this area.

WHICH ACTIVITIES WILL BE ANALYSED?

R&D investments

The Benchmark will capture the financial resources that each company dedicates to R&D for antibacterial and antifungal medicines and vaccines. To balance out differences in the amounts of resources available to companies in scope, the Benchmark will focus on the proportion of total revenue derived from pharmaceuticals that each company invests in R&D for its projects in scope.

R&D pipelines

The Benchmark uses a mix of quantitative and qualitative metrics to examine the clinical and preclinical pipelines of the companies in scope. The R&D research area focuses on antibacterial and antifungal medicines and vaccines that address priority pathogens: namely those identified by the World Health Organization (WHO) and Centers for Disease Control (CDC) as posing the greatest threat to public health and for which there is an urgent need to develop new medicines and vaccines (see appendix I). The Benchmark will report on the nature and number of projects targeting these priority pathogens that each company has in its R&D pipeline, including new and adaptive medicines and vaccines (A.2.1) (referring to R&D to create new formulations or label extensions).

The Benchmark will also evaluate the degree to which products in clinical development are of value for public health (indicator A.2.2); the number of vaccines in pipelines (A.2.3); the number of projects that target "urgent" and "critical" pathogens as defined by the CDC and WHO, respectively (A.2.4). It will draw on assessments published by WHO and The Pew Charitable Trusts of existing antimicrobial pipelines (including considerations for non-traditional products). As in previous iterations, the 2021 AMR Benchmark will highlight projects that have clear clinical value beyond WHO's criteria for innovation.

Access and stewardship planning

Planning ahead for access helps to ensure companies take account of public health needs during product development. Such planning, conducted early on, can help to create more

rapid access to new medicines and vaccines at more affordable prices following their entry to markets. Access plans can include equitable pricing strategies, widespread registration strategies and non-exclusive voluntary licensing agreements. For new antimicrobial medicines, these access plans must be coupled with stewardship plans to ensure that, upon commercialisation, new products can be used appropriately and remain effective over time. Companies are expected to have plans in place for pipeline projects in Phase II and beyond. The Benchmark assesses the extent to which companies create and disclose plans to make new products swiftly accessible upon market entry, and ensure they are used appropriately thereafter. A list of strategies that companies can use to start planning for access and stewardship ahead of commercialisation can be found in Appendix III.

	Indicator	Rationale	Change since 2020
A.1	**R&D investments** R&D investments (including in-kind) dedicated to the development of antibacterial and antifungal medicines and vaccines targeting priority pathogens in the fiscal year 2019 and 2020, developed in-house or through collaborations (as long as the assessed company investment represents 50% or more of the project costs).	To characterise the overall financial resources dedicated to R&D for antibacterial and antifungal medicines and vaccines focusing specifically on priority pathogens as defined by WHO and the CDC.	No change
A.2.1	**Pipeline size** The size of a company's R&D pipeline targeting priority pathogens, including antibacterial and antifungal medicines and vaccines (new chemical/biological entities and adaptations) developed in-house or through collaborations.	To characterise the degree to which a company focuses on antibacterial and antifungal R&D, in addition to financial information.	No change
A.2.2	**Novelty of pipeline** The novelty of new investigational clinical antibacterial and antifungal medicines targeting priority pathogens that the company is developing (in-house or through collaborations). A new product candidate in development is defined as containing at least one new component (entity) not previously approved.	To encourage companies to invest in innovative therapeutic approaches that reduce the risk of (cross-) resistance, thus increasing the useful life of the molecule.	No change
A.2.3	**Vaccines in the pipeline** The number of new vaccines that the company is developing for priority pathogens in scope (in-house or through collaborations).	Vaccination against priority pathogens can have a positive impact in minimising AMR by reducing transmission of infection and use of antimicrobials, which helps to lower the risk of new resistance genes developing or resistant strains being selected for.	No change
A.2.4	**Projects targeting critical priorities** The number of projects that target a 'critical' pathogen (as defined by WHO) and/or 'urgent' pathogen (as defined by the CDC). These pathogens include carbapenem-resistant (CR) *Acinetobacter spp., Candida auris, Clostridioides difficile,* CR or ESBL-producing *Enterobacteriaceae,* drug-resistant *Neisseria gonorrhoeae* and *CR Pseudomonas aeruginosa.*	To measure a company's commitment to global health priorities through its focus on developing antibacterial and antifungal medicines and vaccines against those microorganisms identified as posing the most critical and urgent threats to public health.	No change
A.3	**Access and stewardship planning** The proportion of late-stage antibacterial and antifungal R&D projects targeting priority pathogens, for which the company provides information about having plans in place for 1) access in countries in scope and where burden of disease is higher; and 2) stewardship on a global base. This indicator applies to late-stage R&D projects in Phase II and III of clinical development (developed in-house or through collaborations) and recently approved products.	To describe efforts to ensure that, upon commercialisation, successful antibacterial and antifungal medicine and vaccine candidates targeting priority pathogens are made available rapidly and affordably and can be used appropriately.	No change

RESEARCH AREAS

B Responsible Manufacturing

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

This Research Area compares company strategies to limit the impact of antibacterial manufacturing upon antimicrobial resistance (AMR). During pharmaceutical manufacturing, antibacterial residue can be released into the environment in factory wastewaters. This can contribute to the development of AMR, as bacteria naturally present in water and soil are exposed to antibacterial ingredients that can trigger the emergence and/or selection of resistance genes.[15-17] Manufacturing practices and management systems that give rise to poor-quality products can also contribute to the development of AMR, since bacteria are more likely to become resistant when medicines containing a lower-than-optimal amount of the active ingredient are used to treat infections.[18]

There are three main routes through which companies can minimise the risk that their manufacturing operations will contribute to the development of AMR. These routes are addressed in each of the three indicators in this Research Area, and are as follows: (1) adoption of a clear and thorough environmental risk-management strategy that applies to a company's own manufacturing sites, to the sites of its third-party suppliers of active pharmaceutical ingredients (APIs) and/or drug products, and to external waste-treatment plants*; (2) publication of information on the risk-management processes implemented and their outcomes, including antibacterial discharge levels, and; (3) adoption of specific policies and actions to uphold high-quality manufacturing standards for antibacterial medicines, accepted by recognised authorities.

In this Research Area, the Benchmark assesses large research-based pharmaceutical companies and generic medicine manufacturers in scope. The antibacterial sales volumes or values for these companies demonstrate that they are prominent players in multiple manufacturing chains, with significant influence over their upstream suppliers. Some of these companies are also prominent producers of antibacterial APIs. The Benchmark does not directly assess other large API producers that have less prominent sales of finished products, but the activities of some are covered indirectly as suppliers of the companies in scope.

KEY CHANGES FOR 2021

In its evaluation of companies' environmental strategies (B.1) and transparency (B.2), the 2021 Benchmark will bring back into scope assessment relating to public waste- and wastewater-treatment plants. For the 2020 Benchmark, public treatment plants were excluded as, given national and/or regional regulations, companies reported having little power to negotiate contractual terms with these plants, in particular wastewater treatment plants. Nonetheless, public and private plants can play an important role in minimising the risk of AMR development.[19] In 2021, the Benchmark will consider a wider set of actions that companies can take to minimise AMR risk related to waste streams sent from their production sites to both public and private plants. These will still include stringent actions such as contractual terms requiring private plants to monitor discharge limits, but will also newly cover other preventative or *ad hoc* measures adopted, e.g., in collaboration with public or private plants.

WHICH ACTIVITIES WILL BE ANALYSED?

Environmental risk-management strategy
During pharmaceutical manufacturing, products with antibacterial activity are often released into the environment via wastewaters or solid waste (such as sludge). This release increases the risk that resistant bacteria will develop and resistance genes will spread in the environment. Companies can minimise that risk by adopting a robust environmental risk-management strategy. The Benchmark will assess how companies manage and dispose of their antibacterial waste, including how they limit levels of antibacterial residue in wastewaters. It will also look at how they apply relevant policies and/or practices to third-party suppliers and external waste-treatment plants.

Disclosure on environmental risk management
The Benchmark examines whether companies implement specific strategies to manage environmental AMR risks associated with antibacterial manufacturing discharge, as well as whether they publish certain elements of these strategies, and their outcomes. Publishing such details allows independent third parties to analyse and compare the processes and performances of different companies, and promotes the dissemination of good practice. Publication can also give procurers of antibacterial medicines (such as governments and other public institutions) the information necessary to identify companies that manufacture responsibly.[20,21]

The Benchmark will look at how much information a company publishes about its strategies and audit results. Stakeholders are asking for companies to publish amounts of antibacterials discharged from their own and suppliers' manufacturing sites (as quantified by chemical analysis or mass balance estimation). The publication of less detailed information

*Including any waste treatment or disposal contractor, e.g., wastewater treatment plants, incineration plants and landfills.

may also be taken into account by the Benchmark in its evaluation, provided the information is useful to third parties. This is now explicitly referenced in the indicator. Even limited transparency can support companies and stakeholders in mapping out a path towards fuller disclosure.

Manufacturing high-quality antibacterials

To help curb the development of antibacterial resistance, companies can uphold high standards in antibacterial manufacturing. This can minimise the likelihood that poor-quality medicines (those with subtherapeutic doses of antibacterial ingredients, below the amount required for therapeutic effect) will reach patients. The Benchmark will assess mechanisms that companies have put in place at their own (and third-party) manufacturing sites to maintain high-quality production of antibacterial medicines. It will focus on the ways companies engage with suppliers to increase accountability and minimise risks, particularly in areas where suppliers find it difficult to meet quality standards.

	Indicator	Rationale	Change since 2020
B.1	**Environmental risk-management strategy** The company has an environmental risk-management (ERM) strategy to minimise the environmental impact of manufacturing discharge of antibacterials. This applies to: (a) its owned and/or operated manufacturing sites; (b) third-party suppliers of antibacterial active pharmaceutical ingredients (APIs) and drug products; and (c) external waste treatment plants. The strategy includes, for (a), (b) and (c), the following elements: (i) implementation of waste treatment/management practices for both liquid and solid antibacterial-containing wastes, taking AMR risk into account; (ii) on-site auditing of compliance with the strategy; (iii) setting of antibacterial discharge limits based on predicted no-effect concentrations (PNECs) for resistance selection; and (iv) quantification of the levels of antibacterials discharged in wastewaters (by chemical analysis or mass balance estimation) to assess and minimise the risk that limits are surpassed.	To assess the comprehensiveness of a company's strategy to minimise the impacts of antibacterial production on resistance and the degree to which the strategy is extended to the company's suppliers and providers of waste treatment/disposal services.	Modified
B.2	**Disclosure on environmental risk management** The company publishes the following elements of its ERM strategy, which should be easily accessible on the main company website and dated: (i) the specific waste treatment/management practices adopted to minimise environmental impact of wastewaters and solid waste from antibacterial manufacturing; (ii) results of strategy audits, detailed or with some level of aggregation and/or anonymisation, conducted at the company's manufacturing sites, third-party sites that manufacture antibacterial APIs and drug products for the company and/or external waste-treatment plants; (iii) limits set for antibacterial discharge from own sites, third-party supplier sites and/or external wastewater treatment plants, along with methodological and evidential bases; (iv) levels (concentrations) of antibacterial discharge from own sites, third-party supplier sites and/or external wastewater treatment plants, along with the methodology used for quantification; and (v) names and/or locations, including with some level of aggregation, of third parties manufacturing individual antibacterial APIs and drug products and/or of external waste-treatment plants. The Benchmark values detailed disclosures more highly than aggregate/anonymised ones.	To assess how much information a company makes available publicly to allow independent third parties to analyse and compare companies' environmental risk-management processes and performances.	Modified
B.3	**Manufacturing high-quality antibacterials** The company reports systems in place to ensure, maintain and/or improve the production of high-quality antibacterial APIs and drug products at its own and third-party manufacturing sites, in a manner consistent with the international standards on current Good Manufacturing Practice (cGMP) developed and accepted by recognised national and international authorities, such as the FDA, EU and WHO. Non-conformities reported by such authorities may be taken into account in the Benchmark's assessment.	To assess the risks that a company will produce antibacterial medicines with subtherapeutic dose levels (and/or of sub-optimal quality), which can contribute to the development and spread of antibacterial resistance.	No change

RESEARCH AREAS

C Appropriate Access & Stewardship

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

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

This Research Area looks at how companies are working to increase access to their antibacterial and antifungal medicines and vaccines, while also ensuring these will be used appropriately (stewardship). The two issues are closely interlinked and need to be considered jointly. In Appropriate Access & Stewardship, the Benchmark assesses companies' strategies to expand access to these medicines and vaccines in the 102 countries identified as most in need of better access to such products (see Geographic Scope). It also considers their stewardship initiatives for these products globally.

Antibacterial and antifungal medicines and vaccines are essential tools in treating infectious disease worldwide. Yet millions of people live without reliable access to these medicines, or lack information to use them appropriately. Issues of access and stewardship are especially relevant in countries where healthcare systems have limited resources, and for whom the burden of infectious diseases is high. Limited resources, for example, can reduce capacity to prevent and manage such diseases, particularly resistant infections.[22]

Limitations in access to quality-assured antibacterial and antifungal medicines and vaccines arise for a variety of reasons. These include low availability (such as when new and on-patent medicines are not registered for sale in countries in need); lack of affordability of on- and off-patent/generic products; disruptions in the supply chain; and issues that result from less mature regulatory systems. Such restrictions may lead to patients purchasing or being prescribed medicines that do not meet either their medical need or the quality standards needed for treatment, which can increase the risk of resistance.[23,24] Stewardship programmes are also important to delay the emergence and spread of resistance. In this Research Area, the Benchmark assesses large research-based pharmaceutical companies and generic medicine manufacturers. The companies in scope have antibacterial and/or antifungal products on the market, and play an important role in expanding access and ensuring stewardship for these products.

To expand access, they can implement strategies relating to product registration, accessibility, affordability and improving supply chains. Challenges around appropriate access to products remain significantly higher in some countries, resource-limited countries with high burdens of disease, referred to by the Benchmark as 'access countries'. The Appropriate Access indicators are dedicated to measuring how companies plan for access to antibacterial and antifungal medicines and vaccines in these particular countries; and/or how they are already addressing these challenges there. Regarding stewardship, companies can take action in a range of areas including surveillance and implementing strategies to ensure that sales and marketing practices counter the risks of inappropriate use.

KEY CHANGES FOR 2021

To assess how companies make their on-patent products available and affordable, in 2021, the Benchmark will make separate examinations of on-patent medicines and on-patent vaccines. This is because companies have different roles and opportunities for expanding access to vaccines than for antibacterial and antifungal medicines. In general, vaccines are more profitable than medicines: there is greater international demand than for antimicrobial medicines, and agencies such as UNICEF and Gavi the Vaccine Alliance give global support to facilitate registration and marketing.

Further, the Benchmark has updated its assessment criteria to enable a more detailed assessment of how companies ensure the quality and uninterrupted supply of their products. Pricing indicators are adjusted to examine how companies determine the greatest needs and gaps in accessibility, and the strategies they use to increase affordability and expand access. A selection of "forgotten antibiotics" – older products that are effective but no longer widely marketed – will be highlighted as part of the registration and affordability analyses.

WHICH ACTIVITIES WILL BE ANALYSED?

▸ACCESS

Registration

To make their products available in different countries, companies must first file their products for registration with the local regulatory authorities. It is important that filing is done as widely and rapidly as possible after a product is approved, particularly if that product is innovative or superior to those already on the market. The Benchmark will look for evidence that companies are filing their on- and off-patent antibacterial and antifungal medicines and vaccines for registration in countries with the lowest levels of income, and with the highest levels of inequality and public health need.

The Benchmark will assess all the on-patent antibacterial and antifungal medicines and vaccines that each company produces. It will also assess each company's off-patent/generic products, prioritising those on the World Health Organization's current Model List of Essential Medicines (EML). This lists products that the WHO considers effective, safe and cost-effective, and which it deems essential for every health system. In particular, the Benchmark will pay special

attention to anti-tuberculosis and antifungal medicines on the EML, and to antibacterial medicines the WHO categorises as Access, Watch and Reserve.[25] The Access category includes antibacterials with wide indications and lower resistance potential than medicines in the other two categories. The Watch category includes products with high resistance potential – these are the main targets of stewardship programmes. Finally, the antibacterials classified as Reserve are to be used only as a last resort to treat multi-drug-resistant infections. The Benchmark will also assess and report on the registration of relevant forgotten antibiotics in the WHO's 2019 EML. These older antibiotics, no longer widely marketed, are still considered safe and effective for treating infections from susceptible and resistant bacteria.[26]

Expanding access and affordability

The lack and/or inadequate use of antibacterial and antifungal medicines and vaccines creates substantial morbidity and mortality, so it is essential for products to be made both accessible and affordable. For these medicines and vaccines, the Benchmark will consider companies' efforts to identify the greatest needs for their products and any gaps in accessibility. Companies will be assessed on how they set prices, both at country level and for different populations within each country. In addition to assessing pricing strategies such as tiered pricing, as well as donations, the Benchmark will consider other strategies to expand the accessibility of products. Examples include decisions to license patented medicines to promote generic competition, and collaborations with organisations that procure medicines on a global or regional basis (such as Gavi, the Vaccine Alliance; Global Drug Facility; the Global Fund; and the Pan American Health Organization's Revolving Fund). The Benchmark will assess the geographic reach of such efforts to ensure affordability and accessibility, and will consider evidence for commitments made by companies to expand access to more people including those in underserved and vulnerable populations in low- and middle-income countries.

Ensuring continuous supply

When supply chains are fragile or demand increases unexpectedly, this can lead to shortages in medicines and vaccines. In turn, this can have a profound impact on access, especially in resource-limited settings. The Benchmark will examine upstream and downstream mechanisms used by companies to ensure an uninterrupted supply of quality products, and to prevent "stockouts" (situations in which stock is used up). It will assess the supply of APIs, holdings of buffer stock, how companies share data with external stakeholders to anticipate demand, capacity-building initiatives, and strategies to mitigate the circulation of substandard and/or falsified medicines.

▶STEWARDSHIP

Educational stewardship activities

Companies often organise activities for healthcare professionals (HCPs) to educate them about the usage of products they make. Through these activities, companies can help to raise awareness of antimicrobial resistance and inform prescription practices to encourage appropriate use. While there is no clear consensus as to whether companies should engage in such activities, when companies do choose to engage, the consensus view is that they must take steps to mitigate the risk of conflict of interest. In this regard, the Benchmark will examine, for example whether companies use non-branded materials in their educational activities for HCPs, issue unrestricted grants to independent third parties to develop educational activities, and/or pledge not to provide financial or material incentives to participants.

Responsible promotional practices

One of the strategic pillars of the global effort to address AMR is to ensure antimicrobial medicines are used appropriately and only when needed. This requires companies to avoid incentivising sales agents to, for example, mis-sell or oversell products. Companies can lower the risk of sales agents behaving in unethical ways by minimising focus on sales volumes in their incentive schemes. The Benchmark will look at the style and nature of incentives offered to companies' sales agents, and at whether these reward high volumes of sales. By adopting incentive targets that are based on quality of service, behaviour and other competencies, for example, companies can fully or partially decouple incentives from sales.

Stewardship-oriented adaptations for patients

When medicines are prescribed or bought over the counter, the quality of information provided with them can improve the likelihood that they will be used appropriately. The Benchmark will assess whether companies have adapted their brochures and packaging in ways that encourage patients to use antibacterial and antifungal medicines appropriately. For example, companies can provide brochures in local languages or offer pictograms to help populations in which illiteracy is an issue.

AMR surveillance

Surveillance systems play a critical role in helping companies and others to monitor, control and ultimately prevent the rise and spread of infectious diseases and antimicrobial resistance. The Benchmark examines whether companies have their own AMR surveillance systems; are involved in building capacity for new surveillance activities; and support or contribute to existing local, national and global systems. Further, it assesses whether companies share raw surveillance data publicly through open-access data platforms: for example, on the AMR Register established by the Wellcome Trust and the Open Data Institute.

	Indicator	Rationale	Change since 2020
C.1.1	**Registration of on-patent antibacterial and antifungal medicines** The company files to register its on-patent antibacterial and antifungal medicines in the countries with the lowest levels of income, highest levels of inequality and highest public health need.	When a company files to register its new antibacterial and antifungal medicines in low- and middle- income countries where disease burden and inequality are higher, this demonstrates a commitment to enter markets in need, and to provide access to products in these markets. Registration is a key step to ensure these products will be available where needed.	Modified
C.1.2	**Registration of off-patent/generic antibacterial and antifungal medicines** The company files to register its off-patent and generic antibacterial and antifungal medicines in countries with the lowest levels of income, highest levels of inequality and highest public health need.	When a company files to register off-patent/ generic products in low- and middle-income countries where disease burden and inequality are higher, this demonstrates a commitment to enter markets in need, and to provide access to its products. Registration is a key step to ensure these products will be available where needed.	No change
C.1.3	**Registration of on-patent antibacterial and antifungal vaccines** The company files to register its on-patent antibacterial vaccines in countries with the lowest levels of income, highest levels of inequality and highest public health need.	When a company files to register its new antibacterial vaccines in low- and middle-income countries where disease burden and inequality are higher, this demonstrates a commitment to enter markets in need, and to provide access to products in these markets. Registration is a key step to ensure these products will be available where needed.	New
C.2.1	**Expanding access to on-patent antibacterial and antifungal medicines** The company makes efforts to expand access to and ensure affordability of on-patent antibacterial and antifungal medicines in an appropriate manner to underserved populations in countries in scope. Company demonstrates the following: • Evidence of efforts to assess need and gaps in access for populations living in access countriaes • Evidence of efforts to close this gap (alone or in partnership) via methods that address patients' ability to pay across the whole income pyramid, via voluntary licensing, equitable pricing, donations and other means (e.g. by collaborating with regulatory authorities, public health organizations and generic companies to expand access of their products) • Evidence showing the number of patients that benefitted has increased and is sustained over time (long term access) • Plans to ensure the continued expansion of access to underserved populations in access countries	When a company addresses the accessibility and affordability of its most innovative antibacterial and antifungal medicines, this can help low- and middle-income countries to reduce their burdens of infectious diseases, including resistant infections.	Modified

Indicator	Rationale	Change since 2020
C.2.2 Expanding access to off-patent/generic products antibacterial and antifungal medicines The company makes efforts to expand access to and ensure affordability of off-patent antibacterial and antifungal medicines in an appropriate manner to underserved populations in countries in scope. Company demonstrates the following: • Evidence of efforts to assess need and gaps in access for populations living in access countries • Evidence of efforts to close this gap (alone or in partnership) via methods that address patients' ability to pay across the whole income pyramid, via equitable pricing, donations and other means (e.g. by collaborating with regulatory authorities, public health organisations and other companies to expand access of their products).* • Evidence showing the number of patients that benefitted has increased and is sustained over time (long term access) • Plans to ensure the continued expansion of access to underserved populations in access countries	When a company addresses the accessibility and affordability of its off-patent/ generic antibacterial and antifungal medicines, this can help low- and middle-income countries to reduce their burdens of infectious diseases, including resistant infections.	Modified
C.2.3 Expanding access to on-patent antibacterial and antifungal vaccines The company makes efforts to expand access to and ensure affordability of on-patent antibacterial vaccines in an appropriate manner to underserved populations in countries in scope. Company demonstrates the following: • Evidence of efforts to assess need and gaps in access for populations living in access countries • Evidence of efforts to close this gap (alone or in partnership) via methods that address patients' ability to pay across the whole income pyramid, via voluntary licensing, equitable pricing, donations and other means (e.g. by collaborating with regulatory authorities, public health organizations and other companies to expand access of their products) • Evidence showing the number of patients that benefitted has increased and is sustained over time (long term access) • Plans to ensure the continued expansion of access to underserved populations in access countries	When a company addresses the accessibility and affordability of its innovative vaccines, this can help low- and middle-income countries to reduce their burdens of infectious diseases, including resistant infections.	New
C.3 Ensuring continuous supply The company applies multiple strategies both upstream and downstream to ensure the uninterrupted supply of quality products. These include the following components: • Evidence to ensure sufficient supply of APIs • Bilateral data-sharing with countries or regions for demand planning. • Buffer stock for key antibacterial and antifungal medicines(including duration and reporting of shortages) • Capacity building initiatives to strengthen supply chain in low- and middle-income countries • Mitigation of the circulation of substandard and falsified medicines (including how the company verifies the credentials of suppliers and customers downstream, and to whom it reports encounters of falsified medicines)	Accessibility relies on companies having strategies to ensure a continuous supply of on- and off-patent antibacterial and antifungal medicines and vaccines. To ensure an uninterrupted supply of good quality products, companies need to prepare for stockouts by ensuring the supply of APIs, keeping sufficient buffer stock, and aligning with external stakeholders on supply and demand. When people are assured of a continuous supply, this decreases the chance they will resort to obtaining substandard or falsified medicines, which can increase the risk of AMR emerging and spreading	Modified

*On publication, this list incorrectly included voluntary licensing due to a proof-reading error.

Indicator	Rationale	Change since 2020
C.4 Educational stewardship activities The company has a clear strategy to ensure that any conflict of interest (COI) is mitigated in its (support of) antibacterial and antifungal stewardship educational activities directed at healthcare professionals. To mitigate COI, the company provides an unrestricted grant to an independent third party to develop the educational activity, or if it is developed in-house, the company ensures COI is mitigated through an independent review of the educational activity by a third party such as an accreditation body.	Companies organise educational activities, such as Continuing Medical Education, that can influence and/or change the behaviour of prescribers and potentially affect access to appropriate treatment as well as the use of antibacterials and antifungals. Conflicts of interest are inherent in this area, so companies need to limit their role accordingly. Those involved in educational stewardship must put in place robust safeguarding strategies, policies, and procedures to mitigate any conflicts of interest in educational activities directed at healthcare professionals.	No change
C.5 Responsible promotional practices Responsible promotional practices when engaging with healthcare professionals include sales practices that aim to avoid overselling of antibacterials and antifungals by either not promoting such products or by decoupling incentives for sales agents from sales volumes. In addition, the company adapts its marketing materials to include AMR trends and guidelines for healthcare professionals.	Promotional practices used to sell antibacterial and antifungal medicines can lead to bias in prescribers' practices, and could mean products are prescribed inappropriately. To limit prescriber bias and reduce the risk of inappropriate prescription, companies need to implement responsible promotional practices by altering sales incentives to prevent overselling or mis-selling.	No change
C.6 Stewardship-oriented adaptations for patients The company adapts its brochures and/or its packaging to facilitate the appropriate use of antibacterial and antifungal products by patients. The company considers the needs of the patient population, including language, literacy, and paediatric use (if relevant). In addition, the company aims to improve adherence to treatment and considers local environmental conditions to preserve the effectiveness.	To encourage appropriate use of medicines and limit the emergence of antimicrobial resistance, companies may need to adapt brochures and packaging to guide patients about how to use products. For example, brochures can be written in a native language, or include pictograms instead of text.	No change
C.7 AMR surveillance The company has, supports, and/or contributes to antibacterial and antifungal surveillance programmes to track resistance to pathogens, and shares such data publicly.	By publicly sharing data on the surveillance of resistance, companies can assist in the effort to monitor the rise of resistance to antibacterial and antifungal medicines. Such data is an essential tool for governments and researchers to measure burdens of resistant infections. Sharing data also helps in forecasting and prioritising objectives for the design of stewardship policies.	Modified

Appendices

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

In the Research & Development Research Area, the Benchmark will assess the size and public health value of a company's pipeline of investigational antibacterial and antifungal medicines and vaccines. The disease scope for the 2021 AMR Benchmark includes the pathogens, with their specific resistance profiles, from the priority pathogens lists published by World Health Organization (WHO)* and the Centers for Disease Control and Prevention (CDC)** (see full list below). Modifications to the disease scope will be considered by the Benchmark Research Team according to any relevant updates to these priority lists, including the upcoming publication of a WHO priority list for fungal infections (in discussion at the time of publication of this report)***.

Indicator A.2.4 of the Benchmark will assess companies' projects targeting the most critical priorities in these lists, i.e. targeting the pathogens classified by the CDC and WHO as "Urgent" or "Critical", respectively.

Pathogen	WHO Priority List*	Resistance profile	CDC Biggest Threats**	Resistance profile
BACTERIA				
Acinetobacter spp.	Critical	Carbapenem	Urgent	Carbapenem
Bordetella pertussis			Watch	Drug-resistant
Campylobacter spp.	High	Fluoroquinolones	Serious	Drug-resistant
Clostridioides difficile			Urgent	
Enterobacteriaceae	Critical	Carbapenem Extended-Spectrum ß-Lactamase (ESBL)	Urgent Serious	Carbapenem Extended-Spectrum ß-Lactamase (ESBL)
Enterococcus faecium	High	Vancomycin (VRE)		
Enterococcus spp.			Serious	Vancomycin (VRE)
Haemophilus infuenzae type b (Hib)	Medium	Ampicillin		
Helicobacter pylori	High	Clarithromycin		
Mycobacterium tuberculosis	R&D priority		Serious	Drug-resistant
Mycoplasma genitalium			Watch	Drug-resistant
Neisseria gonorrhoeae	High	Cephalosporins Fluoroquinolones	Urgent	Drug-resistant
Pseudomonas aeruginosa	Critical	Carbapenem	Serious	Multidrug-resistant (MDR)
Salmonella spp.	High	Fluoroquinolones		
Salmonella non-typhoidal & serotype typhi			Serious	Drug-resistant
Shigella spp.	Medium	Fluoroquinolones	Serious	Drug-resistant
Staphylococcus aureus	High	Methicillin Vancomycin-intermediate and resistant	Serious	Methicillin (MRSA)
Streptococcus (group A)			Concerning	Erythromycin
Streptococcus (group B)			Concerning	Clindamycin
Streptococcus pneumoniae	Medium	Penicillin-non-susceptible	Serious	Drug-resistant
FUNGI				
Aspergillus fumigatus			Watch	Azole-resistant
Candida auris			Urgent	
Candida spp.			Serious	Drug-resistant

REFERENCES

* WHO. (2017). Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics.
** U.S. Centers for Disease Control and Prevention (CDC). (December, 2019). Antibiotic resistance threats in the United States, 2019.
*** WHO. (2020). First meeting of the WHO Antifungal Expert Group on Identifying Priority Fungal Pathogens: meeting report.

APPENDIX II. CONCEPTS USED IN EVALUATING ANTIMICROBIAL STEWARDSHIP

This appendix gives an overview of activities relevant to the Stewardship indicators within the Appropriate Access & Stewardship research area. It describes in detail what the expectations are of the companies assessed in the 2021 AMR Benchmark.

The next table describes for each Stewardship indicator: (a) the type of activity that is evaluated in the indicator; and (b) which group the activity is directed at.

Stewardship activities relating to healthcare professionals or patients

Stewardship activity	Directed at	Relevant in indicator
Educational activities (such as CME*)	Healthcare professionals	C.4 Educational Stewardship Activities
Promotional activities + materials	Healthcare professionals	C.5 Responsible Promotional Practices
Product packaging	Patients	C.6 Stewardship-oriented Adaptations for Patients
AMR surveillance	Public health authorities; researchers; public	C.7 AMR Surveillance

*CME: Continuing Medical Education

The table below describes examples of sales practices that are considered best practice, as well as current practices from the 2020 AMR Benchmark.

Current vs. best sales practices

Best sales practices	Current sales practices
No promotion of (selected) antibacterial and/or antifungal medicines	Promotion of antibacterial and/or antifungal medicines directed at healthcare professionals
Full decoupling of incentives for sales agents from sales volumes	Partial decoupling of incentives for sales agents from sales volumes (e.g. 25% variable pay)

NB: Variable pay may be linked to sales volumes.

This table gives an overview of materials relevant in indicator C.6 Stewardship-oriented adaptations for patients and gives examples of each type of material from the 2020 AMR Benchmark.

Stewardship-oriented adaptations for patients

Type of material	Product-specific or general	Goal	Example of adaptation
Packaging	Product-specific	At a minimum adheres to local regulations	Johnson & Johnson: Packaging a six-month treatment regimen (188 tablets) in a single bottle to enable patients to follow a full course of treatment without needing to make multiple visits to a pharmacy or clinic.
Brochures (package insert)	Product-specific	At a minimum adheres to local regulations	GSK: Developing a graphics-based smartphone application to educate patients in low-literacy environments.
Leaflets	General	To educate patients on AMR	Cipla: General patient education leaflets at the pharmacy or clinic on what antifungal resistance is and how to prevent it.

This is an overview of the most common types of data that can be generated in AMR surveillance programmes. Its benefits and examples of data platforms containing such data are presented in the table below.

AMR surveillance data

Type of AMR surveillance data	Benefits	Examples of data platforms
Results	Peer-reviewed journal articles and graphics-based databases on the results of surveillance data can be helpful in providing insight into where resistance to specific medicines is occurring.	Peer-reviewed journal articles; Results database
Raw data	By using and combining the raw data from companies' surveillance programmes, third-party researchers can explore the potential for further research, beyond the specific questions asked by the companies themselves.	The AMR Register (https://amr.theodi.org/)
Clinical trial data	Clinical trial data that contains surveillance data includes more patient-specific information such as the age, outcomes and comorbidities. This is valuable as it gives more detail about the proportion of resistant infections and the impact on fatality.	The YODA project (https://yoda.yale.edu/)

APPENDIX III. GUIDANCE TO ACCESS AND STEWARDSHIP PLANNING

This appendix provides a list of strategies for access and stewardship accompanying late-stage R&D projects, determined as phases II and III of clinical development and recently approved products.

The following are examples of access and stewardship planning commonly expected to be developed and arranged while a product is still in development, via commitments, explicit plans and contracts between company and governments and distributors, NGOs, and local stakeholders. This is not an exhaustive list as many ways to expand access and ensure proper stewardship can be developed. Companies applying one or more of these plans will be credited in the AMR Benchmark.

ACCESS STRATEGIES	*Detail*
Registration	Prioritise filing in countries, including LMICs, with high disease burden and high resistance
	Prioritise fast registration within 6-12 months or concurrently with launching in US/EU
WHO Prequalification of Medicines Programme	Facilitate eligibility of products for UN procurement and accelerated registration; relevant for access to countries with less mature national regulatory authorities
WHO Collaborative Procedure for Accelerated Registration	Accelerated registration mechanism
EMA Article 58	Facilitate access to essential medicines in LMICs
Responsible IP and Licensing Arrangements	Waiver patent rights and/or non-enforcement of rights in select geographies
	Plan for voluntary licensing arrangements to expand access
Managed Access Programmes	Implement programmes in high-burden countries, LMICs
	Compassionate Use, Special Access Schemes/Programmes
Product Donation Programmes	Identify populations in need with no capacity to pay and plan to donate as appropriate, working with local partners
Special Importation Waivers	Expand access for specific populations where there is an expressed need
Sustainable Manufacturing and Supply	Plan shortage mitigation strategies
	Forge and maintain local manufacturing commitments to keep costs low and shorten supply chains
Equitable pricing	Price-caps to ensure limits on mark-ups by third parties
	Price-volume agreements
	Tailored strategies for expanding access in LMICs, such as assessments to determine the appropriate strategies needed to consider disease burden, public health value, income, ability to pay, and local healthcare structure

STEWARDSHIP STRATEGIES	*Detail*
Surveillance	Plan for adequate monitoring of resistance emergence and trends
	Share data through open data platforms
Responsible Promotion	Do not promote developed antibiotics
Availability of Companion Diagnostics	Plan for adequate availability of diagnostics, as applicable
	Plan for susceptibility testing of pathogens, as applicable

APPENDIX IV. DEFINITIONS

Access plan
[Working definition, used for analysis]
An access plan is a plan set up to ensure that public health needs are taken into consideration during R&D. These plans may be developed in-house or through collaborations and include commitments, strategies, concrete provisions and other agreed-upon measures (typically developed in partnership) to enforce accountability. Access plans facilitate availability, accessibility and affordability for patients in countries within the scope of the Benchmark (e.g., registration commitments, equitable pricing strategies, sufficient supply commitments, non-exclusivity in specified territories, waiving of patent rights, royalty-free provisions and applying for WHO prequalification).

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

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

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

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

Antibacterial medicine
[Working definition, used for analysis]
Antimicrobial medicine used to treat bacterial infections by directly targeting the bacteria that cause the infection or the disease process (as opposed to targeting the symptoms of the infection). See also Antibiotic medicine.

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

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

Antifungal medicine
[Working definition, used for analysis]
Antimicrobial medicine used to treat fungal infections by directly targeting the fungi that cause the infection or the disease process (as opposed to targeting the symptoms of the infection).

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

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

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

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

Appropriate use of antimicrobials
The cost-effective use of antimicrobials, which maximises clinical therapeutic effect while minimising both drug-related toxicity and the development of antimicrobial resistance [WHO Global Strategy for Containment of Antimicrobial Resistance, 2001].

Clinical-stage drug development
[Working definition, used for analysis]
Clinical-stage drug development comprises phases I through III of clinical development. Products approved (or awaiting approval) between 22 June 2019 (end of the period of analysis for the previous edition of the Benchmark) and 30 April 2021 are also categorised as late-stage.

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

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

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

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

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

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

Finished product
See Drug product.

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

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

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

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

Late-stage drug development
[Working definition, used for analysis]
In the context of the pharmaceutical R&D pipeline, medicine and vaccine candidates in Clinical phase II or Clinical phase III are considered to be in late-stage clinical development. Products approved (or awaiting approval) between 21 June 2019 (end of the period of analysis for the previous edition of the Benchmark) and 30 April 2021 are also categorised as late-stage by the Benchmark.

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

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

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

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

Period of analysis
[Working definition, used for analysis]
The 2020 AMR Benchmark report will assess company activities taking place during a period of analysis going from 21 June 2019 and 30 April 2021. For the R&D research area, projects need to be ongoing, approved or awaiting approval by the end of the period of analysis.

Pre-clinical-stage drug development
[Working definition, used for analysis]
Pre-clinical-stage drug development comprises the discovery and pre-clinical phases of drug development.

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

Priority pathogen
[Working definition, used for analysis]
Priority pathogens are pathogens for which new medicines and vaccines are highly needed. The Benchmark identified this set of priority pathogens based on the WHO priority pathogens list as of 25 February 2017 and the CDC's US Biggest Threats list as of December 2019.

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

Public-private partnership
[Working definition, used for analysis]
A public-private partnership (PPP) is a partnership between one or more public organisations and the private sector for providing a public asset or service, in which the private party bears significant risk and management responsibility, and remuneration is linked to performance. The Benchmark also considers a partnership between a non-profit organisation and the private sector to be a PPP.

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

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

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

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

APPENDIX V: REFERENCES

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