



# AMR INDUSTRY ALLIANCE 2020 PROGRESS REPORT

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# FOREWORD

The prospect of antimicrobial resistance (AMR) rolling back decades of modern medical advances is not part of some dystopian future. It is here and now, and happening across the globe.

When I first began investigating AMR in 2012, while England's Chief Medical Officer, even I was surprised at the size of the problem: People were already dying from routine surgery, simple wounds, and common infections, which too often could not be treated with available antibiotics to which bacteria had developed resistance.

By 2030, antimicrobial resistance could force up to 24 million people into extreme poverty, and by 2050 the estimated number of AMR-related deaths may reach up to 10 million.<sup>1</sup> Yet, many of those deaths are preventable and every effort must be made to stop the global rise of drug-resistant infections. As we enter a new decade, AMR is spreading faster than ever, and all stakeholders—including governments, the life sciences industry, academics, healthcare providers, philanthropic donors, and the public health community—must make combating this complex public health challenge one of their highest priorities. Business as usual is simply not an option. We must look for novel multisectoral, public-private partnerships and stronger engagement between organizations and different sectors of the life sciences industry.

The complexity of AMR requires coordinated action at the highest political level. As co-convenor of the UN Interagency Coordination Group on AMR (IACG), I oversaw the publication of the IACG report, *No Time to Wait: Securing the Future from Drug-Resistant Infections*.<sup>2</sup> Released in April 2019, the report calls on governments, international organization, industry, and other stakeholders to adopt a “One Health” approach and a bold set of commitments to ensure equitable and affordable access to existing and new quality-assured antimicrobials. Recognizing that challenges of AMR are complex and multifaceted, the report lists a number of recommendations, including some that cover R&D, access, and appropriate use. Those areas, along with manufacturing, are key to the AMR Industry Alliance.

## FIGHTING AMR: A KEY ROLE FOR INDUSTRY

IACG called for greater private-sector action and partnerships on AMR at global, regional, national, and local levels. We must all work together to address the challenge of drug-resistant infections. We must provide access to quality, life-saving medicines where needed as more people continue to die from a lack of antibiotics than from drug-resistant infections.<sup>3</sup> We must also ensure prudent use of existing drugs. Vaccines that help prevent infections and diagnostics that help accurately identify and appropriately guide treatment decisions are both important means to slow the rise of resistance.<sup>4</sup> In addition, we must increase our commitment to investing in the future. Public and private funders alike must promote innovation and development of new, quality-assured antimicrobials (particularly antibiotics), novel compounds, diagnostics, and vaccines.

The AMR Industry Alliance was established as a venue for advancing partnerships across the public and private sectors, promoting proactive industry actions and partnerships, and enabling coordination across subsectors. The Alliance also seeks to drive progress in curbing AMR within the life sciences industry through its bold set of shared goals and commitments to improve access to high-quality antimicrobial products, invest in R&D, support appropriate use, and minimize environmental risk.

I have been particularly heartened to see the work undertaken to tackle the manufacturing–environment pathway for antibiotics. As part of this work, the Alliance developed a common framework for responsible antibiotic manufacturing. This project draws on the extensive work done by its members since 2016, when 13 leading members signed the AMR Industry Roadmap committing them to reduce the environmental impact of antibiotics production and promote best practice across the wider industry. The framework and associated “safe discharge targets” (termed “predicted no-effect concentrations,” or PNECs), published 2 years ahead of schedule, help ensure the effective management of pharmaceutical waste to minimize conditions that may increase the development and spread of resistant bacteria.<sup>5</sup> I look to the industry to embrace these targets and ensure that compliance with them becomes the new “normal” in global manufacturing.

In this second biennial report, Alliance members provide detailed survey data that give a valuable snapshot of industry progress on AMR and show some encouraging areas of progress and innovation. Eighty-four percent of relevant companies are engaged in late-stage R&D, or have at least one AMR-relevant product/platform in clinical development. Eighty percent of members with commercial products declare having access strategies in place. The progress reported in manufacturing is encouraging, with good uptake of the Alliance framework, especially by members with longer tenure. Nearly half (44%) of all Alliance manufacturing member-owned sites report meeting the framework requirements. Adherence to the new and exacting PNECs projected over time appears strong, with 56% of products manufactured at owned sites anticipated to meet these targets within 3 years, according to industry responses.

At the same time, many challenges lie ahead for the life sciences industry. The survey has revealed the investment of approximately USD1.6B into development of AMR-relevant products to tackle AMR in 2018.<sup>1</sup> Since the previous Progress Report was published in 2018, there have been exits of large research-based biopharmaceutical companies (e.g., Novartis, Sanofi, and AstraZeneca) and biotechnology companies (e.g., Achaogen’s and Melinta’s bankruptcies). Current investments are not enough to drive a sustainable and robust R&D ecosystem for antibiotics, and investments may further decrease in the coming years if market conditions remain unchanged. Alliance members reported that this trend is likely to continue. Close collaborations among governments, the industry, investors, and other funding sources are required to improve antibiotic reimbursement systems and implement much-needed new incentives. Significant challenges across the R&D value chain<sup>6</sup> remain including barriers to drug discovery, regulatory hurdles, and low returns on investment, and we have not yet seen fundamental policy or regulatory changes to the way antibiotics are reimbursed or valued.

The battle against the growing challenge of AMR may well be won or lost in the next decade. Hence, finding ways to accelerate R&D investment, expand access to quality-assured antimicrobials and vaccines, and promote novel diagnostic tools and technologies as a means of cutting unnecessary use is of utmost importance. On these fronts, governments, industry, and other stakeholders must work together, pulling out all the stops to put in place more effective regulations, improve market mechanisms and incentive systems, leverage existing stewardship and prevention strategies, and further strengthen public-private partnerships. I look to the AMR Industry Alliance to play its part at the forefront of these efforts.

*Professor Dame Sally Davies, U.K. Special Envoy on Antimicrobial Resistance and co-convenor of the UN Interagency Coordination Group (IACG) on AMR*

<sup>1</sup> This figure is a conservative estimate based on data received from 56 companies (excluding generics). Some companies provided an investment range rather than a specific figure and one company was unable to disclose its total R&D investment breakdown (please refer to the Methodology Note for details of calculation). Please note that differences in methodology and participating companies make direct comparison of 2016 versus 2018 challenging. Data from 2016 were from 22 companies.

# EXECUTIVE SUMMARY

Every year at least 700,000 people die from drug-resistant infections, or antimicrobial resistance (AMR).<sup>7</sup> If AMR remains unchecked, the annual death toll could climb to 10 million by 2050<sup>8</sup> and the economic impacts could be on par with the 2008 financial crisis.<sup>9</sup>

The rapid development and spread of AMR is a global public health crisis, undermining the many advances in medical treatment that are underpinned by the availability of safe and effective antimicrobials. Without effective antimicrobials, preventing and treating infectious diseases will become more challenging, and common medical treatments and simple surgeries such as cancer chemotherapy and caesarean sections will carry significantly higher risks for patients.<sup>10</sup> AMR also poses challenges for the treatment of lung infections for people with cystic fibrosis,<sup>11</sup> and limits treatment options for those with kidney disease.<sup>12</sup>

AMR is a global problem. Resistant bacteria, fungi, and other pathogens know no borders. The complex social, scientific, and economic issues driving AMR cannot be resolved without strong collaboration between the private and public sectors. Protecting patients and counteracting a public health crisis, which can potentially undermine entire health systems, requires a coordinated global response by all stakeholders, including governments, civil society, academia, international health agencies, health care providers, and the life sciences industry.

The AMR Industry Alliance (“the Alliance”) was established in 2017 to report on and drive progress on AMR by the life sciences industry. Representing a diverse coalition of biotechnology, diagnostics, generics, and large research-based biopharmaceutical companies and associations, Alliance members commit to action in four key areas: research & science, access, appropriate use, and manufacturing.

# ALLIANCE COMMITMENTS



## RESEARCH & SCIENCE

- Invest in research and development for innovative antibiotics and antibiotic dosage forms, vaccines, new technologies, and diagnostics.
- Continue to advocate for policies that support sustainable investment in AMR-relevant innovation.
- Partner with policymakers, payers, and other relevant stakeholders on new reimbursement, valuation, and commercial models that support appropriate patient access and sustainable supply of antibiotics and AMR-relevant vaccines and new technologies and diagnostics.
- Support collaboration and sharing of relevant non-proprietary data with different stakeholders (e.g., academia, consortia, small or medium-sized enterprise (SMEs), public researchers, and industry) to help address key scientific and public health challenges.



## ACCESS

- Address barriers to patient access to the most appropriate treatment, vaccine, or diagnostic.
- Work in collaboration with policymakers to create an economic and regulatory environment that enables the sustainable supply of quality-assured antibiotics.
- Work to reduce the prevalence of substandard and falsified AMR-relevant products



## APPROPRIATE USE

- Contribute to slowing the emergence of resistance by preventing infections by promoting vaccination and reduction of inappropriate use of antibiotics through expanded use of diagnostics.
- Support appropriate use of antibiotics by working closely with other partners on awareness campaigns, continued education for healthcare professionals, and generation of evidence to support appropriate use and stewardship.
- Collect and share surveillance data with public health bodies and healthcare professionals to improve understanding of resistance trends, monitor the effectiveness of antibiotics, inform appropriate antibiotic and vaccine use, and develop adapted infection control strategies.
- Ensure that any promotional activities for antibiotics are aligned with the goal of advancing stewardship.



## MANUFACTURING AND THE ENVIRONMENT

- Review Alliance members' own manufacturing and supply chains to assess good practice in controlling releases of antibiotics into the environment.
- Establish a common framework for managing antibiotic discharge, and start to apply it across their own manufacturing and supply chains by 2018.
- Work with stakeholders to develop a practical mechanism to transparently show that Alliance member supply chains meet the framework's standards.
- Work with independent technical experts to establish science-driven, risk-based targets for discharge concentrations of antibiotics and develop good practice methods to reduce environmental impacts of manufacturing discharges by 2020.

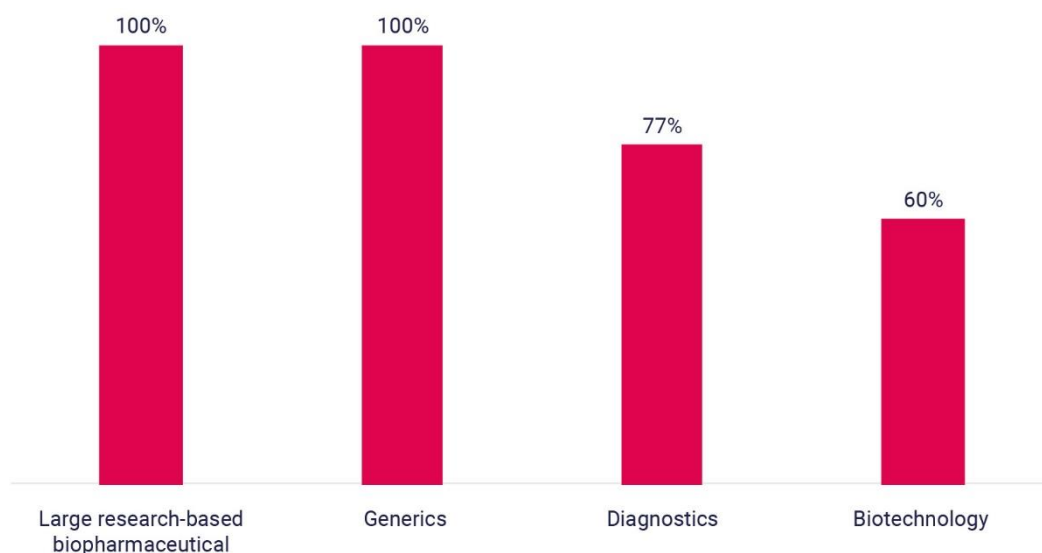
## ABOUT THE REPORT

Similar to the Alliance's first biennial report, the second report is based on a comprehensive member survey that tracks progress in fulfilling commitments made by Alliance members. The survey forms the basis of Alliance progress reports. The first report was published in January 2018 based on results of a survey conducted in 2017 in which 37 out of 101 eligible members participated. The response rate nearly doubled in 2019, with 65 out of 91 eligible members responding to the Alliance survey, resulting in a response rate of 71.4%. The purpose of the survey conducted in 2019 among all member companies of the Alliance representing the four life sciences subsectors—large research-based biopharmaceutical, generics, diagnostics, and biotechnology companies—was to collect information on the activities of Alliance members and offer a unique insight into the status of actions taken by those leading organizations in the life science industry who elected to join the Alliance and play their part in addressing AMR. By highlighting best practice, the Alliance seeks to drive progress on AMR across the life sciences industry.

Taken together, the Alliance likely represents approximately one third of the global antibiotic supply<sup>ii</sup> and nearly half of AMR-relevant products in clinical development. With a higher survey response rate, the report provides a detailed snapshot of member companies' collective efforts, highlighting best practice examples from the industry and identifying opportunities for companies and other stakeholders to drive further progress in the fight against AMR.

The report contributes to the global response to the AMR challenge by documenting Alliance members' activities in the areas of research & science, access, appropriate use, and manufacturing. It not only offers consolidated data on member companies' AMR-related actions and partnerships, but it also gives an account of a variety of antimicrobial products and diagnostic tools that are already available on the market or in development. The report includes a number of case studies from all four sectors of the life sciences industry. The case studies present efforts by individual member companies and demonstrate their strong commitment to investing in AMR-related research & science; improving access to and optimizing use of antimicrobials, vaccines, and diagnostics tools; and promoting the responsible manufacture of antibiotics.

<sup>ii</sup> Calculation based on 2018 sales data from IMS Padds. The data are based on sales in 67 countries, excluding India; they cover 300 molecules and concern antibiotics for human use only.



RESPONSE RATES TO THE AMR INDUSTRY ALLIANCE MEMBER SURVEY BY SECTOR (TOTAL: 13 LARGE RESEARCH-BASED BIOPHARMACEUTICAL, 7 GENERICS, 10 DIAGNOSTIC AND 35 BIOTECHNOLOGY COMPANIES)

The report provides a unique snapshot of the life sciences industry’s collective efforts and leadership in delivering on their commitments to tackle the rise of antimicrobial resistance.

The Research & Science chapter shows that the level of R&D investment in clinical development is likely insufficient to meet global health needs. This contrasts with a more vibrant and robust biotechnology preclinical pipeline and new rapid infection detection tests that are being developed by diagnostics companies. This mismatch means that many of these early-stage compounds may never reach patients unless new mechanisms and incentives are put in place to improve current market conditions and support the development and commercialization of novel solutions to tackle AMR. Of the companies surveyed for the Alliance report, 74% are likely to increase investments in AMR if the commercial environment improves.

The Access chapter highlights how Alliance companies are acting on commitments to improve patient access to appropriate, high-quality antibiotics as well as vaccines and diagnostics that can help prevent, detect, and treat drug-resistant infections.

Results in the Appropriate Use chapter showcase how Alliance members are supporting stewardship. All companies reported that they are investing in a wide range of measures to promote appropriate use of antibiotics in order to slow the emergence of resistance, prolong the effectiveness of antimicrobials, and improve health outcomes for patients.

The Manufacturing Environmental chapter reports that Alliance members, which own a total of 208 antibiotic manufacturing sites, are two years ahead of schedule in establishing an industry standard for reducing the potential environmental risks from antibiotic production, including emissions that may contribute to the emergence of resistant bacteria. The Alliance has set out a common framework for responsible antibiotic manufacturing to reduce the environmental impact of production. So far, the findings show that more than 80% of participating companies have assessed all their antibiotic manufacturing sites against this new industry standard and 82% meet or partially meet the framework’s requirements. Manufacturing Members also conveyed the framework requirements to just more than half the 900 plus suppliers they use.

Looking to the future, the report makes recommendations on how Alliance members and the broader life sciences industry can contribute further to the global response to AMR. This includes accelerating the sharing of data to promote innovation and making surveillance data publicly available, including data on infection rates, AMR patterns, and antibiotic use. Partnerships already feature strongly in many



areas of Alliance company activities. The report proposes areas where new or deeper partnerships with governments, patients, and providers are required, such as improving market conditions necessary for sustainable development and commercialization of novel solutions to AMR, and strengthening local healthcare and laboratory capabilities to support effective diagnosis and treatment of drug-resistant infections.

Below is the overview of key findings in each of the Alliance's four areas of work.

## RESEARCH & SCIENCE

### RESEARCH & SCIENCE HIGHLIGHTS<sup>iii</sup>

**Industry remains the dominant funder of AMR-relevant R&D:** Overall, in 2018 Alliance members invested more than US\$1.6B into the development of AMR-relevant products to combat AMR. These include antibiotics, antifungals, and novel technologies; vaccines; and diagnostic platforms and assays. Alliance member companies are developing ~50% of the Pew Charitable Trusts<sup>iv</sup> lists of ‘Antibiotics Currently in Global Clinical Development’<sup>13</sup> and ‘Nontraditional Products for Bacterial Infections in Clinical Development’.<sup>14</sup>

**Investment levels are threatened:** The overall economic environment remains challenging for novel antibiotics, and the investment figure reflects several exits both by large research-based biopharmaceutical companies and biotechnology companies since the previous report. Despite important investment from diagnostics companies, the overall Alliance investment figure is lower than that reported in the previous report. Alliance members reported that this decline in AMR-relevant investment is likely to continue unless governments take action to improve antibiotic reimbursement and implement new incentives.

**Alliance companies are engaged in multi-stakeholder efforts to find solutions:** Ninety percent of relevant companies engage in national and international partnerships to combat AMR. This includes engaging in public–private partnerships such as CARB-X, the Human Vaccine Project, and Innovative Medicines Initiative’s COMBACTE partnership, as well as working directly with non-governmental organizations, academia, government departments, international agencies such as the World Health Organization, and hospital and medical laboratories, to advance solutions on AMR.

### ADVANCING PRODUCTS THAT COMBAT AMR

Alliance member R&D investments are focused on the microorganisms that pose the greatest threats to human health, including those listed on the World Health Organization (WHO) Priority Pathogen List<sup>15</sup> and the “biggest threats” identified by the U.S. Centers for Disease Control and Prevention.<sup>16</sup> In response to these globally agreed priority areas, Alliance members continue to build the R&D pipeline to combat AMR, which includes antibiotics, antifungals, vaccines, novel approaches or technologies, diagnostic platforms and assays, and other AMR-relevant products. There are encouraging compounds in Alliance member company pipelines, particularly from biotechnology companies, and many new rapid infection detection tests are being developed by diagnostics companies. Alliance members are developing ~50% of the Pew Charitable Trusts’ lists of ‘Antibiotics Currently in Global Clinical Development’<sup>17</sup> and ‘Nontraditional Products for Bacterial Infections in Clinical Development’.<sup>18</sup>

Overall, in 2018 a total of 56 Alliance members invested more than US\$1.6B into the development of AMR-relevant products to tackle AMR, including 24 antibiotics and antifungals, 11 vaccines, 16 diagnostic platforms or assays, 10 non-traditional approaches, and one other AMR-relevant product. This is a subset of the overall Alliance and private-sector investment in AMR-relevant R&D. Since the

<sup>iii</sup> Companies from the large research-based biopharmaceutical, biotechnology, and diagnostics sectors were asked to respond to some or all of the survey in relation to Research & Science.

<sup>iv</sup> PEW is an independent, non-partisan, non-profit organization dedicated to serving the public across a number of focus areas. Within its work in health, PEW has developed the Antibiotic Resistance Project, which addresses key AMR issues.

public sector invests approximately US\$500M per year in AMR-relevant R&D,<sup>19</sup> this report shows that the life sciences industry remains by far the dominant funder of AMR-relevant R&D.

However, these investment levels are threatened. The overall economic environment remains challenging for novel antimicrobials and the investment figure reflects several exits of large research-based biopharmaceutical companies (e.g., Novartis, Sanofi, and AstraZeneca) and biotechnology companies (e.g. Achaogen's bankruptcy), which occurred since the previous progress report was published in January 2018. Despite important increases in investment by diagnostics companies, the overall investment figure is likely not sufficient to deliver the tools needed to address AMR. And investment levels may further decrease in the coming years if governments do not take urgent action to improve antibiotic reimbursement systems and implement new incentives for development

These potential changes to investment levels were flagged in the previous Alliance report, where 30% of Alliance companies active in antimicrobial R&D said they would likely decrease investment in this area if no new incentives were established and commercial models remained the same.<sup>20</sup> Since that report, no country has made fundamental changes to the way that antimicrobials are valued and reimbursed, or implemented any new pull incentive.<sup>21</sup> While some novel reimbursement approaches have been proposed, notably in Sweden, the U.K. and U.S., they have not yet been implemented. Until a package of incentives, including reimbursement reform and novel pull incentives to address the well-documented economic challenges in the antibiotic market, are introduced, private investment into antibiotic development is likely to continue to decline.

Despite the lack of progress with pull incentives, according to the survey results 74% of companies are likely to increase investments in AMR-relevant R&D if the commercial environment improves. To unlock greater investment and successfully bring more products in the pipeline all the way to patients who need them, Alliance members continue to advocate and partner with governments in the development of new reimbursement models and pull incentives that would strengthen the commercial viability of antimicrobial R&D.

## ADVANCING DIAGNOSTICS R&D

Advancing the diagnostics pipeline is a crucial element of industry solutions and responses to AMR, helping to improve patient health in countries all around the world. Alliance diagnostics members are actively pushing this agenda, significantly increasing the resources they dedicated to this urgent issue over the past 2 years. Across the Alliance, 15 diagnostic platforms or assays are in the clinical pipeline. Seventy percent of Alliance diagnostics members are active in clinical and early stage R&D, developing reagents, hardware, software, and middleware. These solutions provide significant economic and medical value, giving healthcare providers easy-to-use systems that provide fast, accurate information and access to data analytics that can support clinical decision making and follow-up of the epidemiology.

# ACCESS

## ACCESS HIGHLIGHTS<sup>v</sup>

An estimated 5.7 million people a year die from treatable bacterial infections: The majority of these deaths occur in low- and middle-income countries (LMICs), where access to appropriate antimicrobials remains a significant health challenge.<sup>22</sup> Alliance companies are acting on commitments to improve patient access to appropriate, high-quality treatments, vaccines, and diagnostics, while at the same time upholding appropriate use principles.

81% of respondents reported having developed **comprehensive strategies to improve access**

63% of respondents partner with governments, non-governmental organizations (NGOs), industry trade groups, local healthcare institutions, and others to **expand patient access to their AMR-relevant products**

47% of responding companies reported experiencing product **supply chain disruptions**, despite ongoing efforts to build supply chain resilience

## EXPANDING ACCESS

AMR is a growing global threat. The unmet need for AMR is significant but enhancing access to antimicrobials in low- and middle-income countries remains challenging. Lower income countries with high burdens of infectious diseases and weak health systems often struggle to provide even basic access to generic antibiotics. There are additional challenges to enhancing appropriate access to novel antimicrobials designed to overcome emerging drug resistance.<sup>23</sup> Enhanced access to antimicrobials (aligned with antimicrobial stewardship) can address this unmet medical need and slow the spread of AMR.

While there is global attention to the importance of expanding access to antimicrobials, there is no consensus yet on how to expand appropriate access to antibiotics in LMICs with weak health systems. More people die globally from lack of access to antibiotics than AMR,<sup>24</sup> but how can we improve access to antimicrobials for those in need while curbing inappropriate and excessive use? The Alliance supported a study by the Center for Disease Dynamics, Economics & Policy (CDEPP) to unpick these complex challenges and identify ways to progress.<sup>25</sup> Efforts are needed by many stakeholders to strengthen health systems and expand universal health coverage.

Eighty percent of Alliance member access strategies cover low-income countries. All large research-based biopharmaceutical and generics companies with commercialized products on the market have formalized access strategies in place, compared with 78% of diagnostics companies. A total of 43% of biotechnology companies with commercialized products on the market reported having access strategies in place, which is not surprising given the focus and nature of their businesses.

Strategies include expanding product registration, tiered pricing, compassionate use programs, and product donations. Specifically, members' access plans cover: registration (84%), affordability (72%), partnerships (60%), and efforts to boost health systems' capacity and appropriate use (60%). Just 32% of reporting companies publish their access strategies, a key area for improvement.

<sup>v</sup> Companies from all sectors were asked to respond to some or all of the survey in relation to Access.

## ENSURING CONTINUOUS SUPPLY OF ANTIMICROBIALS

Forty-seven percent of respondents reported disruptions in their supply chain of AMR-relevant products during the reporting period, down from nearly two thirds in the previous report. All generics and large research-based biopharmaceutical companies reported working closely with vendors and relevant authorities to address supply chain challenges. Activities reported to be underway to address supply chain challenges included diversifying supplier bases, continuing to implement robust quality systems and controls, building supplier capacity, and strengthening buffer stocks of vaccines and antimicrobials.

The safe supply of antimicrobials also requires curbing the black market in substandard and falsified medical products that endanger patients and contribute to spreading drug-resistant infections. The majority (88%) of large research-based biopharmaceuticals and all generics companies reported taking pre-emptive measures, including tamper-proof packaging, product serialization, and the establishment of counterfeit management teams. Members also work with the healthcare community, regulatory authorities, and law enforcement agencies to raise awareness of counterfeiting of diagnostic and biopharmaceutical products (i.e., vaccines and antimicrobial and antifungal drugs) and to work in partnership to monitor distribution channels.

# APPROPRIATE USE

## APPROPRIATE USE HIGHLIGHTS<sup>vi</sup>

The inappropriate and excessive use of antimicrobials contributes to the spread of AMR. In response, Alliance members reported engaging in a wide range of activities to promote antimicrobial stewardship to slow the emergence of resistance, prolong the effectiveness of antimicrobials, and improve patient outcomes.

**80%** of companies report **revising promotional activities** to align with antimicrobial stewardship

**76%** of companies have formal **appropriate use and stewardship plans**

**70%** of companies **collect AMR surveillance data**

**50%** of companies measure the **outcomes and impact** of their stewardship plans

## PROMOTING SAFE USE OF ANTIMICROBIALS

Stewardship plans adopted by large research-based biopharmaceutical, generics, diagnostics, and biotechnology companies cover a wide range of activities targeting patients, physicians, and the public. The most common activities to promote appropriate use of antimicrobials by Alliance members focus on: education (80%), surveillance (73%), early and appropriate diagnosis (70%), generating evidence for appropriate use (60%), and promotion of appropriate use separately from promotion of products (50%). Reducing uncontrolled use (30%), supporting infection prevention and control (IPC) as well as water, sanitation, and hygiene (WASH) programs (30%) are activities that currently few Alliance members undertake. In the future more members could work alongside governments and public health agencies to support them in the roll-out of IPC and WASH programs.

Stewardship aims to ensure that each patient receives the right drug for the right pathogen at the right time; prompt and accurate diagnosis of infection is an important component of these efforts. This means both knowing what pathogen is causing the infection (identification), how best to treat it (susceptibility), and how to do so in the fastest possible time. Diagnostic tools are crucial to ensuring that the use of antimicrobials can achieve the best patient and public health outcomes, including reducing the incidence of sepsis and reducing the inappropriate prescription of antimicrobials.

Increasingly, companies' commercial promotional activity also takes account AMR and the need for strong antimicrobial stewardship. Eighty percent of companies reported promoting products in ways that align with the goal of advancing stewardship. Examples of programs designed to promote appropriate use of antimicrobials include: placing messages on drug packaging to encourage patients to complete antimicrobial courses; distributing relevant materials in hospitals, schools, and at conferences; and developing non-branded materials that explain risks related to AMR. In addition, some companies work with international health organizations and NGOs to raise global public awareness of AMR and educate about the importance of using antimicrobials as prescribed.

While members and governments recognize the important role that vaccines can play in combatting AMR, this element continues to be under-prioritized for action. Progress towards achieving universal

<sup>vi</sup> Companies from all sectors were asked to respond to some or all of the survey in relation to Appropriate Use.

vaccination for high-burden diseases that contribute to AMR has been limited – for both bacterial and non-bacterial pathogens. Four companies that develop vaccines highlighted the role of prevention through vaccination programs in their appropriate use strategies. Members are continuing to invest in developing effective new AMR-relevant vaccines – including for several pathogens for which no vaccine is currently available, as a key step in the battle to contain drug resistance.

## DETECTING RESISTANCE TRENDS

Surveillance of drug resistance is critical to the fight against AMR, supporting the appropriate use of antimicrobials and informing new products and platforms. Of relevant companies, 70% reported collecting such data on their products, and many are sharing these data with public health agencies, researchers, and prescribers.

Surveillance activities performed by generics, large research-based biopharmaceutical companies, and diagnostic companies range from local, hospital-level surveillance through monitoring of national and global trends. Diagnostic companies of the Alliance develop and deploy tools and technologies for early identification of resistant infections, which generate evidence that supports diagnostics' clinical utility and promotes optimal use of antimicrobials.

# MANUFACTURING

## MANUFACTURING & ENVIRONMENTAL HIGHLIGHTS<sup>vii</sup>

Responsible manufacturing reduces potential environmental risks from antibiotic production, including emissions that may contribute to the emergence of resistant bacteria.

2 years ahead of schedule, the Alliance published predicted no-effect concentrations (PNECs), which can be used to establish **discharge targets** for antibiotic manufacturing sites

83% of manufacturing company members have assessed all of their own antibiotics manufacturing sites against the Alliance's new manufacturing **framework**

82% of owned sites **meet the framework's requirements** wholly or in part

56% of products made at member-owned sites are expected to be made in accordance with discharge targets **within the next 3 years** and **88% within the next 7 years**

24% of products made at supplier sites are expected to be made in accordance with discharge targets **within the next 3 years**

Recognizing the need to take action to reduce potential environmental risks from antibiotic production, including emissions that may contribute to the emergence of resistant bacteria, the Alliance's Manufacturing Working Group is proactively leading on this issue.

Members not only established an industry standard for the environmental management of antibiotic manufacturing, but they did so two years ahead of schedule by developing unified, science-driven, risk-based targets, known as predicted no-effect concentrations (PNECs), to be used in the environmental assessments for factory discharges of antibiotics. Members have published an associated peer-reviewed paper, including the list of PNECs, for approximately 120 antibiotics.<sup>26</sup> The Alliance expects that these PNECs will be used by all companies that manufacture antibiotics when establishing discharge targets for antibiotics in waste-water emissions from manufacturing plants. Manufacturing members of the Alliance are committed to meeting these low discharge targets. To give some context PNECs are typically established at the microgram/liter level (parts per billion). For a factory supplying one million antibiotic tablets per year, with the concentration of antibiotic in the collected waste water equalling the PNEC of 1 microgram per liter, collecting all the waste water produced during the year would not contain enough antibiotic to extract to make one tablet.<sup>viii</sup>

The Alliance is increasingly recognized as an influential leader in this important area of AMR and, encouragingly, other organizations are adopting its framework. For example, Medicines for Europe, a trade association and an Alliance member, has committed to ensure that adherence to the Alliance's manufacturing framework and discharge targets is a condition of membership of all its association's generics company members (whether they are a member of the Alliance or not).

<sup>vii</sup> Companies from the large research-based biopharmaceutical and generics sectors, who have manufacturing operations, were asked to respond to the survey in relation to Manufacturing.

<sup>viii</sup> Calculation basis: 100 tonne/yr API factory (equivalent to 200 million tablets) producing 100M3/day effluent at PNEC 1ug/l Yields 0.35 tablets in effluent per 1 million tablets produced.



There are ongoing efforts to bring in new members to the Alliance and expand the adoption of recently established manufacturing standards. The Alliance has also supported a pilot project in India to encourage six local companies to adopt the framework and PNEC measures. Including non-Alliance companies in this work helps spread the awareness and uptake of these best practice standards.

## MAKING ANTIBIOTICS RESPONSIBLY

The Common Antibiotic Manufacturing Framework<sup>27</sup> (“the framework”), which was published in January 2018, provides companies with minimum site requirements to meet environmental standards and with an appropriate methodology to conduct risk assessments.

Alliance members reported a total of 208 antibiotic manufacturing-owned sites. As of June 2019, 92% of these sites have been assessed by members against the requirements of the framework, with 82% of assessed sites partially or fully meeting the requirements, and 18% not yet meeting them. Similarly, 32% of members’ supplier sites have been assessed by members against the requirements of the framework, with 33% of these supplier sites meeting the requirements, 37% partially meeting them, and 30% not meeting them. All Alliance manufacturing members reported making 624 antibiotic products at owned facilities, 88% of which are expected to be manufactured meeting the PNEC targets within the 7-year timeframe.

Achieving PNEC adherence across supply chains takes time, as technically complex assessments and/or analytical measurements need to be completed in many cases across large supply chains. Where action may be needed to reduce emissions concentrations, such action may be procedural and relatively straightforward, but could be more complex and time consuming in cases that involve using an alternative supplier and securing the necessary drug regulatory approvals or capital investments, for example, at supplier sites over which member companies may have limited influence.

Given that the PNECs are new, not all members were able to assess performance of their own and their suppliers’ sites against the PNECs at the time of the survey. The goal is to have all members achieve PNEC adherence across their full supply chains within the next 3 to 7 years.

## NEXT STEPS

### RESEARCH & SCIENCE

- In partnership with patients and providers, continue to advocate for governments to implement the package of policy reforms that would create market conditions that support sustainable investment into and commercialization of AMR-relevant R&D as well as diagnostics, vaccines, improvements to existing therapies, complementary technologies, and novel solutions. This could include piloting new payment mechanisms and pull incentives.
- Collaborate with international organizations, NGOs, research institutions, funders, and donors to accelerate development of new treatments for drug-resistant infections, particularly those prevalent in LMICs.
- Work with health systems and the broader pharmaceutical industry to ensure that vaccines, diagnostics, novel antibiotics, and other AMR-relevant products are appropriately valued.
- Strengthen partnerships on R&D within and outside the Alliance by making information available on companies' various platforms publicly available to deepen the current understanding of resistance trends and resistance mechanisms and to promote innovation.
- Increase Alliance membership to cover a greater proportion of companies active in clinical R&D of AMR-relevant products.

### ACCESS

- Encourage Alliance members to incorporate access to antimicrobials into R&D plans and increase transparency by making these access plans public.
- Increase Alliance membership to cover a greater proportion of the global supply of antimicrobials, with a particular focus on generic companies.
- Collaborate with local health authorities and policy makers to explore and support initiatives that will strengthen the long-term sustainability of the antimicrobial product market, improve supply chain security and continuity, and reduce drug shortages for AMR-relevant products. Initiatives could include improvements to contracting practices and incentives for investing in responsible manufacturing and continuity of supply.
- Work in partnership with local governments and funding agencies to strengthen local healthcare and laboratory capabilities to support effective diagnosis and treatment of drug resistant infections.
- Promote timely access to less expensive generic antibiotics through voluntary licensing agreements, particularly in lower- and middle-income countries, where there are systems in place to ensure appropriate use. Partner with funders and public health agencies to strengthen health system capacity.
- Partner with governments and NGOs to strengthen and expand programs that clear regulatory burdens that may otherwise reduce broad global registrations of critical antimicrobials. Pilot new payment and reimbursement mechanisms that enable appropriate patient access to antimicrobials.

## APPROPRIATE USE

- Continue to engage stakeholders, including the general public, to raise awareness on AMR and appropriate use. This includes scaling up educational activities and promoting the use of smarter prescription tools that are adapted to local contexts. It also includes providing timely and accurate microbiological data.
- Increase sharing of AMR surveillance data by Alliance members and support initiatives to increase public reporting of infection rates, antimicrobial resistance patterns, and antibiotic use.
- Encourage Alliance members to share best practice and align product-related promotional activities with the goal of supporting appropriate use.
- Strengthen external stakeholders' awareness of the critical role that diagnostics and vaccines have in supporting antimicrobial stewardship.
- Encourage Alliance members to engage in more activities for appropriate use, including increased work on IPC and WASH. This includes sharing best practices, for example, through independent educational webinars and research grants.

## MANUFACTURING & ENVIRONMENT

- Accelerate implementation of the common manufacturing framework across members' supply chains, and encourage Alliance members to take appropriate action to address facilities that do not meet expectations.
- Periodically update PNECs as new data becomes available and in light of relevant scientific advances, and consider developing further technical guidance to support broader risk assessments (e.g., for solid wastes and other antimicrobials).
- Review anticipated PNEC adherence to better understand members' projections and, where appropriate, explore mechanisms to encourage faster progress.
- Determine the relative merits of self-assessment compared with independent third-party assessment against Alliance standards.
- Leverage the Alliance's expertise to engage and inform regulators as a means to support appropriate oversight of antimicrobial manufacturing.

# INTRODUCTION

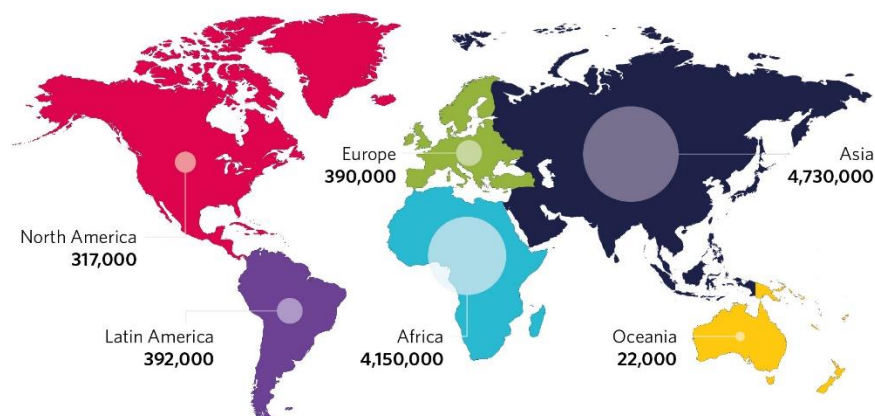
## THE GLOBAL AMR CHALLENGE

For 80 years, antimicrobials, and in particular antibiotics, have played a crucial role in modern medicine, treating infections and underpinning common medical procedures including surgery, childbirth and cancer treatments. The spread of antimicrobial resistance (AMR) is undermining the efficacy of these medicines and procedures and presents a growing threat to global public health and human development.

Antimicrobial resistance is a natural process. It occurs when a micro-organism harmful to humans (e.g. bacteria, viruses, fungi, and parasites) evolves to prevent an antimicrobial (e.g. an antibiotic, antifungal, antiviral, or antiparasitic) from working against it. However, this natural process has been accelerated by the inappropriate use of antimicrobials, in both humans and animals.

The consequences of AMR are serious and global. In many parts of the world, resistance to antimicrobials is making treatment for some common infections ineffective in more than half of patients.<sup>28</sup> Without effective antimicrobials, common medical treatments and simple surgeries such as , cancer chemotherapy, joint replacements, caesarean sections, and organ transplants are becoming increasingly high-risk for patients.<sup>29</sup> AMR also poses challenges for the treatment of lung infections for people with cystic fibrosis,<sup>30</sup> and limits treatment options for those with kidney disease.<sup>31</sup>

AMR affects people in countries with all levels of income, requiring urgent and coordinated global responses. Each year, at least 700,000 people die from drug-resistant infections,<sup>32</sup> and about half a million new cases of multi-drug-resistant tuberculosis are diagnosed.<sup>33</sup> An estimated 5.7 million people a year die from treatable bacterial infections, the majority in low- and middle-income countries.<sup>34</sup> But high-income are not immune. In the U.S., in 2017 around 3M antibiotic-resistant infection occurred, with almost 48,000 people dying as a result.<sup>35</sup> Experts believe the annual overall global death toll could soar to 10 million by 2050,<sup>36</sup> resulting in a sustained global economic impact similar to, and likely worse than, the 2008 financial crisis.<sup>37</sup>



**FIGURE 1:** PROJECTED DEATHS ATTRIBUTABLE TO AMR EVERY YEAR BY 2050 ((ADAPTED FROM GANGULY, N. ANTIMICROBIAL RESISTANCE IN DEVELOPING COUNTRIES.)<sup>38</sup>

The nature and scale of this challenge calls for collaboration across governments, the life sciences industry, healthcare providers, civil society, and patients to ensure effective and rapid action to contain AMR.

## INDUSTRY'S ROLE IN DRIVING SHARED SOLUTIONS

The G7,<sup>39</sup> G20,<sup>40</sup> World Health Organization,<sup>41</sup> many world leaders have recognized AMR as a global health emergency and have called for comprehensive actions as a response. The global life sciences industry has an important role to play in the multi-stakeholder effort to contain AMR, and the AMR Industry Alliance (Alliance) is one of the largest private-sector coalitions supporting collaborative and sustainable solutions. Established in May 2017, the Alliance represents more than 100 biotechnology, diagnostics, generics, and large research-based pharmaceutical companies and associations committed to combatting AMR.

Members across these industry subsectors have adopted shared goals and commitments and are taking global actions to address drug resistance. These efforts focus on four key commitment areas are summarized below:



## RESEARCH & SCIENCE

- Invest in research and development for innovative antibiotics and antibiotic dosage forms, vaccines, new technologies, and diagnostics.
- Continue to advocate for policies that support sustainable investment in AMR-relevant innovation.
- Partner with policymakers, payers, and other relevant stakeholders on new reimbursement, valuation, and commercial models that support appropriate patient access and sustainable supply of antibiotics and AMR-relevant vaccines and new technologies and diagnostics.
- Support collaboration and sharing of relevant non-proprietary data with different stakeholders (e.g., academia, consortia, small or medium-sized enterprise (SMEs), public researchers, and industry) to help address key scientific and public health challenges.



## ACCESS

- Address barriers to patient access to the most appropriate treatment, vaccine, or diagnostic.
- Work in collaboration with policymakers to create an economic and regulatory environment that enables the sustainable supply of quality-assured antibiotics.
- Work to reduce the prevalence of substandard and falsified AMR-relevant products



## APPROPRIATE USE

- Contribute to slowing the emergence of resistance by preventing infections by promoting vaccination and reduction of inappropriate use of antibiotics through expanded use of diagnostics.
- Support appropriate use of antibiotics by working closely with other partners on awareness campaigns, continued education for healthcare professionals, and generation of evidence to support appropriate use and stewardship.
- Collect and share surveillance data with public health bodies and healthcare professionals to improve understanding of resistance trends, monitor the effectiveness of antibiotics, inform appropriate antibiotic and vaccine use, and develop adapted infection control strategies.
- Ensure that any promotional activities for antibiotics are aligned with the goal of advancing stewardship.



## MANUFACTURING AND THE ENVIRONMENT

- Review Alliance members' own manufacturing and supply chains to assess good practice in controlling releases of antibiotics into the environment.
- Establish a common framework for managing antibiotic discharge, and start to apply it across their own manufacturing and supply chains by 2018.
- Work with stakeholders to develop a practical mechanism to transparently show that Alliance member supply chains meet the framework's standards.
- Work with independent technical experts to establish science-driven, risk-based targets for discharge concentrations of antibiotics and develop good practice methods to reduce environmental impacts of manufacturing discharges by 2020.

**FIGURE 2: KEY AMR INDUSTRY ALLIANCE COMMITMENTS**

This comprehensive agenda illustrates the breadth of industry’s efforts and actions aimed at combatting AMR. The timeline below shows key external and AMR Industry Alliance milestones to date, including the evolution of industry commitments from the 2016 Davos Declaration to this second progress report.

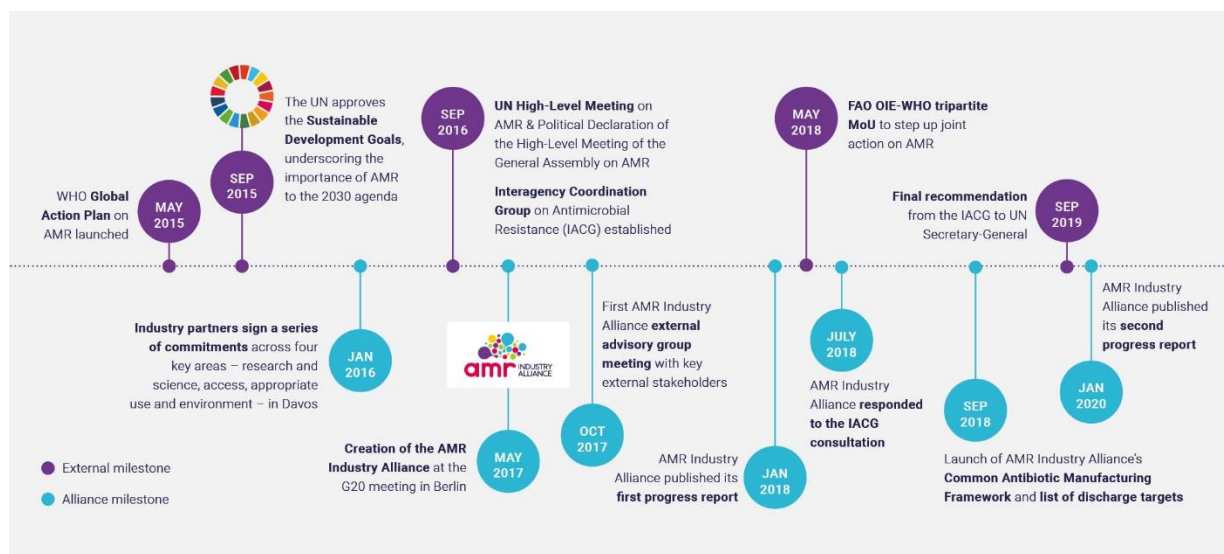


FIGURE 3: GLOBAL AND AMR INDUSTRY ALLIANCE MILESTONES<sup>42</sup>

## ABOUT THIS REPORT

The AMR Industry Alliance drives private sector advances on AMR and tracks progress against members’ public commitments. This second biennial progress report captures member activities since January 2018 and assesses the Alliance’s overall progress against its commitments. It highlights innovative, industry-led strategies and solutions, and case studies of frontline action against AMR, from across the Alliance’s broad membership. The findings also illustrate the challenges members face in tackling AMR. Based on this wealth of data, the report ends with recommendations for next steps to increase industry’s impact.

The report content presents data on a wide variety of AMR-relevant products. These include therapeutic agents or technologies that have the potential to treat or prevent infectious diseases and/or combat resistance, such as antimicrobials, vaccines, diagnostics, and novel approaches to address AMR.

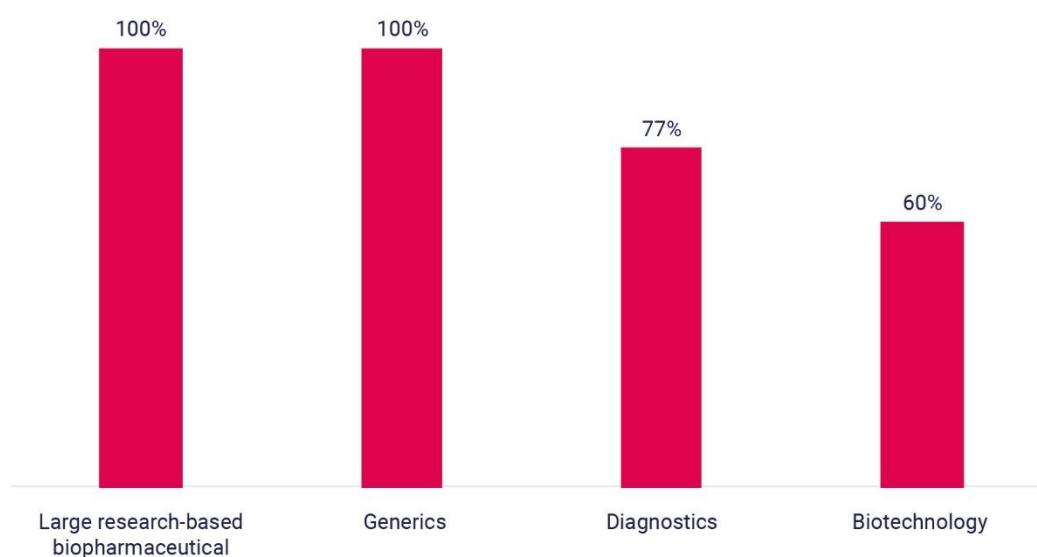
## ABOUT THE AUTHORS: SUSTAINABILITY

SustainAbility is a consultancy and think tank, enabling businesses to lead on the sustainability agenda. For the Alliance’s inaugural progress report, published in January 2018, SustainAbility helped translate the commitments made by Alliance members in the 2016 Davos Declaration and the subsequent Industry Roadmap to Combat Antimicrobial Resistance into metrics. SustainAbility surveyed Alliance members based on these metrics, analyzed the results, and authored the report with the Alliance Board and Secretariat.

SustainAbility was engaged on the same basis to support this second progress report.

## METHODOLOGY

All Alliance member companies were invited to submit data quantifying their efforts on AMR through a survey tool distributed to all Alliance member companies. This report is based on an analysis of survey responses from 71% of Alliance member companies (65 of 91). This participation rate represents an encouraging 75% increase from the 2018 report, when only 36% (36 of 101) of member companies participated, with the largest growth coming from the biotechnology-sector where participation more than doubled from 17 to 35. In addition, all 13 large research-based biopharmaceutical company members, and all 7 member generics companies took part, along with 10 diagnostics companies. While more progress could still be made, the Alliance has delivered on its commitment to work with all member companies to encourage participation and make the reporting process more accessible. See Appendix 1 for a list of all Alliance member companies and survey respondents.

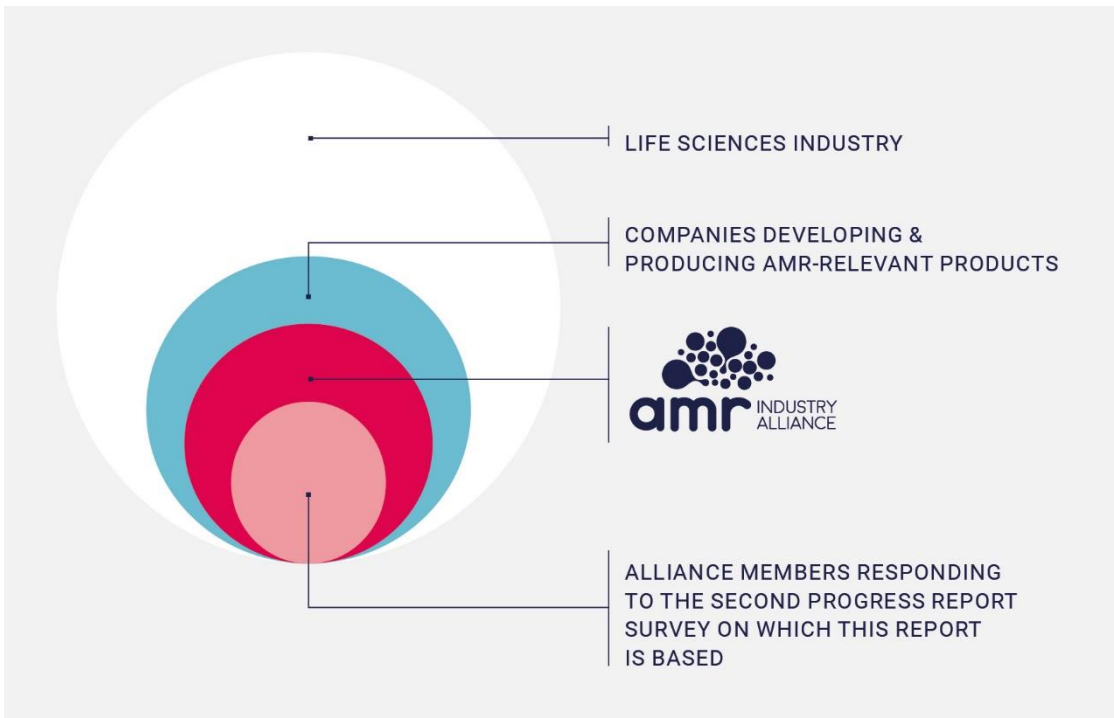


**FIGURE 4:** RESPONSE RATES TO THE AMR INDUSTRY ALLIANCE MEMBER SURVEY BY SECTOR (TOTAL: 13 LARGE RESEARCH-BASED BIOPHARMACEUTICAL, 7 GENERICS, 10 DIAGNOSTIC AND 35 BIOTECHNOLOGY COMPANIES)

The 65 Alliance members who participated in the survey represent nearly 20,000 employees, including around 3000 in antimicrobial development and the others spread across AMR-relevant roles such as medical functions, sales and marketing, regulatory, and government affairs. The Alliance represents a significant portion of the antimicrobial medicines market: based on 2018 data reported, we estimate that the Alliance represents approximately 31% of the antibiotics market: this includes almost all large research-based biopharmaceutical companies.<sup>ix</sup> This figure does not consider other, non-antibiotic AMR-relevant products, such as diagnostics or vaccines. Despite this broad participation, the report's findings are drawn from a subset of Alliance members and may therefore not represent the entire Alliance and the broader life sciences industry. All findings are derived from the data provided by responding companies. In reporting results for each sector, SustainAbility focused on the relevant reporting companies.

<sup>ix</sup> Calculation based on 2018 sales data from IMS Padds. Data are based on sales in 67 countries, excluding India; they cover 300 molecules and include antibiotics for human use only.





# RESEARCH & SCIENCE

## THE ALLIANCE'S RESEARCH & SCIENCE COMMITMENTS

- Invest in research and development for innovative antibiotics and antibiotic dosage forms, vaccines, new technologies, and diagnostics.
- Continue to advocate for policies that support sustainable investment in antimicrobial resistance- (AMR-) relevant innovation.
- Partner with policymakers, payers, and other relevant stakeholders on new reimbursement, valuation, and commercial models that support appropriate patient access and sustainable supply of antibiotics and AMR-relevant vaccines, new technologies, and diagnostics.
- Support collaboration and sharing of relevant non-proprietary data with different stakeholders (e.g., academia, consortia, small- and medium-sized enterprises, public researchers, and industry) to help address key scientific and public health challenges.

AMR occurs when a pathogen evolves to survive antimicrobial treatment. As drug resistance develops and spreads, healthcare providers have fewer options to treat resistant pathogens—leading to prolonged common infections and jeopardizing medical advances ranging from chemotherapy to organ transplantation to surgery.<sup>43</sup> For this reason, new tools to tackle emerging resistance will always be needed. However, relatively few are in development. Over the past two decades, the number of biotechnology and large research-based biopharmaceutical companies conducting AMR-relevant research and development (R&D) has significantly declined.<sup>44</sup> There are growing concerns that resistance is outpacing new therapies: since 1980, no new antibiotic drug class has been approved.<sup>45</sup>

Antibiotic discovery and development present specific scientific, regulatory, and economic challenges.<sup>46</sup> In recent years governments and other key stakeholders have taken some action to support antibiotic discovery and development, including through grants for early-stage research, partnerships for clinical development, and regulatory reform.<sup>47</sup> For its part, the life sciences industry continues to fund and undertake the discovery and development of AMR-relevant products. Indeed the U.S. FDA has approved nine novel antibiotics since the publication of the 2018 Report, although not all target AMR-relevant pathogens.<sup>48</sup> Whether or not current market conditions support sustainable commercialization remains to be seen.

This second progress report finds that the life sciences industry remains by far the dominant funder of AMR-relevant R&D. In 2018, 56 Alliance companies invested US\$1.6B in R&D dedicated to AMR-relevant products and platforms. Total government support for the same period was approximately US\$500M.<sup>49</sup> Due to changes in the methodology, direct

comparisons between investment levels reported in both progress reports are not possible. However, we believe overall private investment<sup>x</sup> is likely to have decreased.

The findings in this report likely reflect the challenges across the R&D value chain,<sup>50</sup> including barriers to drug discovery, regulatory hurdles, and, in particular, a lack of a sustainable return on investment. Despite the challenges, the life sciences industry continues to invest in R&D to meet public health needs and is pursuing a wide range of approaches to tackle AMR. This section provides an overview of survey findings on R&D, a discussion of progress in AMR-relevant product and platform development, and an analysis of key investment challenges and solutions supported by Alliance members.

**US\$1.6B** INVESTMENT BY 56 ALLIANCE MEMBERS IN AMR-RELEVANT R&D

**~50%** OF THE PEW CHARITABLE TRUSTS' LIST OF "ANTIBIOTICS CURRENTLY IN GLOBAL CLINICAL DEVELOPMENT" AND "NONTRADITIONAL PRODUCTS for BACTERIAL INFECTIONS in CLINICAL DEVELOPMENT" BEING DEVELOPED BY ALLIANCE MEMBERS

## STAKEHOLDER COMMENTARY

Most assessments of the current clinical pipeline of antibiotics find it to be fragile and inadequate for the unmet medical need. The preclinical pipeline is more encouraging because it has a high percentage of products that would represent new classes or new mechanisms of action if they are technically successful and obtain funding to progress to clinical testing, then regulatory approval.<sup>51</sup>

We also need to be mindful not to abuse the new drugs currently in development. To that end, investment in solutions that promote prevention, including vaccines, and appropriate use, including diagnostics, is needed at a level commensurate with the investments in revitalizing the antibiotics pipeline.

Improving the future clinical pipeline will require more generous funding for R&D to advance these preclinical products, including more substantial private investment, which has decreased in the past few years. Private capital appears to be waiting on the sidelines for changes in antibiotics reimbursement, as the current systems disincentivizes innovation.

In short, an economics problem is a root cause of our medical science problem. The Alliance should be applauded for its work to move the needle on antibiotic reimbursement and for its continued support for investment in R&D in challenging circumstances.

*Kevin Outterson, Founding Executive Director, CARB-X, Boston, MA, United States*

<sup>x</sup> A platform is the system(s) and tests (made up of instruments, reagents, and software) that can be used to diagnose infections.

## INDUSTRY R&D INVESTMENT: A MIXED PICTURE

In 2018, 56 Alliance members reported investing US\$1.6B into AMR-relevant R&D.<sup>xi</sup> These investments do not include funding as part of public–private partnerships, such as that of CARB-X, the European Innovative Medicines Initiative (IMI), and the U.K.’s Global Antimicrobial Resistance Innovation Fund (GAMRIF).

As discussed earlier, methodological changes (see boxed text) make it inappropriate to make direct comparisons between this report and the previous report, but R&D funding is likely to have declined between the 2016 and 2018 fiscal years. Only 15 companies reported their R&D investment in both time periods.<sup>xii</sup> On a like-for-like comparison for this set alone, the approximate investment figures dropped from US\$1.9B in 2016 to US\$1.2B in 2018.

Much of the overall reduction in Alliance investment is driven by changing investment from the large research-based biopharmaceutical sector, which still represents the majority of Alliance investment in AMR-relevant R&D. The diagnostics and biotechnology sectors reported increases in funding between the two reports, but this may be attributed to a larger pool of respondents and companies’ reevaluations of how they classify AMR-relevant R&D. Overall, 52% of relevant responding companies (excluding generics) reported increased levels of investment to boost R&D in AMR in the reporting period and 26% reported constant levels.

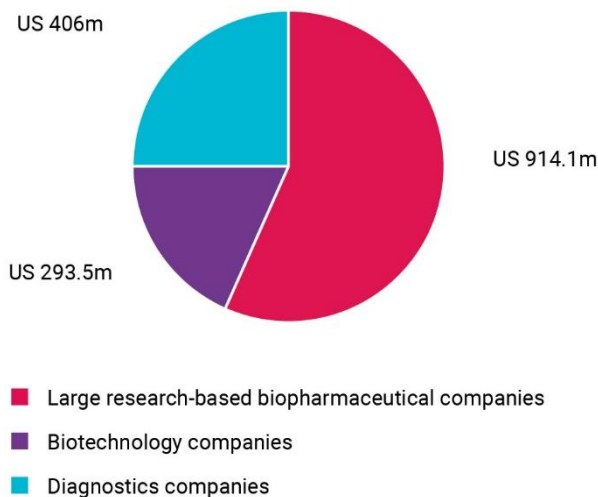
The overall investment figure is likely insufficient to deliver the tools needed to address AMR, and investment levels may further decrease in the coming years if governments do not take urgent action to improve antibiotic reimbursement systems and implement new incentives for development. These changes to investment levels were flagged in the previous Alliance report, where 31% of all respondents (and 50% of large research-based biopharmaceutical companies) warned that they would likely decrease investment if no policies addressing these economic challenges were implemented.<sup>52</sup> The reasons for the probable decline in R&D investment are multifaceted, and include:

- There has not been progress in addressing the economic drivers of declining private investment in antibiotic R&D, such as valuation, reimbursement, and incentivization.<sup>53</sup>
- Since the first progress report, three large research-based pharmaceutical companies have publicly exited antibiotic R&D.<sup>54</sup>
- Annual investment figures fluctuate significantly and are highly dependent on where individual products are in clinical development. Late-stage development (disproportionately funded by large research-based biopharmaceutical companies) is significantly more expensive than early-stage development. Therefore, the decline in funding could also be attributed fewer products being in late-stage development in 2018.
- In addition, while the number of companies submitting data has increased, not all companies who provided investment data for the first progress report have done so for this report.

<sup>xi</sup> This figure is a conservative estimate based on data received from 56 companies (excluding generics). Some companies provided an investment range rather than a specific figure and one company was unable to disclose its total R&D investment breakdown. Please note that differences in methodology and participating companies make direct comparison of 2016 and 2018 challenging.

<sup>xii</sup> These 15 companies consisted of 6 large research-based biopharmaceutical companies, 6 biotechnology companies, and 3 diagnostics companies.

These economic drivers of declining private investment in AMR-relevant R&D are clear and have been well documented by multiple policy and academic researchers.<sup>55</sup> Although there have been some positive signals—such as the U.K. National Health Service/NICE plan to pilot a subscription-style payment model<sup>56</sup> and U.S. Centers for Medicare & Medicaid Services reforms to reimbursement of novel antibiotics,<sup>57</sup> no country has yet made fundamental changes to the way antibiotics are reimbursed or valued. Furthermore, no progress has been made by any governments in the implementation of novel market-based pull incentives.<sup>58</sup> Alliance members reported that a downward trend in investment is likely to continue unless governments take action to improve reimbursement systems and implement new incentives for development.



**FIGURE 5: INVESTMENT IN AMR-RELEVANT R&D PER SECTOR, 2018 (USD) (TOTAL: 56)**

### ACHAOGEN AND MELINTA BANKRUPTCIES HIGHLIGHT AMR INVESTMENT CHALLENGES

In recent years, the antibiotic market challenges have led some research-based biopharmaceutical companies to exit the space. Those companies that remain, including many biotechnology companies, struggle to remain commercially sustainable. Two prominent examples are Achaogen and Melinta. Achaogen is a biotechnology company that received approval for plaxomicin in 2018, an innovative product designed to treat multidrug-resistant infections. In its first year, Achaogen reported less than US\$1M of sales, and the company filed for bankruptcy in spring 2019—despite having received more than US\$200M in development support.

Melinta Therapeutics is a biotechnology company with four approved novel antibiotics, one of which, meropenem/vaborbactam, also received more than US\$100M in development support under BARDA. Following a year of warning signs related to the company’s debt obligations, in late 2019 Melinta initiated voluntary proceedings under Chapter 11 Bankruptcy. During the process, Melinta will continue to operate with no disruption to supply, distribution, promotion, or support of their antibiotics.

## CHANGES IN THE AMR R&D INVESTMENT FIGURE CALCULATION

Due to methodological changes, it is not appropriate to make direct comparisons of R&D funding between this report and the previous progress report.

For the first progress report, responding companies were asked to provide their exact amount of investment in AMR-relevant R&D. However, member feedback raised concerns regarding the potential impact this approach might have on investor confidence, particularly in relation to smaller companies, or had policies that prohibited disclosing exact R&D expenditures. In response to this feedback, the methodology for collecting and calculating the overall investment figure was changed.

Companies with investment figures below US20M were asked to choose from a series of investment value ranges. These companies were assigned the median value of that range. Companies with investments above US20M were asked to provide a specific investment value. These specific and median values were combined to calculate the overall investment figure presented in this report.

The calculated total investment figure is a conservative estimate based on data received from 56 companies—11 large research-based biopharmaceutical, 35 biotechnology, and 10 diagnostics companies. This excludes generics, companies not currently active in R&D, and one company that did not disclose its AMR-relevant R&D figure. For the previous progress report, 22 companies provided investment data—7 large research-based biopharmaceutical, 12 biotechnology, and 3 diagnostics companies.

## ADVANCING PRODUCTS THAT COMBAT AMR

Even in the face of continued challenges, Alliance members continue to build R&D pipelines to address AMR. Alliance members are the largest investors in AMR-relevant R&D, exceeding total government support of US500M by a factor of three.<sup>61</sup> Eighty-four percent of relevant members (excluding generics) are engaged in relevant preclinical R&D or have at least one AMR-relevant product/platform in clinical development. Nearly all Alliance member R&D is focused on the microorganisms that pose the greatest threats to human health, including those listed on the World Health Organization (WHO) Priority Pathogen List<sup>62</sup> and the “biggest threats” identified by the U.S. Centers for Disease Control and Prevention (CDC).<sup>63</sup> In total Alliance members reported having 61 AMR-relevant products in clinical stage R&D. This includes 24 antibiotics and antifungals, 11 vaccines, 15 diagnostic platforms or assays, 10 novel approaches, and 1 other AMR-relevant product. Alliance members are developing around 50% of the Pew Charitable Trusts’ list of ‘Antibiotics Currently in Global Clinical Development’<sup>64</sup> and ‘Non-traditional Products for Bacterial Infections in Clinical Development’.<sup>65</sup>

Programs covered a broad spectrum of innovative products and approaches, including novel drug classes and mechanisms of action, new technologies, and vaccines. Diagnostics companies also reported early development of technologies and platforms such as genetic AMR databases and innovative software to help physicians optimize prescriptions.

## ANTIBIOTIC AND ANTIFUNGAL CANDIDATES IN DEVELOPMENT

To maximize potential positive impact on public health, the Alliance members' clinical pipelines mainly focus on the highest unmet medical needs. Specifically, 75% of responding companies' antibiotics or antifungals in clinical development during the reporting period are aimed at bacteria featured in the WHO list of priority pathogens<sup>66</sup> and 92% are aimed at bacteria and fungi featured in the CDC's Biggest Threats list.<sup>67</sup>

In total, members reported 24 antibiotic and antifungal products in clinical development.<sup>xiii</sup> These products are summarized in Appendix 4. Alliance members are developing around 50% of the Pew Charitable Trusts' list of 'Antibiotics Currently in Global Clinical Development'<sup>68</sup> and 'Non-traditional Products for Bacterial Infections in Clinical Development'.<sup>69</sup>

### ADDITIONAL INDICATIONS AND REFORMULATIONS OF EXISTING ANTIMICROBIALS

Although a significant focus is on the development of new antimicrobials, the full medical and economic value of existing antimicrobials can be realized through their reformulation and the development of additional indications for their use. These investments in further indications give prescribers valuable information on how they can be used appropriately for different populations, particularly because many novel antimicrobials are coming to market through facilitated regulatory pathways that enable approval based on small trials.

Alliance Member MSD (known as Merck and Co., Inc. in the U.S. and Canada) ran three Phase III trials for the use of existing antibiotics in the treatment of hospital-/ventilator-acquired bacterial pneumonia in 2018, a key unmet medical need with high mortality.

Alliance Member Xellia's R&D focuses on improving the efficacy and safety profile of existing anti-infectives as well as developing new drug products. In 2018, it had eight new formulations in early- and clinical-stage R&D, including Gram-positive and Gram-negative antibiotics and one antifungal.

### MSD RESEARCHES NEXT GENERATION ANTIBIOTICS

MSD's Exploratory Science Center in Cambridge, MA, focuses on the earliest stages of AMR-relevant discovery research. Since 2017, its scientists have explored the most promising areas of emerging disease biology: how antibiotics affect the human microbiome, drug conjugates, new technologies, and non-traditional approaches. Ultimately, the aim is to shift focus from broad-spectrum antibiotics to drugs with pharmacokinetic properties and therapeutic windows that are effective against pathogens while mitigating additional impacts on a patient's microbiome.

<sup>xiii</sup> An important consideration is the fact that product development milestones could be subject to change, particularly with products in early clinical development where regulatory hurdles may be greater or uncertain, therefore impeding or delaying further product development. The analysis in this report does not reflect that assumption. Therefore, the number of antibiotic products currently in clinical and late-stage development across the Alliance may be different from what has been reported because products may have since been approved or halted.

## THE ALLIANCE IN ACTION: SCYNEXIS DEVELOPING IBREXAFUNGERP AS AN ALTERNATIVE TREATMENT FOR PATIENTS WITH RESISTANT FUNGAL INFECTIONS, INCLUDING *CANDIDA AURIS*

Multidrug-resistant fungal pathogens are a growing global problem. In June 2016, CDC issued an extraordinary alert for infections caused by *Candida auris*, a new multidrug-resistant fungal species responsible for a series of hospital outbreaks. Recognizing the severity of this new pathogen, CDC added *C. auris* as an “Urgent Threat” in the newest CDC Antibiotic Resistance Threats in the United States.

In 2016, SCYNEXIS began preclinical studies to assess the activity of its investigational oral antifungal, ibrexafungerp, against *C. auris*. In 2017, the company initiated an open-label study of the drug for treatment of patients with infections caused by *C. auris*, the CARES study, the first clinical study of this organism. Two patient cases demonstrating the efficacy of oral ibrexafungerp in *C. auris* infections from the CARES study were presented in Spring 2019. The study is ongoing and expanding into other countries where *C. auris* has become a major problem.

Making ibrexafungerp available through this clinical trial provides an essential alternative treatment option for these vulnerable patients and enables SCYNEXIS to receive important data on the efficacy and safety of this new therapeutic.

## THE ALLIANCE IN ACTION: SUMMIT THERAPEUTICS ADVANCES PRECISION ANTIBIOTIC FOR BOWEL INFECTION

The increasing use of antibiotics has triggered a rise in *Clostridioides difficile* infection (CDI), a serious, persistent, and sometimes fatal bowel infection that is a result of the disruption of the gut microbiome. There are more than 1 million cases a year in the United States and Europe, and approximately 29,000 deaths in the United States alone.

In response, Summit Therapeutics’ R&D program is advancing ridinilazole, a precision mechanism antibiotic that targets CDI bacteria without perturbing a patient’s microbiome. This will help reduce CDI disease recurrence rates. The program is supported by the Biomedical Advanced Research and Development Agency, part of the U.S. Department of Health and Human Services. The Wellcome Trust provided earlier support.

In a Phase II patient clinical trial, it proved to be a more effective treatment than the current frontline CDI antibiotic, vancomycin, as well as highly preserving of the patients’ microbiome. Results of a Phase III clinical trial are due in 2021.



## VACCINE CANDIDATES IN DEVELOPMENT

Vaccines hold significant promise in the field of AMR.<sup>70</sup> Successful development of new vaccines and achievement of universal vaccination will be important milestones in curbing AMR. Vaccines offer the potential for sustained protection against life-threatening infections and their associated consequences. By helping to prevent infections, vaccines can reduce the need for antibiotics and help prevent potential overuse and inappropriate use of common antibiotics—which may result in resistant strains.<sup>71</sup> This helps to prolong the effectiveness of antimicrobials when they need to be used to treat infections.<sup>72</sup>

Four Alliance members are involved in clinical stage development of 11 AMR-relevant vaccines. These products are summarized in Appendix 5.

### THE ALLIANCE IN ACTION: JOHNSON & JOHNSON SEEKS INNOVATIVE VACCINES FOR LEADING CAUSES OF HOSPITAL INFECTIONS

Antimicrobial resistance is making antibiotics used to fight dangerous infections caused by Extra-intestinal Pathogenic *Escherichia coli* (ExPEC) and *Staphylococcus aureus* less effective.<sup>73,74</sup> ExPEC and *S. aureus*, both prone to AMR, are now the leading causes of hospital-acquired infections and bacteremia,<sup>xiv</sup> causing more fatalities than all other bacterial infection-related deaths combined.<sup>75,76</sup>

Janssen, a Johnson & Johnson company, has a vaccine in development to protect older adults against life-threatening disease caused by the 10 most prevalent subtypes of ExPEC. This is currently in clinical Phase I/IIa to assess dosing. In addition, Janssen is in the discovery phase of a vaccine with the potential to prevent serious infectious diseases caused by *S. aureus*, which in turn would reduce dependency on antibiotics and AMR public health risk.

To develop and bring these transformational vaccines to the market, Janssen collaborates with the Innovative Medicines Initiative, with GSK on its ExPEC vaccine, and with academic, biotechnology, government, and advocacy organizations.

## ADVANCING THE DIAGNOSTICS PIPELINE

The diagnostics sector is another important front in combating AMR. By developing rapid infection detection tests, it supports healthcare providers in the delivery of targeted and effective treatments.

Advancing the diagnostics pipeline is a crucial element of industry solutions and responses to AMR, helping to improve patient health in countries with all levels of income. Alliance diagnostics' members are actively pushing this agenda, significantly increasing the resources they have dedicated to this urgent issue over the past two years. Seventy percent of Alliance diagnostics' respondents are active in early- and clinical-stage R&D, developing reagents,

<sup>xiv</sup> Bacteremia is the presence of bacteria in the bloodstream.

hardware, software, and middleware. Across the Alliance, 15 diagnostic platforms or assays are in the clinical pipeline. These products are summarized in Appendix 6.

These solutions provide significant economic and medical value, giving healthcare providers easy-to-use systems that provide fast, accurate information and access to data analytics that can support clinical decision making and follow-up of the epidemiology. However, Alliance members are concerned that the failure of many governments to promote preventative healthcare models may hinder future investments in this important area.

#### THE ALLIANCE IN ACTION: BIOMÉRIEUX LEADS EUROPEAN EFFORT TO QUANTIFY DIAGNOSTICS' VALUE TO COMBAT AMR

Through its co-leadership on the Value Dx Project, bioMérieux is accelerating pan-European efforts to quantify the medical, economic, and public health value of diagnostics for combating AMR.

Antibiotics are often overused and unnecessarily prescribed in community clinical settings. The goal is to demonstrate and assess—in the specific case of community-acquired acute respiratory tract infections—the value of diagnostics as a fundamental tool to optimize antibiotic treatments. The project seeks to facilitate and accelerate rigorous assessment and implementation of diagnostic technologies in healthcare settings by establishing the needed infrastructure, methods, processes, and approaches. It also aims to evaluate and solve major hurdles to adopting diagnostics for acute respiratory tract infections in community settings, including clinical education, psychosocial barriers, organizational challenges, and regulatory and reimbursement issues.

Value DX is coordinated by bioMérieux, the University of Antwerp, and the Wellcome Trust, with a EUR14M budget over 4 years. Funding is provided by the IMI 2 Joint Undertaking, supported by the EU's Horizon 2020 research and innovation program, the European Federation of Pharmaceutical Industries and Associations (EFPIA), bioMérieux, Janssen Pharmaceutica N.V., Accelerate Diagnostics S.L., Abbott Laboratories, Bio-Rad Laboratories, Becton Dickinson (BD), and the Wellcome Trust.

#### EXPLORING BREAKTHROUGH NOVEL APPROACHES

In addition to deploying traditional tools—antibiotics, antifungals, vaccines, and diagnostics—companies are pursuing new technologies to expand the frontiers of AMR solutions. These hold great promise to address AMR alone or in combination with other antimicrobials.

Seven biotechnology companies and two large research-based biopharmaceutical companies reported pursuing novel approaches. Ten products are in clinical development. Examples include monoclonal antibodies, microbiome modulators, biofilm dispersants, and virulence inhibitors. These products are summarized in Appendix 7.

## THE ALLIANCE IN ACTION: COMBIOXIN COMPOUND COMBATS SEVERE PNEUMONIA

Pneumonia is the leading killer among infectious diseases. Its worldwide toll<sup>77</sup> on human life and healthcare systems in 2017 included an estimated 2.6 million deaths, of whom 75% were under age 5 or over 70, according to the Global Burden of Disease.

With resistance on the rise, companies are exploring new approaches. One frontrunner is CAL02, a novel antivirulence liposomal agent developed by Combioxin, a clinical-stage biotechnology company.

For use alongside antibiotics, CAL02 is active against virulence effectors produced by Gram-positive and Gram-negative bacteria, protecting tissues and organs so that patients' immune systems can better combat infection, and does not prompt the emergence of new resistance.

In a small clinical trial (19 patients with severe pneumonia),<sup>78</sup> it proved its ability to treat pneumonia much more effectively than antibiotics alone. Non-clinical studies demonstrate that the therapy is also effective when administered alone. Given these early findings, Combioxin believes CAL02 can address an urgent medical need and potentially reduce critical care costs.<sup>79</sup>

## THE ALLIANCE IN ACTION: AEQUOR'S NOVEL MOLECULES COUNTER BIOFILM ASSOCIATED WITH HOSPITAL-ACQUIRED INFECTIONS

Bacteria and fungi can form biofilms that stick to surfaces inside the human body. This process enables microbial cells to become tolerant and resistant to antibiotics, thus making infections more difficult to treat.<sup>80</sup>

Pathogenic bacterial biofilms are recognized as causing or exacerbating numerous chronic infections, including cystic fibrosis pneumonia, chronic otitis media, and recurrent urinary tract infections.<sup>81</sup> The consequences for patients and healthcare providers include increased morbidity, extended hospital stays, higher hospital charges, and increased in-hospital mortality.<sup>82</sup>

Current antimicrobials and antibiotics are designed to kill only free-floating microorganisms and cannot remove the biofilm once it forms. After discovering 30+ novel small molecules that remove bacterial and fungal biofilm in minutes and prevent its formation for days, Aequor is looking to develop antibiofilm agents and new antibiotics. The company expects ultimately to gain approval for a large portfolio of new drugs that combat broad-spectrum AMR infections and diseases.

## THE ALLIANCE IN ACTION: BIOVERSYS PURSUES BREAKTHROUGH TREATMENT FOR DRUG-RESISTANT TB

Tuberculosis (TB) is in the top 10 causes of death globally, and the leading cause of death from a single infectious agent. WHO estimates that 10 million people contracted TB in 2017, mostly in low- and middle-income countries (LMICs), and 1.6 million of those people died. Resistance to common anti-TB drugs is growing, with an estimated 558,000 new cases in 2017.<sup>83</sup>

BioVersys is pursuing a novel treatment in this area of high-unmet medical need by targeting drug-resistant forms of mycobacterium TB. The Swiss-based biotechnology company is collaborating with GSK to develop a compound that will boost the efficacy of, and reverse resistance to, the common anti-TB antibiotic ethionamide (ETH).

Currently in preclinical trials, TRIC-TB seeks to improve ETH by developing “booster” molecules that would improve efficacy at a fraction of the existing dose. If successful, the compound would enable lower doses of ETH that would shorten patient treatment times, reduce adverse side effects, and improve relapse rates.

In June 2019, BioVersys received a EUR6.9M grant from the EU Innovative Medicines Initiative (IMI) to fund further preclinical research and early clinical development of candidate molecules. The Wellcome Trust provided earlier funding.

## ADVANCING R&D THROUGH GLOBAL PARTNERSHIPS

Among the 57 responding companies that conduct relevant R&D, 90% reported engaging in national and international partnerships to further the global effort to combat antimicrobial resistance.

The findings demonstrate growing industry efforts to coordinate action across sectors and disciplines. In responding to calls from governments and international health organizations for bold collaborative action, Alliance members cited working with non-governmental organizations (NGOs) and foundations, academic institutions, government departments, international agencies such as WHO, and hospital and medical laboratories. Many also engage in public-private partnerships, with CARB-X, the Human Vaccine Project, and IMI among the most prominent. Examples of different collaborations across the Alliance are outlined below

**Prevention through vaccines:** Large research-based biopharmaceutical companies are active on this front. Since 2016, Pfizer has contributed to the Human Vaccine Project’s efforts to identify human immune responses associated with optimal vaccine protection.<sup>84</sup> The project seeks to overcome scientific barriers hindering the development of new and improved vaccines against infectious diseases such as influenza, dengue, and HIV. MSD is working with the Wellcome Trust to expand access to new and improved vaccines (see case study).

## THE ALLIANCE IN ACTION: MSD AND THE WELLCOME TRUST INVEST IN TRANSFORMATIVE AFFORDABLE VACCINES

Tens of millions of children and adults lack access to life-saving vaccines in low- and middle-income countries, representing a huge gap in global preventive healthcare provision. Due to the lack of commercial return, private-sector investment is also limited in new vaccines for diseases that mainly affect low-income countries.

Further complicating efforts to expand access, pharmaceutical companies are grappling with how best to adapt existing vaccines for effective delivery in developing and emerging countries—including through greater thermostability, easier administration, and especially affordability.

In 2009, MSD and the Wellcome Trust jointly established the non-profit Hilleman Laboratories in Delhi, India, with a mission to develop affordable vaccines that address gaps in low-resource settings where disease burden is often highest. A decade later, the first-of-its-kind initiative<sup>85</sup> has several promising programs underway evaluating early-stage vaccine candidates. These include an optimized cholera vaccine; a vaccine for Shigella, which causes severe diarrhea and dysentery; and a low-cost Meningococcal conjugate vaccine.

**Addressing scientific challenges:** Alliance companies across several sectors reported engaging with the IMI’s COMBACTE (Compacting Bacterial Resistance in Europe) partnership, a collaboration between industry and academia. Members are investigating the epidemiology and clinical impact of resistant infections and designing and implementing more efficient clinical trials for the development of antibiotics and innovative approaches against AMR. Below are some examples of Alliance activities under the COMBACTE partnership.

BioMérieux	BioMérieux’s 3-year project targets <i>Clostridioides difficile</i> infections, merging expertise on clinical, diagnostic, and therapeutic issues to gain insight into the disease’s epidemiology across Europe.
Da Volterra	Da Volterra undertook an observational study of hospital patients receiving antibiotic treatment. The goal was to anticipate the incidence of CDI and antibiotic-associated diarrhea, and changes in the diversity and composition of intestinal microbiota in patients aged 50 or older who receive antibiotics during hospitalization. Da Volterra is now preparing a pivotal study with DAV132, its microbiota protective therapy under the COMBACTE Partnership.
AiCuris	AiCuris is working to tackle hospital-acquired infections in critically ill patients in intensive care units. This led to the discovery of an innovative antibiotic, AIC499, now in Phase I and II clinical development, that shows potent antibacterial activity against Gram-negative pathogens.

GSK	GSK partners with COMBACTE to optimize trial logistics with novel antibacterial agents to achieve more efficient testing and innovative statistical methods and clinical trial design.
Pfizer	As a strategic partner of COMBACTE-CDI and COMBACTE-CARE, taking the role of European Federation of Pharmaceutical Industries and Associations coordinator in 2017, Pfizer seeks to accelerate breakthrough research and drug and vaccine development. THE COMBACTE-CARE consortium also receives support from BARDA and other global partners.

**Low-cost drug resistance detection:** Some diagnostics companies are collaborating on lower cost solutions for disease genotyping and resistance detection. For example, Qiagen partners with the Foundation for Innovative New Diagnostics to evaluate a rapid, affordable, and scalable TB susceptibility testing regimen for low- and middle-income countries. Qiagen’s projects aim to generate evidence for global adoption of commercial, targeted next generation sequencing for drug-resistant TB.

**Bringing novel diagnostics into clinical use:** BioMérieux reported partnering with the PERFORM (Personalized Management of Febrile Illness) Consortium, which aims to bring into use better tests to distinguish between bacterial and viral infections by 2021. A coalition of 18 academic institutions and life sciences companies from 10 countries, PERFORM received EUR18M from the European Commission’s Horizon 2020 Health program.

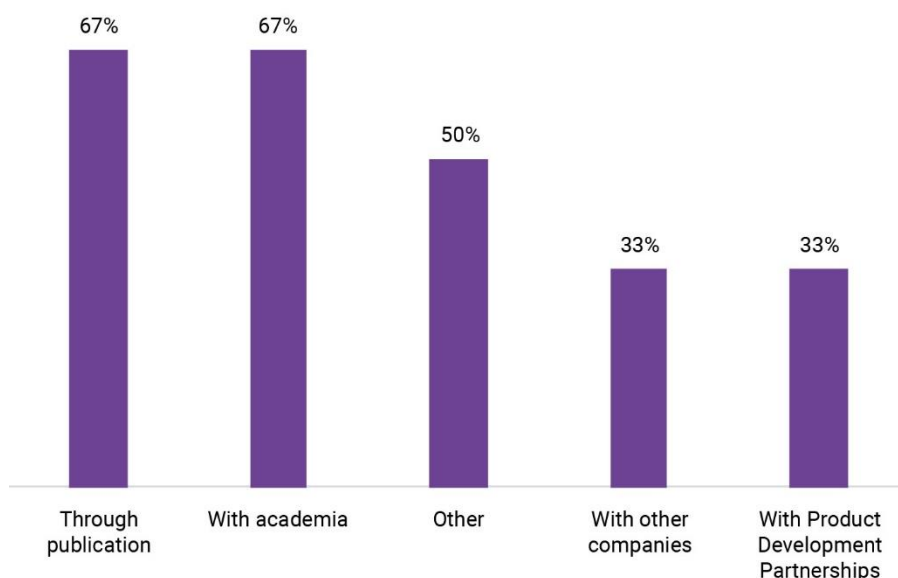
**Technology innovation in microbiology:** Some diagnostics and large research-based biopharmaceutical companies also reported having research partnerships that address the latest challenges in microbiology. Examples included the French government-funded BIOASTER Technology Research Institute, which seeks to advance vaccine safety and efficacy, rapid diagnostic testing, and applications of human and animal microbiota.

## EXCHANGING DATA ON OFF-PROTECTION ANTIBIOTICS

The industry is advancing the global knowledge base critical to countering AMR by facilitating data exchange on off-protection antibiotics.<sup>xv</sup> All large research-based biopharmaceutical companies reported sharing data with each other and external stakeholders. They do so primarily by publishing clinical trial results, surveillance data, and the findings and impacts of stewardship activities. Sharing such information encourages wider innovation as companies develop new antibiotics or other AMR-relevant products.<sup>86</sup>

Findings on the different means that members used to share data are highlighted in Figure 6.

<sup>xv</sup> Data exchange on off-protection antibiotics refers to making data (e.g., regulatory dossier or information related to dosing and manufacturing processes) on off-protection antibiotics available to external stakeholders, where off-protection is when a product is no longer protected from competition due to expiration of proprietary protections (e.g., patents, data exclusivity, etc.).



**FIGURE 6:** PROPORTION OF LARGE RESEARCH-BASED BIOPHARMACEUTICAL COMPANIES THAT FACILITATED DATA EXCHANGE ON OFF-PROTECTION ANTIBIOTICS THROUGH DIFFERENT MEANS (%)<sup>xvi</sup> (TOTAL: 12)

## ALLIANCE MEMBER COLLABORATIONS TO IMPROVE INVESTMENT CLIMATE

Alliance members continue to pursue advocacy and collaboration with policymakers and other stakeholders to drive sustainable investment in AMR-relevant R&D. Among survey respondents, 83% of companies across all sectors are involved in such efforts. Companies reported different approaches, depending on their commercial needs:

- **Testing new payment models:** Several Alliance members are part of a joint working group between the pharmaceutical industry and U.K. government to design and trial a new subscription-based payment model developed by National Institute for Health and Care Excellence (NICE) and the National Health Service (NHS). The Association of the British Pharmaceutical Industry leads the trial, with GSK, MSD, Pfizer, and Shionogi among companies involved. Fedora Pharmaceuticals is providing input to Canada’s policy on AMR in an effort to promote push–pull incentives.
- **Informing high-level discussions and global policy debates:** Several large research-based biopharmaceutical companies participate in policy discussions<sup>xvii</sup> and government dialogues through industry associations such as EFPIA, the European Business Enterprise, the Biotechnology Innovation Organization (BIO), and the Japan Pharmaceutical Manufacturers Association. Proposals to develop new incentives are under consideration in the U.S. and U.K., Japan, France, Germany, Sweden, and Norway.

<sup>xvi</sup> Please note that companies report sharing data on off-protection antibiotics by several means at the same time.

<sup>xvii</sup> These include expert meetings with organizations such as the UN General Assembly, UN Conference on Trade and Development, One Health Commission, WHO, The Organisation for Economic Co-operation and Development, World Economic Forum, Global Health Innovative Technology Fund, Infectious Diseases Society of America, The Pew Charitable Trust, and Margolis Center for Health Policy.

- **Advocating for incentives:** Alliance companies across sectors are heavily engaged in alliances such as The Global Antibiotic Research and Development Partnership (GARDP), the Biotech Companies in Europe Combating Antimicrobial Resistance (BEAM), the Antimicrobial Innovation Alliance, and IMI. Members collaborate on incentive mechanism proposals for AMR-relevant R&D to present to governments.
- **Assessing the value of novel antibiotics:** Industry peers are collaborating on new elements to incorporate into Health Technology Assessment<sup>xviii</sup> value frameworks that better capture the societal value of novel antibiotics, and can attract new investment. This work has brought together regulators, reimbursement agencies, clinicians, and industry to inform national and EU policymaking.
- **Enhancing clinical trial design:** Alliance companies are engaged in public–private partnerships to improve clinical trial designs and streamline regulatory processes. These include the Duke Trials Transformation Initiative, a partnership of 80 organizations working to develop, and drive adoption of, clinical trial best practices.
- **Advancing the discovery and development of innovative antibiotics:** Alliance companies are prominent members of public–private partnerships addressing critical healthcare needs. Johnson & Johnson launched an international research consortium<sup>87</sup> with European biotechnology companies to advance the discovery of TB antibiotics and promote increased investment.

## MARKET REFORMS ARE CRITICAL TO SUSTAINABLE R&D

There is broad alignment across policymakers (including the governments of the G7<sup>88</sup> and G20<sup>89</sup>), academia, and industry that market reforms are urgently needed to enable sustainable private investment in AMR-relevant R&D. Many Alliance respondents highlighted the perceived lack of concrete action to address the well-documented barriers in this area despite years of discussion and effort. The current AMR-relevant pipeline is considered to be insufficient for the global health challenge that AMR poses: without improving market conditions, this situation is likely to get worse.<sup>90</sup>

However, were market conditions to improve, most relevant companies (74%) reported that they were likely to increase R&D investment. Were market conditions to remain the same, 62% reported that they would only maintain current investment levels, and 19% said they would decrease investments. Smaller biotechnology companies warned that R&D programs would be nearly impossible to fund without improved market conditions.

Alliance members reiterated the importance of a package of incentives that can stimulate investment in R&D across the lifecycle, from discovery to bringing products onto the market. Alliance members stressed that this package should include policies to improve antimicrobial reimbursement and help stabilize the market as well as to create pull incentives that reward the approval of novel antimicrobial products that address unmet needs.

Members also highlighted the need for incentives that support the development and uptake of AMR-relevant diagnostics. They underlined the need for greater and more cohesive efforts to

<sup>xviii</sup> Health Technology Assessment is a multidisciplinary process to assess the social, economic, organizational, and ethical issues of a health intervention or technology. The main purpose of conducting the assessment is to inform policy decision-making.



improve the regulatory environment, market access, and clinician guidelines that promote the pivotal role of diagnostics in antimicrobial stewardship efforts.

Taken together, these solutions have significant potential to change market dynamics around the development and commercialization of AMR-relevant products and, the survey suggests, would have a positive impact on the industry's investment decisions.

## MARKET SOLUTIONS

The unique challenges and dynamics of the antimicrobials market require targeted measures to establish an economic environment that incentivizes increased private investment in AMR-relevant R&D.

To this end, Alliance companies and industry associations such as International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)<sup>91</sup>, EFPIA<sup>92</sup>, BEAM<sup>93</sup> and BIO<sup>94</sup> support incentive approaches that could create the conditions to drive a predictable and sustainable return on investment. A suite of interventions, adapted to local conditions, will be needed. To be viable and meet medical needs, reward mechanisms would need to be funded primarily by developed countries while ensuring access and appropriate use for AMR-relevant products in developing countries.<sup>95</sup>

Examples of these incentive packages include:

- Push incentives that reduce risk of AMR-relevant product R&D, including regulatory reform, grants, and R&D tax credits.
- Reform reimbursement to better align with the societal value of AMR-relevant products, both within current models of reimbursement as well as in new value-based subscription-based models.
- Pull incentives that reward the successful approval of novel AMR-relevant products that meet critical unmet needs, such as market entry reward or transferable market exclusivity vouchers.

## NEXT STEPS

### RESEARCH & SCIENCE

- In partnership with patients and providers, continue to advocate for governments to implement the package of policy reforms that would create market conditions that support sustainable investment into and commercialization of AMR-relevant R&D as well as diagnostics, vaccines, improvements to existing therapies, complementary technologies, and novel solutions. This could include piloting new payment mechanisms and pull incentives.
- Collaborate with international organizations, NGOs, research institutions, funders, and donors to accelerate development of new treatments for drug-resistant infections, particularly those prevalent in LMICs.
- Work with health systems and the broader pharmaceutical industry to ensure that vaccines, diagnostics, novel antibiotics, and other AMR-relevant products are appropriately valued. Partner with governments on new reimbursement mechanisms and pull incentives.
- Strengthen partnerships on R&D within and outside the Alliance by making information available on companies' various platforms publicly available to deepen the current understanding of resistance trends and resistance mechanisms and to promote innovation.
- Increase Alliance membership to cover a greater proportion of companies active in clinical R&D of AMR-relevant products.

# ACCESS

## THE ALLIANCE'S ACCESS COMMITMENTS

- Address barriers to patient access to the most appropriate treatment, vaccine, or diagnostic.
- Work in collaboration with policymakers to create an economic and regulatory environment that enables the sustainable supply of quality-assured antibiotics.
- Work to reduce the prevalence of substandard and falsified AMR-relevant products.

With 5.7 million deaths each year attributed to lack of access to antimicrobials,<sup>96</sup> effective solutions to combat AMR must also address the challenges of patient access to essential antimicrobials, diagnostics, and vaccines. This is especially the case in low- and middle-income countries (LMICs), which have high burdens of infectious diseases and weak health systems. Enhanced access to antimicrobials—aligned with antimicrobial stewardship to ensure appropriate use—will save lives and is critical to global efforts to slow the spread of drug-resistant infections.

Multiple barriers often stand in the way of sustaining a country's steady access to AMR-relevant products, particularly in LMICs. According to the Center for Disease Dynamics, Economics & Policy (CDDEP), in a report supported by the Alliance, market entry challenges, poor stewardship, supply chain disruptions, and insufficient quality control all hinder much-needed access to antimicrobials, and particularly antibiotics.<sup>97</sup> In addition, the World Health Organization (WHO) has identified the relatively high prevalence of substandard and counterfeit antimicrobials as one of the main problems that law enforcement and health authorities face in LMICs.<sup>98</sup> In response, Alliance members are partnering with developing country governments to remove such products from the market.

Addressing these complex access challenges requires ambitious strategies and sustained commitments from all stakeholders across the public and private sectors. The life sciences industry has an important role to play in expanding and sustaining appropriate access to antimicrobials. Since the first progress report, Alliance members surveyed have taken a range of actions to expand access to their products. They have also expressed their ongoing commitment to work with governments and other partners to create a conducive environment for a more sustainable global supply of quality-assured antimicrobials.

**74%** OF ALL ALLIANCE RESPONDENTS WITH COMMERCIALIZED PRODUCTS IMPLEMENTED **ACTIVITIES TO EXPAND ACCESS**

**81%** DEVELOPED DETAILED ACCESS **STRATEGIES**

## STAKEHOLDER COMMENTARY

While the overuse of antibiotics makes headlines as an emerging global threat, the high death toll from the lack of access to antibiotics is a public health crisis today.

Every year, 5.7 million people die from treatable bacterial infections, the majority in low- and middle-income countries. Life-saving medicines routinely fail to reach countries most in need, with fewer than 5 of 21 new antibiotics entering markets between 1999 and 2014 registered in most sub-Saharan African countries.<sup>99</sup>

Why is this so? The culprits are numerous, ranging from supply chain storage, transportation, and oversight issues to in-country regulatory hurdles, poor medical facilities, lack of local manufacturing, and high patient co-pays. Overcoming these barriers, identified in a 2019 report by CDDEP,<sup>100</sup> will take concerted action from governments, pharmaceutical companies, healthcare institutions, and international public health bodies. The examples in this chapter show the many ways in which Alliance members are playing their part.

*Ramanan Laxminarayan is founder and director of the Center for Disease Dynamics, Economics & Policy in Washington, D.C.*

## INDUSTRY SUPPORTS GLOBAL ACCESS

Global attention is being paid to the importance of expanding access to antibiotics. For example, commitments related to appropriate antibiotic access are included in industry's Davos Declaration (January 2016) and multiple G20<sup>101, 102</sup> statements. In April 2019, the UN Interagency Coordination Group (IACG) on AMR released its recommendations to governments to improve appropriate access to antibiotics<sup>103</sup> and to address the global crisis of AMR.<sup>104</sup>

The IACG report highlights the need to:

- Make improvements in existing industry surveillance systems to better forecast demand;
- Address financing deficiencies to allow market entry of AMR-relevant products;
- Strengthen health systems' capacity to ensure product quality and safety; and
- Tackle the problem of substandard and falsified products entering markets.

Solving these and other AMR-related problems will require sustained, multisector action at all levels. As a result, the IACG report calls on stakeholders to sustain and strengthen existing partnerships and build new ones.

The latest survey of Alliance members demonstrates that members are already taking action to support appropriate access. Many relevant companies already collaborate closely with suppliers, governments, and regulatory authorities, among others, to ensure and improve access to quality antimicrobials. They also pursue robust risk management and mitigation strategies to ensure uninterrupted supply of the tools needed to combat AMR.

The data presented in this chapter focus on Access and are primarily derived from the 48% of reporting Alliance members that currently have AMR-relevant products or platforms on the market. Some Alliance members without AMR-relevant products or platforms on the market

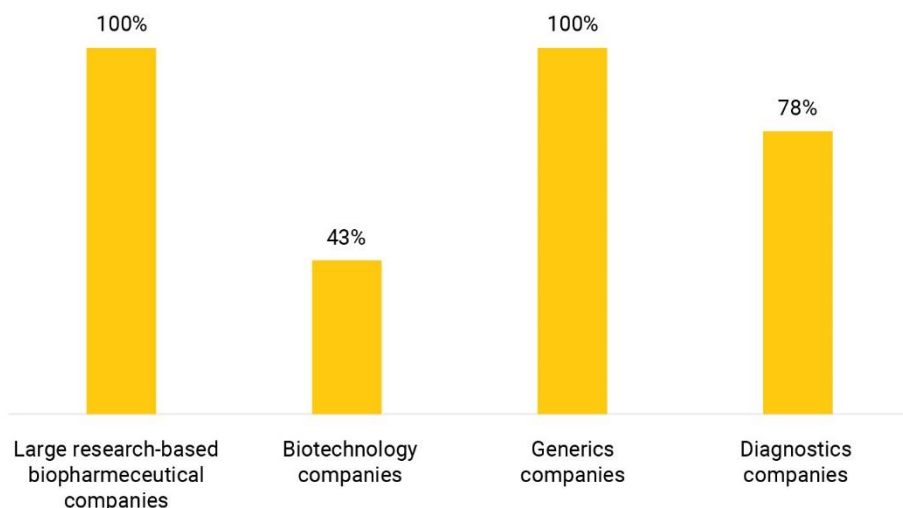
also reported having formal access strategies in place, while others highlighted their participation in public-private partnerships to expand access.

### ACCESS VERSUS EXCESS

Many reporting companies emphasized the need to pursue access and stewardship efforts in tandem, particularly in relation to antimicrobials. For example, without careful use by healthcare providers and patients, expanding access to broad-spectrum antimicrobials—which are widely prescribed to treat a variety of infections—can increase resistance. The Appropriate Use chapter provides data and best practices of how the industry is working to support stewardship and appropriate use.

## ACCESS STRATEGIES

A key commitment made by Alliance members is to address barriers to patient access to the most appropriate treatment, vaccine, or diagnostic. To this end, Alliance members are investing in a variety of programs to support appropriate access that are captured in formal access strategies, policies, or plans. As with appropriate use, sustaining and expanding access requires collaboration among suppliers, healthcare authorities, providers, patients, and other relevant stakeholders operating both locally and nationally. Alliance member corporate access strategies commonly include policies for increased product registration, measures to improve affordability (within and among countries), and health systems strengthening and partnerships (Figure 8).



**FIGURE 7:** PROPORTION OF ALLIANCE MEMBERS WITH COMMERCIALIZED PRODUCTS THAT HAVE ACCESS POLICIES, STRATEGIES, OR PLANS (%) (TOTAL: 25)

Eighty-one percent of companies with commercialized products have access policies, strategies, or plans in place. The following sections provide further examples of Alliance member activities to expand access.

An encouraging note is that all large research-based biopharmaceutical and generics companies reported having formal strategies to improve access. The numbers were lower for

biotechnology (43%) and diagnostics companies (78%), but still likely represent an increase from 2 years ago, when 38% and 25% of such companies, respectively, reported having access strategies.

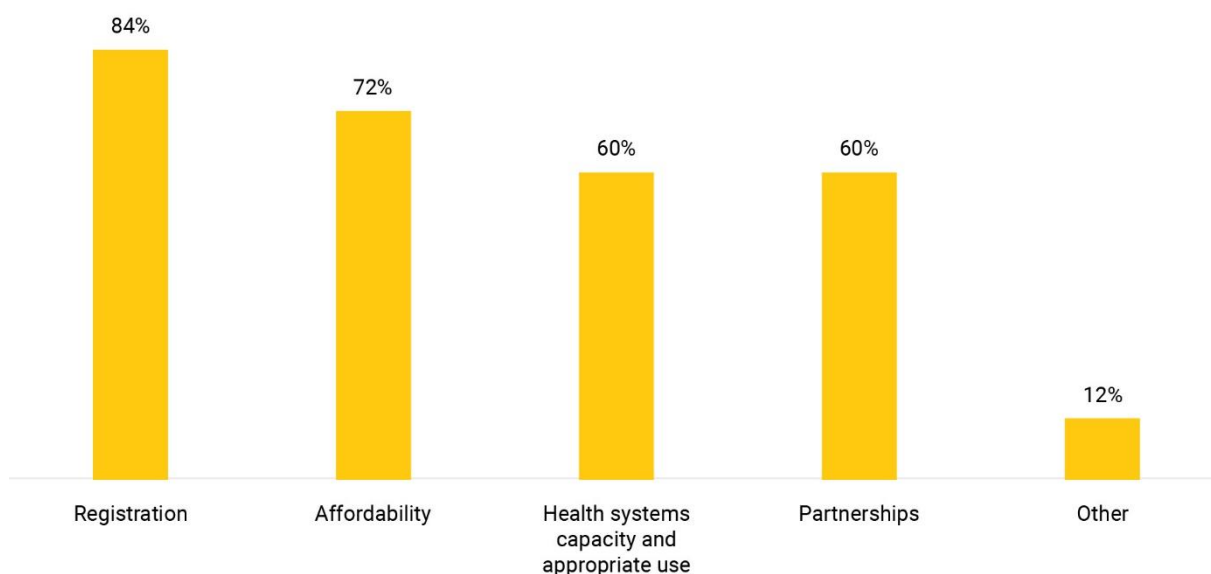
Eighty percent of companies with product-related access policies or plans and strategies were active in LMICs, where millions of people die every year due to lack of access to safe, effective, and affordable antimicrobials.<sup>105</sup>

However, only 32% of reporting companies (five large research-based biopharmaceutical and three generics companies) with access strategies made them publicly available, making this an area where progress is needed. The need for transparency must be balanced with a recognition that for some companies, in particular generics, elements of access strategies such as tenders may contain sensitive business information, and disclosure could negatively impact competition.

## BROAD INDUSTRY ACTIVITY TO EXPAND ACCESS

Seventy-four percent of companies with AMR-relevant products or platforms on the market reported pursuing activities to increase access. The reported data show a disparity between the number of companies that have an access strategy in place and those that are actively implementing access activities. This discrepancy is likely attributable to strategies being developed before a given company is ready to implement them.

The most common access activities cited by survey participants were plans to expand registration of antimicrobial products, improve their affordability, and strengthen supply chains. The majority of companies reported taking tangible steps to build health systems capacity and appropriate use, and expand access through partnerships (Figure 8). Forty-eight percent of responding companies reported having plans in place across all these areas.



**FIGURE 8:** ALLIANCE MEMBER ACCESS PLANS BY ACTION AREA (%) (TOTAL: 25)

Several of the largest Alliance members, including GSK, MSD, Johnson & Johnson, Pfizer, Mylan, bioMérieux, and BD, engage in access activities as part of broader sustainability strategies that set targets to support patient access and affordability of antimicrobial products.

**Accelerating global product registration:** Alliance members must obtain market authorization/regulatory approval before marketing the product in a country. Alliance members reported working with governments to expedite product registrations by strengthening regulatory functions of relevant agencies. Others reported that they were assessing emerging markets' regulatory and commercialization needs, at an early stage, as part of their R&D milestones. Despite the commitments related to accelerating product registration by large research-based biopharmaceutical companies, there is still a delay in registration of novel antimicrobials. A recent study found that fewer than 5 of 21 new antibiotics entering markets between 1999 and 2014 were registered in most sub-Saharan African countries.<sup>106</sup> This finding highlights the need for coordinated efforts between industry and governments to prioritize registration of novel products in high-burden countries that have demonstrated capacity to expand appropriate access.

**Ensuring affordability:** Companies continue to employ pricing strategies that support affordable access to medicines in high-need countries. MSD, Johnson & Johnson, Teva Pharmaceuticals, Mylan, and Sandoz reported pursuing tiered or differential pricing approaches, based on countries' socioeconomic context, distribution channels, and public health needs. Otsuka provides voluntary licensing agreements to industry peers to commercialize delamanid for the treatment of tuberculosis (TB) in the LMICs and high-burden countries where it does not have local operating companies. Members also reported sharing intellectual property with non-profits such as the TB Alliance as a strategy to ensure access and lower drug prices through partnerships.

**Product donations:** All large research-based biopharmaceutical members work with non-governmental organizations (NGOs) and in public-private partnerships to donate products to vulnerable populations in low-income countries. Vaccine provision is often the focus of these efforts for companies with relevant portfolios.

#### THE ALLIANCE IN ACTION: SANDOZ'S PEDIATRIC DEVELOPMENT PROGRAM

In late 2018, Novartis, which owns Sandoz, announced a strategic partnership with the Global Antibiotic Research & Development Partnership (GARDP) to accelerate the development and availability of generic antibiotic treatments for children in low- and middle-income countries.

The two organizations plan to improve and adapt existing generic antibiotic formulations and dosing regimens for newborns and children, with a particular focus on heat-stable pediatric formulations. Sandoz is currently in the final stages of development/registration for a more child-friendly amoxicillin dispersible tablets formulation to treat infections of the lungs, airways, and related organs.

With tuberculosis one of the top 10 causes of death globally,<sup>107</sup> and drug-resistant strains constituting a growing challenge, expanding access to effective treatment is a public health priority in low- and middle-income countries. Alliance members are deploying expertise, resources, and innovative partnerships to improve access and outcomes for TB patients. Three examples are highlighted below.

### MYLAN

Tuberculosis accounts for more than a quarter of deaths due to AMR.<sup>108</sup> The worst affected are patients whose infection is resistant to first and second line therapies. Mylan is partnering with TB Alliance, a non-profit drug developer, to make a promising new drug, pretomanid, available to such patients in LMICs at an affordable cost.

In 2019, the U.S. Food and Drug Administration (FDA) approved pretomanid, in combination with bedaquiline and linezolid, for treatment of adults with extremely drug-resistant TB and treatment-intolerant and non-responsive, multidrug resistant (MDR) TB. Clinical trials showed an 89% cure rate among 107 patients studied. Mylan will commercialize pretomanid in LMICs via a non-exclusive license agreement, ensuring patients have affordable and sustainable access.

### JOHNSON & JOHNSON

South Africa is hard hit by the TB epidemic, with around 322,000 new cases every year.<sup>109</sup> In 2018, Johnson & Johnson launched a landmark collaboration with South Africa's government to provide SIRTURO® (bedaquiline)—the first new drug for TB treatment in more than 40 years—at a not-for-profit price. This offer has since been extended to 130 additional eligible countries via the Stop TB Partnership's Global Drug Facility. Through July 2019, approximately 32,000 South African patients with MDR-TB received SIRTURO®.

### OTSUKA

Each year, approximately half a million new cases of MDR-TB are diagnosed globally. Through its FightTBack initiative, Otsuka Pharmaceuticals seeks to expand access to delamanid, an effective treatment, to countries with highest need. The company's collaboration with the Stop TB Partnership Global Drug Facility enables more than 100 eligible low and middle-income countries to procure delamanid. Since 2016, over 18,000 treatment courses have been distributed through this collaboration.



## PROMOTING ACCESS TO DIAGNOSTICS

The diagnostics sector offers the potential to combat AMR in countries with high disease burdens by enabling effective and targeted treatment by healthcare providers. Alliance companies reported that product-related access challenges vary by country and include the healthcare setting, resource availability, simplicity of use, and cost.

Common activities reported by diagnostics companies to promote access included:

- Expanding collaborations with international distribution partners to drive wider product distribution;
- Promoting predictable, efficient, and harmonized regulatory review processes that rely on global data to expedite product approval and speed market entry in various countries;
- Seeking government reimbursement to microbiology labs that conduct diagnostic testing, including interim payments for innovative technologies; and
- Advocating for the inclusion of new diagnostics tools in healthcare guidelines, including launching educational activities and partnerships to encourage clinicians to adopt access and stewardship best practices.

### THE ALLIANCE IN ACTION: QIAGEN EXPANDING ACCESS TO LIFE-SAVING TECHNOLOGY

In 2018, 87% of new TB cases occurred in 30 countries in Asia, Africa, and Latin America.<sup>110</sup> Global diagnostics provider Qiagen is partnering with Ellume, an Australian developer of high-performance diagnostics, on a new test to support TB control in areas with limited infrastructure. QuantiFERON-TB Access will deliver a field-friendly test with ultrasensitive digital detection for TB infection on a portable device.

Launching in 2020, this public health solution has gained recognition by the Joint United Nations Program on HIV/AIDS. TB prevention is key in decreasing the number of treatments for active TB and hence antibiotic exposure and potential resistance.

## PARTNERSHIPS INCREASE ACCESS

Public-private partnerships play an important role in expanding global access to AMR-relevant products or platforms. Sixty-three percent of relevant Alliance members reported partnering with external stakeholders at all levels to support greater access. These collaborations encompass global multisector alliances, NGOs, industry trade organizations, governments and international agencies, and local healthcare institutions.

The focus of reporting companies remained largely on tackling TB in high-burden countries, with few partnerships devoted to expanding access to antibiotics. In addition, AMR-related access programs underway in low- and middle-income countries are not yet being brought to scale.

Typical examples of public-private partnerships are described below.

## EXAMPLES OF PUBLIC-PRIVATE PARTNERSHIPS TO ADVANCE ACCESS

COMPANY	PARTNERSHIPS	DESCRIPTION
BD	Labs for Life	Partnership with the U.S. President's Plan for Emergency AIDS Relief (PEPFAR), the U.S. Centers for Disease Control and Prevention, and governments to advance the capabilities and capacity of laboratories in India, Haiti, Kenya, Mozambique, Ethiopia, and Uganda. <sup>111</sup> The partnership has improved TB diagnosis across these countries and strengthened laboratories' efforts to achieve accreditation.
Johnson & Johnson: Xian Janssen	Joint collaboration with the China National Health Commission, the Chinese Center for Disease Control and Prevention, National TB Program, and Bill & Melinda Gates Foundation	Partners jointly launched the New Drug Introduction and Protection Program aimed at ensuring access to and appropriate use of SIRTURO® in China for the treatment of multidrug-resistant TB. Nearly 100 hospitals are taking part, and more than 1,000 healthcare professionals will receive residential and remote training courses regarding the drug's appropriate use.
Mylan and MSD	PLATINEA (Platform for Innovation of Existing Antibiotics) is a multisectoral collaboration with 15 partners from academia, the public sector, and industry	Uppsala Antibiotic Centre, Linköping University, and Uppsala University Hospital partner with Mylan to ensure accessibility and good use of antibiotics through continuous inventory and prioritization. PLATINEA identifies gaps between public health needs and available antibiotics and generates evidence on new methods to optimize antibiotic use. The project will also evaluate and test new methods to promote rational use of antibiotics as well as investigate the supply chains for existing antibiotics. <sup>112</sup>

## THE ALLIANCE IN ACTION: SANDOZ'S COMMITMENT TO SUPPLYING ESSENTIAL MEDICINES

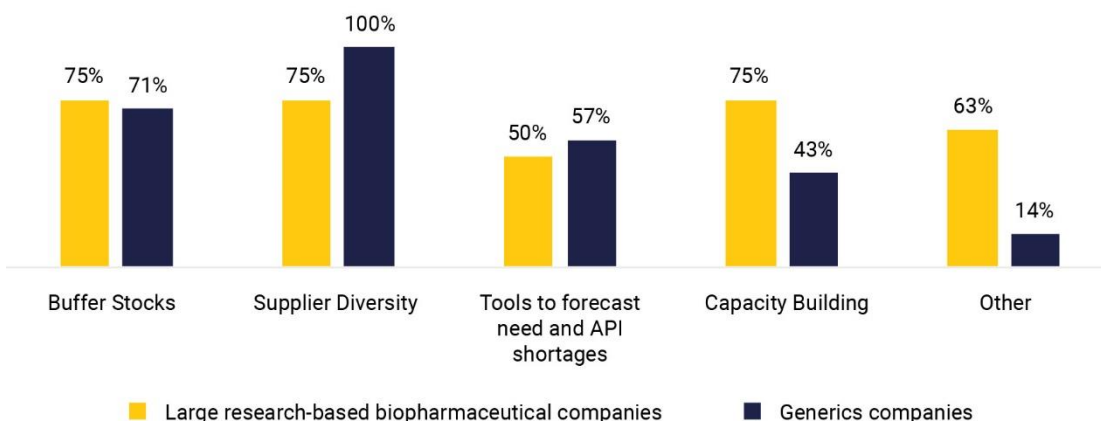
Amoxicillin is a leading broad-spectrum antibiotic indicated for a wide variety of bacterial infections and related conditions. Sandoz, a leading global supplier of this product family, is committed to increasing access for the world's most vulnerable populations through close collaboration with global NGOs and UN organizations and drives access to key products through tenders and/or emergency requests.

These targeted projects have already shown impressive results, including the delivery of more than 1 million amoxicillin courses to UNICEF alone. Specifically, Sandoz supplied 450,000 treatments of amoxicillin, below fully loaded cost, as part of a country-specific UNICEF program for war-torn Yemen.

## PREVENTING AND MANAGING PRODUCT SUPPLY DISRUPTIONS

Shortages of antimicrobials are in large part symptoms of a fragile supply chain.<sup>113</sup> Access to antimicrobials, including antibiotics, is highly affected around the world by supply chain disruptions resulting from production challenges. Industry and governments must therefore work together to ensure that supply chains are continuous, sustainable, and secure. The following section describes the steps the life sciences industry is taking to mitigate the risk of supply disruptions. Governments and procurers also have a role in preventing disruptions, for example, by prioritizing factors not related to price, such as supply security in product tenders, and avoiding winner-take-all decisions.

Although industry efforts are making a difference, a recent analysis by the U.S. FDA warned that drug shortages remain a persistent problem. After analyzing shortages of 163 medicines in the U.S. between 2013 and 2017, the agency pinpointed several root causes. These included the lack of incentives to produce less profitable drugs, lack of rewards for manufacturers with mature quality management systems, and logistical and regulatory hurdles to market recovery following a disruption.<sup>114</sup>



**FIGURE 9:** ACTIONS TAKEN TO ADDRESS SUSTAINABLE SUPPLY BY LARGE RESEARCH-BASED BIOPHARMACEUTICAL AND GENERICS COMPANIES (TOTAL: 15) (API = active pharmaceutical ingredient)

Forty-seven percent of survey respondents reported disruptions in their AMR-relevant product supply during the reporting period. Common challenges cited by companies included the

fragile and opaque nature of supply chains, supplier delays due to capacity and operational constraints, lack of predictable demand for AMR-relevant products, and market failures that result in the lack of specific active pharmaceutical ingredient (API) suppliers. All of these challenges can lead to downstream impacts, causing stock-outs and leading to restricted access to a range of antimicrobials.

The life sciences industry has adopted a number of mechanisms to help prevent drug shortages. These include working with relevant stakeholders, such as governments and national and international agencies, to align supply and demand forecasting and prevent or minimize stock-outs. Companies have also improved their ability to respond to stock-outs by introducing faster, more precise, and less expensive manufacturing approaches, and standardizing the volume of product packs to simplify manufacture and distribution to areas facing drug shortages.

All generics and large research-based biopharmaceutical companies reported working closely with vendors and relevant authorities to address challenges in their supply chains. Mitigating actions focused on diversifying their supplier base, building operational capacity, and ensuring buffer stocks of antimicrobials and vaccines. Alliance members reported the following strategies to maintain a steady product supply:

**Establishing robust quality systems and controls:** Companies worked with relevant health and regulatory authorities, such as the U.S. FDA Office of Drug Shortages, as well as suppliers to address quality issues in manufacturing processes.

**Improving supply chain resilience:** In partnership with strategic suppliers, companies are introducing integrated risk management processes, performance monitoring, and improved vendor agreements.

**Implementing risk mitigation strategies:** Common approaches include holding safety stock, dual sourcing,<sup>xix</sup> prioritizing manufacture of certain products, increasing or shifting plant production, increasing inventory levels for key materials, and assessing alternative suppliers.

**Allocating medicines based on critical need:** Companies are improving allocation based on factors such as unmet medical need, urgency, and local availability of substitutes.

**Assessing demand:** Members collect and analyze surveillance data to identify resistance trends that generate increased demand for certain products.

<sup>xix</sup> Dual sourcing is the supply chain management practice of using two suppliers for a given component, raw material, product, or service.

## ANTIBIOTIC SHORTAGES CAN INCREASE COSTS AND DRIVE RESISTANCE

Pip/Tazo is an antibiotic widely used by hospitals to treat conditions such as cystic fibrosis, pneumonia, urinary tract infections, and neutropenic sepsis. From April to July 2017, the U.K. experienced a significant national shortage of Pip/Tazo due to supply chain disruptions.<sup>115</sup> The Department of Health advised hospitals to restrict its use to severe cases of sepsis and ventilator-associated pneumonia, and to shift treatment toward combination therapy, including the use of meropenem, a last line of defense antibiotic. This led to increases in total antibiotic consumption and related costs<sup>116</sup> and could increase resistance pressure on later line antibiotics.

## THE ALLIANCE IN ACTION: SANDOZ DRIVES REMEDIATION PROGRAM TO HELP MAINTAIN GLOBAL SUPPLIES OF CRITICAL ANTIBIOTIC

Retarpen, or benzathine benzylpenicillin G (BPG), is a WHO-approved essential medicine. It is the only recommended treatment to prevent mother-to-child transmission of syphilis, and it is a first line medication for rheumatic heart disease. A single dose of low-cost BPG ends the syphilis infection risk in adults with no documented risk of antibiotic resistance. Globally, more women who are pregnant suffer from syphilis than from HIV, resulting in over 500,000 adverse pregnancy outcomes annually.

However, a study carried out by WHO a few years ago showed that this commonly prescribed essential antibiotic, which has a typical average cost of just below US2 per vial, was unavailable in 39 out of 114 countries,<sup>117</sup> potentially putting millions of lives at risk. Global supplies of the API for this critical medicine are limited to a handful of suppliers, all based in China.

Sandoz, which has been supplying BPG to many markets worldwide for the past 30 years, faced severe quality issues with its existing API supplier, resulting in repeated stock-outs. Despite high levels of investment required to remediate the situation, and an economically poor business case, Sandoz recognized the high medical need for this critical product and committed to remediating its Retarpen supply situation by 2020. The remediation work is currently proceeding according to plan. While it is difficult to make exact impact forecasts, WHO prequalification should help to ensure that the Sandoz “relaunch” drives global access to this essential medicine.

## THE ALLIANCE IN ACTION: MYLAN ENSURES CONTINUOUS SUPPLY OF ANTIBIOTICS

Mylan's global supply chain has been strategically designed to ensure that patients have access to the right antibiotics at the right time, in all 75 countries where it supplies antibiotics and antifungals. Continuity is an important facet of access in the context of AMR; access to the best antibiotic for a given patient helps to slow the development of resistance. The ability to make or obtain quality raw materials consistently and at reasonable prices is crucial to Mylan's goal of maximizing access to the finished medicines that patients need to maintain their health. Forward-looking systems allow Mylan to see potential supply gaps in the future and take action.

Mylan has robust due diligence, source selection, and risk mitigation processes to better understand supplier capabilities, choose the right supplier(s), and mitigate supply risks. To maintain continuous supply, commercial and supply chain teams connect to review patient requirements and sales forecasts, using a 24-month horizon to meet both the forecast and safety stock requirements to buffer against any potential fluctuations in demand or supply. These forecasts are discussed with each external stakeholder in daily, weekly, and monthly Operational Meetings and Supplier Reviews with a focus on supply continuity. The team then monitors performance through reporting, trend analysis, and consistent business review meetings.

Safety stock and strategic stock further support continuity of supply, among other risk mitigation strategies used by Mylan. In the case of unavoidable supply disruption, a formal allocation process ensures that available medicines are allocated based on critical need.

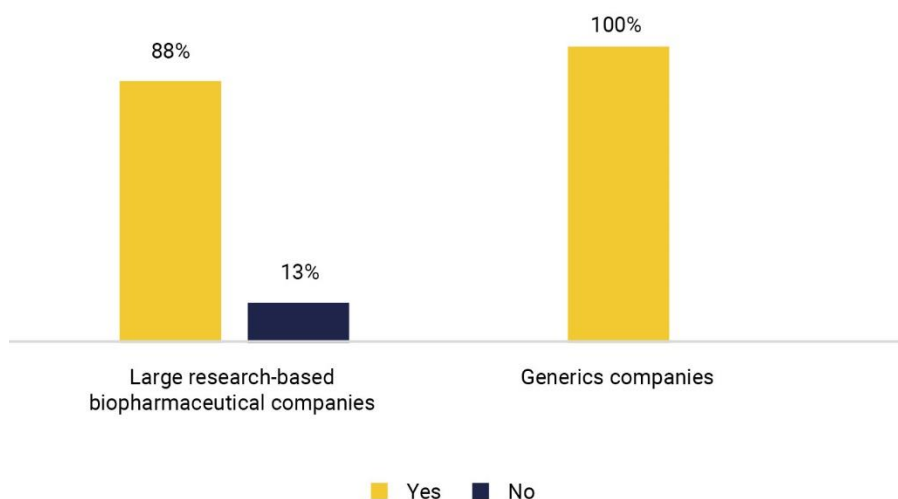
## PFIZER HELPS DELIVER MEDICAL PRODUCTS BY DRONE IN GHANA

Alliance members' efforts to improve patient access include harnessing the latest transport technologies. For example, Pfizer and Zipline, a medical product delivery company, are collaborating with the government of Ghana on a medical drone delivery system for remote rural areas. With additional support from Zipline's partners the Bill & Melinda Gates Foundation, Gavi, and UPS Foundation, the drones deliver nearly 150 essential medical products—including blood, emergency and routine vaccines, and emergency and essential medicines. The program reaches an estimated 2,000 to 2,500 health facilities and 15 million citizens. Pfizer and its partners also aim to collect and leverage real-time data to increase supply chain efficiencies and strengthen Ghana's healthcare system.

## COMBATING SUBSTANDARD AND FALSIFIED PRODUCTS

According to WHO, antibiotics are among the most commonly reported substandard and falsified medical products.<sup>118</sup> Exposing patients to suboptimal doses fuels the evolution of resistance. The growing need for costly second and third line antimicrobial products to counter resistant infections further spurs the underground market of substandard and falsified products, creating a vicious cycle.<sup>119</sup>

This damaging trade in illegal medicines is a global challenge that requires cross-sectoral solutions, stronger partnerships, and wider education of patients and providers. Regulators and local healthcare authorities have a key role to play in ensuring effective oversight and regulation compliance in the supply chain as well as in hospitals and healthcare facilities where treatments are administered.<sup>120</sup> The life sciences industry actively works to reduce the prevalence of substandard and falsified AMR-relevant products and platforms. Eight in 10 relevant responding companies have adopted measures to help reduce the prevalence of substandard and falsified medicines, including all generics manufacturers.



**FIGURE 10:** LARGE RESEARCH-BASED BIOPHARMACEUTICAL AND GENERICS COMPANIES WITH MEASURES IN PLACE TO REDUCE THE PREVALENCE OF FALSIFIED AND SUBSTANDARD MEDICINES (%). (TOTAL: 15)

Examples of member activities underway include:

**Enhancing product safety through packaging and serialization:** Several companies are investing in packaging improvements such as tamper-proof features and in information technology aligned with serialization processes<sup>xx</sup> to check the authenticity of antibiotics.

**Raising awareness:** Members work with the healthcare community and law enforcement agencies worldwide to raise awareness of the antibiotic counterfeiting problem. Fight the Fakes, one such initiative, highlights the human cost of falsified medicines.

**Monitoring across product value chains:** Large research-based biopharmaceutical companies reported working with wholesalers, pharmacies, customs offices, and law

<sup>xx</sup> Serialization is a system used to track and trace the passage of prescription drugs through the entire supply chain, from manufacturing site to patient.

enforcement agencies to increase inspection coverage, monitor distribution channels, and improve surveillance of distributors and repackagers.

**Establishing counterfeit management teams:** Companies are creating specialized management committees to monitor, report, and help prevent cases of counterfeit products. These committees typically include quality, medical, legal, and communications personnel. These internal teams also network with external stakeholders such as WHO and national regulators or health agencies.

#### MERCK KGaA MOBILE LAB DETECTS COUNTERFEIT MEDICINES WORLDWIDE

Merck funds the non-profit Global Pharma Health Fund (GPHF), which combats the spread of counterfeit medicines using trademark GPHF-Minilab™ technology. The mobile minilaboratory delivers rapid drug-quality verification and counterfeit medicines detection, providing low- and middle-income countries with a simple, low-cost screening method. Provided as a self-contained kit, the Minilab can verify 23 antimicrobials. Through 2018, GPHF supplied more than 800 sets to 97 countries.

## NEXT STEPS

### ACCESS

- Encourage Alliance members to incorporate access to antimicrobials into R&D plans and increase transparency by making these access plans public.
- Increase Alliance membership to cover a greater proportion of the global supply of antimicrobials, with a particular focus on generic companies.
- Collaborate with local health authorities and policy makers to explore and support initiatives that will strengthen the long-term sustainability of the antimicrobial product market, improve supply chain security and continuity, and reduce drug shortages for AMR-relevant products. Initiatives could include improvements to contracting practices and incentives for investing in responsible manufacturing and continuity of supply.
- Work in partnership with local governments and funding agencies to strengthen local healthcare and laboratory capabilities to support effective diagnosis and treatment of drug-resistant infections.
- Promote timely access to less expensive generic antibiotics through voluntary licensing agreements, particularly in LMICs, where there are systems in place to ensure appropriate use. Partner with funders and public health agencies to strengthen health system capacity.
- Partner with governments and NGOs to strengthen and expand programs that clear regulatory burdens that may otherwise reduce broad global registrations of critical antimicrobials. Pilot new payment and reimbursement mechanisms that enable appropriate patient access to antimicrobials.



# APPROPRIATE USE

## THE ALLIANCE'S APPROPRIATE USE COMMITMENTS

- Contribute to slowing the emergence of resistance by preventing infections. This will be accomplished by promoting vaccination and reducing inappropriate use of antibiotics through expanded use of diagnostics.
- Support appropriate use of antibiotics by working closely with other partners on awareness campaigns, continued education for healthcare professionals, and generation of evidence to support appropriate use and stewardship.
- Collect and share surveillance data with public health bodies and healthcare professionals to improve understanding of resistance trends, monitor the effectiveness of antibiotics, inform appropriate antibiotic and vaccine use, and develop adapted infection control strategies.
- Align any promotional activities for antibiotics with the goal of advancing stewardship.

While the evolution of antimicrobial resistance is a natural and inevitable process, the inappropriate use of antimicrobials in both people and animals accelerates the development and spread of antimicrobial resistance (AMR). Recognizing this challenge, one of the five strategic pillars of the World Health Organization (WHO) Global Action Plan on Antimicrobial Resistance is to “optimize the use of antimicrobial agents”, while other aspects of appropriate use, including awareness of AMR, surveillance, and increased use of vaccines and diagnostics, are integrated into the other strategic pillars.<sup>121</sup>

Many stakeholders have a role in ensuring antimicrobials are used appropriately, including the life sciences industry. Members of the Alliance have reviewed their capabilities and have made the above commitments to support the appropriate use of antimicrobials consistent with their role. In these efforts, the Alliance supports WHO’s efforts to prioritize optimal use in order to slow the emergence of resistance and prolong the effectiveness of existing antimicrobials.

**88%** of companies collecting surveillance data share them externally

**76%** of relevant companies have formal appropriate use and stewardship strategies

## APPROPRIATE USE DEFINED

Consistent with the definition used by other key stakeholders such as the U.S. Centers for Disease Control and Prevention (CDC)<sup>122</sup> and WHO,<sup>123</sup> the Alliance defines appropriate use of antimicrobials as: “The right patient receiving the right drug at the right dose in the right formulation at the right time for the right duration for the right pathogen and site of infection.” The progress report addresses the different ways that Alliance members are working to ensure patients receive appropriate antimicrobial therapy.

## STAKEHOLDER COMMENTARY

All over the world, the overuse and misuse of antibiotics are rapidly accelerating the pace at which antimicrobial resistance develops and spreads. Although there is increasing awareness of AMR and the need to responsibly use antibiotics, the drivers of inappropriate use are complex. For example, even in countries where diagnostic tools are readily available to help physicians make the right prescribing choice, they are often underused.

Appropriate antibiotic use is a key priority for WHO and a critical element of AMR national action plans. There is an urgent need to preserve existing (and new) antibiotics by developing and implementing more robust user guidelines; this in turn depends on broader access to, and use of, diagnostics and surveillance tools. Donors and governments will need to provide greater support in appropriate prescribing practices in countries, communities, and hospitals, with particular emphasis on making the right tools available and accessible in low-resource settings.

The life sciences industry, including many AMR Alliance members, collects and uses surveillance data to identify and better understand resistance patterns for a number of pathogens. Companies share this information through diverse mechanisms, including peer-reviewed articles, conference abstracts, and, in a few cases, direct access to the data. The private sector should expand these efforts and explore potential partnerships, including with governments, to improve data transparency.

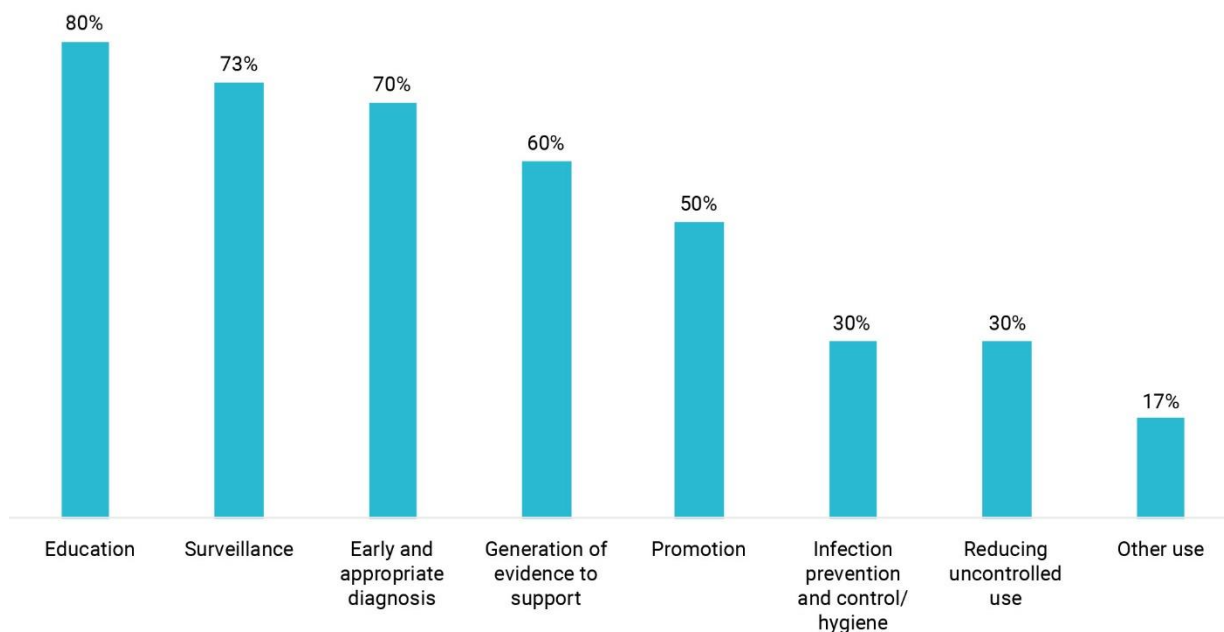
*Cecilia Ferreyra, AMR Medical Officer, FIND (Foundation for Innovative New Diagnostics), Geneva, Switzerland*

## PLANS AND ACTIVITIES TO SUPPORT APPROPRIATE USE AND IMPROVE PATIENT OUTCOMES

A key commitment made by Alliance members is to reduce the spread of AMR by promoting appropriate use of antimicrobials in patients who need them. Alliance members are investing in a variety of programs to support stewardship and appropriate use.

Among relevant companies, including large research-based biopharmaceutical, generics, and biotechnology companies, 76% have developed a formal appropriate use and stewardship plan.<sup>xxi</sup> These plans describe how Alliance members across all sectors are engaged in a wide variety of appropriate use and stewardship activities, as shown in Figure 11. To illustrate these programs, we provide case studies from Alliance members throughout this chapter.

<sup>xxi</sup> This percentage excludes companies who reported that appropriate use and stewardship plans were not relevant to their particular circumstances—for example, because they did not have commercialized products on the market.



**FIGURE 11:** APPROPRIATE USE AND STEWARDSHIP ACTIVITIES ENGAGED IN BY COMPANIES (TOTAL: 30 COMPANIES ENGAGED IN APPROPRIATE USE ACTIVITIES)

The survey findings may reveal some changes in focus since the 2018 progress report. An encouraging finding is that a greater proportion of members are pursuing educational outreach (an increase from 63% to 80% of plans in the past 2 years), surveillance activities (an increase from 63% to 73% of plans in the past 2 years), and reducing uncontrolled use (an increase from 13% to 30% of plans in the past 2 years). Four companies that develop vaccines also incorporate prevention through vaccination programs into their appropriate use strategies.

Half of the companies with an appropriate use and stewardship plan reported measuring the outcomes and/or impact of these activities. Greater industry efforts in this area will be essential to improving interventions and encouraging wider adoption of best practices.

#### EXAMPLES OF INDUSTRY ACTIVITY TO SUPPORT APPROPRIATE USE

**Developing non-antibiotic products or pathogen-specific therapeutics:** As highlighted in the Research & Science section, many Alliance biotechnology companies are developing non-antibiotic products or pathogen-specific treatments. These products can be more focused and reduce the collateral damage to the microbiome caused by broad-spectrum antibiotics, including recurrent *Clostridioides difficile* infections. For example, Peptilogics, an Alliance member, is developing a treatment for prosthetic joint infections that shows promise in reducing routine antibiotic use, shortening patient recovery time, and improving health outcomes.

**Educating physicians on antimicrobials prescriptions:** Many Alliance members conduct in-person and online training, often with partners. For example, Pfizer, the British Society for Antimicrobial Chemotherapy, and the University of Dundee launched a free Massive Open Online Course on safe antimicrobials use in everyday practice. Through February 2019, more than 50,000 healthcare professionals had registered.

**Rolling out vaccination programs:** Alliance members reported several collaborations with non-governmental organizations (NGOs), healthcare providers, and public-private

partnerships such as Gavi, the Vaccine Alliance, to protect vulnerable populations against diseases that may require antibiotic treatment. They also provide vaccines for non-bacterial infections for which antibiotics can be misprescribed. GSK has committed to provide Gavi with more than 850 million vaccine doses at a reduced price by 2024 to help protect some 300 million children. Pfizer, in partnership with Gavi, provided 400 million doses of its pneumococcal vaccine to protect children in 50 countries through March 2019.

**Raising patient awareness:** Alliance members engage in non-product-related activities to promote antimicrobial stewardship (AMS) to patients, healthcare providers, and health policy specialists (see “Strengthening Stewardship Through Education” section in this chapter).

**Promoting the value and impact of diagnostics:** Alliance diagnostics members are working to ensure that the value and impact of diagnostics in promoting antimicrobial stewardship is better understood. For example, Alliance member Qiagen has begun requesting that all of its investigator-initiated studies involving the use of its point-of-care diagnostics for infectious diseases include a measure of impact on antimicrobial stewardship. This helps to expand the evidence base on the effectiveness of diagnostics, which can in turn be used to better inform healthcare providers, academia, and policymakers/regulators.

**Funding AMS quality improvement projects:** Companies reported funding programs to improve global and regional AMS efforts and outcomes. A range of Alliance members also partner with healthcare systems in low- and middle-income countries, and fund research projects to improve and share best practices to support AMS programs. In Latin America, MSD has partnered with CIDEIM, an independent, non-profit microbiology/infectious disease research institute, to establish an AMS Center of Excellence, providing training, guidance, and support to hospitals across the region. MSD has supported the development of several AMS Centers of Excellence around the world to build up a global network to conduct AMS training and education.

## THE ALLIANCE IN ACTION: MSD BUILDING STEWARDSHIP INTO EVERY STEP OF ANTIBIOTIC DEVELOPMENT

In recent years, regulatory agencies have implemented reforms to facilitate the development of novel antibiotics, including the acceptance of smaller clinical datasets. While this has helped to bring antibiotics to market quickly, it has also meant that health care providers may not have the data they need to prescribe novel antibiotics appropriately or to determine how they should fit within an antibiotic stewardship program.

MSD considers access and stewardship early in the R&D process and builds them into product-specific plans for all antibiotics in clinical development. These product-specific plans ensure relevant data are generated to support access and appropriate use.

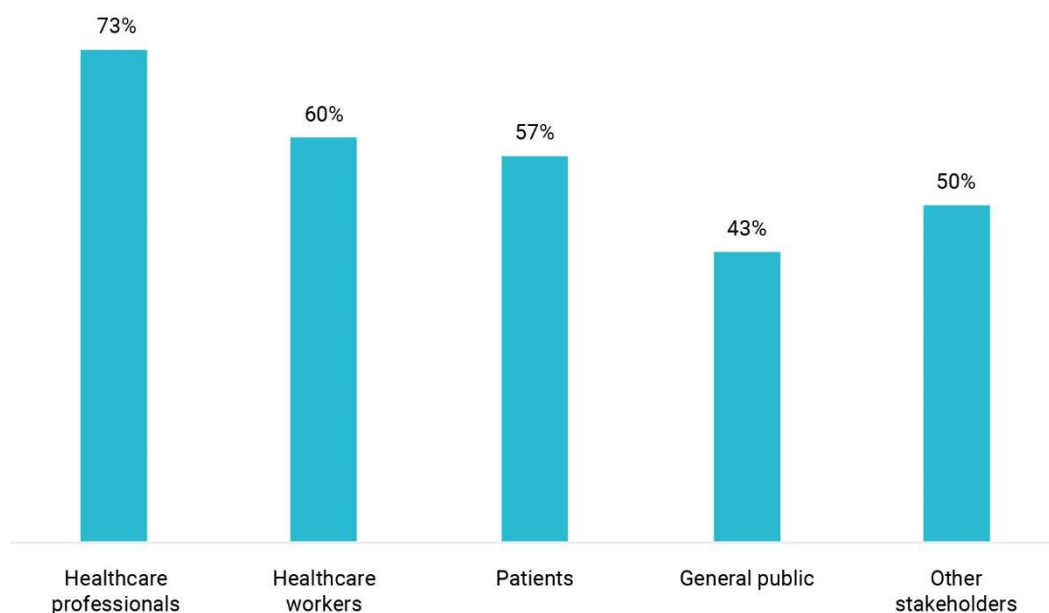
For example, while most novel antibiotics are brought to market based on small urinary tract infection studies, MSD conducted several additional large antibiotic clinical trials for the treatment of hospital-acquired bacterial pneumonia and ventilator-acquired bacterial pneumonia—a critical unmet health need causing significant mortality. The results from MSD’s complex pneumonia trials provide valuable information to

prescribers on how to use these products appropriately. The study populations for these trials also included challenging patients who reflected the population where the products will be used.

MSD continues to generate real-world evidence and support investigator-initiated studies to inform the use of novel agents. These are shared with the scientific community through peer-reviewed publications. For CUBICIN® (daptomycin), MSD has pursued additional post-approval indications for unmet needs and developed both pediatric and more stable and easier-to-use formulations. MSD considers global regulatory requirements when designing clinical trials in order to facilitate broad registration of its antibiotics.

## STRENGTHENING STEWARDSHIP THROUGH EDUCATION

Strengthening stewardship through education with different stakeholders is a key focus for many Alliance members. Alliance member programs across the large research-based biopharmaceutical, generics, and diagnostics sectors include non-promotional activities that aim to increase the understanding of antimicrobial resistance and the importance of the appropriate use of AMR-related products (see Figure 12).



**FIGURE 12:** STAKEHOLDERS ENGAGED BY ALLIANCE MEMBERS THROUGH EDUCATION INITIATIVES (TOTAL: 30 COMPANIES)

Most Alliance members have engaged healthcare practitioners and workers through stewardship education activities, given that these groups are most directly engaged in antimicrobial prescribing and administration efforts. Educational activities also reach other relevant stakeholders, including patients and the general public, although direct engagement is less common with these groups.

Examples of programs to promote stewardship include messaging in drug packaging to encourage patients to complete antimicrobial courses; distributing materials in hospitals, in

schools, and at conferences; and developing non-branded materials that explain AMR risks and key stewardship principles. Alliance members also work in partnership with other stakeholders such as NGOs and global health organizations on the crucial task of raising global public awareness of AMR and the importance of using antimicrobials as prescribed. Some companies are using social media to creatively convey the message (see case study on GSK's Chatbot).

More can be done to increase awareness and understanding of stewardship. While many Alliance members actively support these education efforts, awareness of AMR clearly remains low. Recent assessments of knowledge of AMR in Europe<sup>124</sup> and the U.S.<sup>125</sup> illustrate that opportunities for improvement remain.

Alliance members have adopted strategies to mitigate potential conflicts of interest that may arise in engagements with healthcare providers and other stakeholders. These are aligned with WHO and other guidelines, including those issued by trade associations (e.g., IFPMA, EFPIA, PhRMA, and ABPI), that are related to ethical promotion. Alliance members partner with NGOs, educational organizations, or independent experts, to develop educational content. Alliance members also provided examples of rigorous internal controls, including the removal of product branding and refraining from the use of financial or other incentives to promote participation in AMR-related engagements.

While companies also employ legal, compliance, and quality reviews to ensure high-standard educational materials, less than half (47%) of responding companies subject their educational materials for stewardship activities to peer review. This may be a key area for improvement.

#### THE ALLIANCE IN ACTION: GSK LAUNCHES PATIENT-FRIENDLY AMR CHATBOT

Medzy, shorthand for “medication made easy,” is a digital ChatBot created by GSK to improve patient adherence to antibiotic therapy. Medzy is being piloted in the United Arab Emirates (UAE).

Survey evidence suggests that more than half of the residents (54%) in the Gulf Cooperation Council, of which UAE is a part, find it difficult to remember to take antibiotics, and 30% believe they should stop taking antibiotics once they feel better.

The ChatBot can be accessed via a code, which takes patients to the Facebook messenger platform, one of the most commonly used social media platforms. Within a year of its 2019 launch, GSK expects Medzy to reach 4,000 unique users. If the pilot is successful, GSK plans to expand the ChatBot to other regions with an unmet need for its service.

## THE ALLIANCE IN ACTION: CENTRIENT AND CIPLA COMBAT IRRATIONAL ANTIBIOTIC USE IN CHINA AND INDIA

Inappropriate and overuse of antibiotics in the world's two most populous countries pose a danger to their populations.

In China, where consumption of antimicrobials is trending downward, irrational use remains a key challenge, driving antibiotic resistance and the potential for superbugs. In response, generics manufacturer Centrient Pharmaceuticals is partnering with the China Association of Health Promotion and Education to educate doctors and patients on appropriate use and national prescription guidelines.

Adapting the WHO AWaRe tool, which classifies antibiotics for use, the initiative seeks in particular to curb unnecessary use of higher generation antibiotics. Launched in July 2019, the year-long campaign will cover 70 hospitals in 15 provinces and cities as well as trainings at doctors' conferences.

In India—one of the largest consumers of antibiotics—a combination of irrational usage and lack of information is driving the spread of AMR. Estimates suggest a business-as-usual scenario may result in 2 million AMR-related deaths in India by 2050.<sup>126</sup>

To help avoid this crisis, Cipla delivers educational programs for its most commonly prescribed antibacterial drugs—fosfomycin, azithromycin, and colistin. The generics company, headquartered in Mumbai, targets materials and presentations to healthcare practitioners and patients. Key topics include susceptibility patterns in hospitals and intensive care units and how to manage multiple drug-resistant infections.

## THE ALLIANCE IN ACTION: PFIZER INVESTS IN REGIONAL STEWARDSHIP

In 2018-2019 Pfizer invested US\$3.8M in a new Stewardship Request for Grant program to support education efforts for healthcare professionals and the public in regions with limited resources.

Six projects in Asia-Pacific were awarded 2-year grants under the independent program, launched in collaboration with the Joint Commission, a non-profit organization that accredits global health care organizations. These will help hospitals, healthcare systems, and government agencies generate relevant data, establish stewardship initiatives, and evaluate interventions for clinical impact.

A second, similar partnership, with the International Society for Infectious Diseases, is now reviewing grants from Latin American countries. Pfizer Independent Grants for Learning and Change and Pfizer Medical Affairs took part in both selection processes. Criteria included:

- Portability: Other hospitals/regions can benefit from data
- Innovation: New tools, methods, and plans to improve antimicrobial usage

- Sustainability: Builds local ability on AMR stewardship after grant ends
- Probability: Actual impact on healthcare and antimicrobial resistance

In addition, Pfizer operates an annual global AMR stewardship grant program.

## ENSURING PROMOTIONAL ACTIVITIES ARE ALIGNED WITH STEWARDSHIP

Although pharmaceutical promotion provides valuable information to healthcare providers, it must be done in a way that supports appropriate use of antimicrobials. Eighty percent of Alliance members across the large research-based biopharmaceutical, generics, and diagnostics sectors reported taking measures to align promotional activities with the goal of advancing stewardship. In the 2018 progress report, 70% of respondents had either reviewed their promotional activities against this goal, or intended to do so within 2 years.

Companies reported adapting product promotion activities in the following ways to advance antimicrobial stewardship:

- Including AMR-related educational materials, workshops, campaigns, and in-house training for healthcare professionals in relevant product promotion activity;
- Sharing risk and benefit assessments of relevant products with regards to antimicrobial resistance and appropriate use with healthcare professionals;
- Evaluating promotional materials against WHO, CDC, and other guidelines; and
- Reviewing sales representatives' incentive schemes, for example, by removing volume-based financial incentives for antimicrobial sales teams.

## SHARING INDUSTRY SURVEILLANCE DATA HELPS TRACK DRUG RESISTANCE

Collecting surveillance data on drug resistance trends, and sharing it with public health bodies and healthcare professionals, underpins an evidence-based global response to AMR. Many Alliance members support, and in many cases contribute to, global AMR surveillance efforts.

Effective AMR surveillance enables stakeholders to assess trends in resistance on the global, regional, national, and hospital levels. For drug and diagnostic developers, surveillance data serve the additional purpose of providing early indicators of future unmet medical needs. This, in turn, can guide research efforts to develop new products to address growing resistance to antimicrobial products.

WHO's Global Antimicrobial Resistance Surveillance System<sup>127</sup>, outlines the benefits of effective AMR surveillance, enabling stakeholders to:

- Foster national surveillance systems and harmonized global standards,

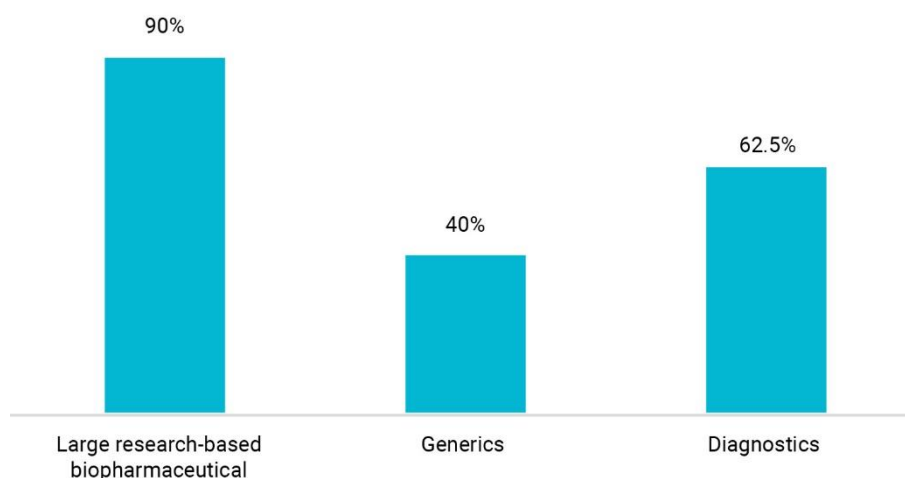


- Estimate the extent and burden of AMR globally by selected indicators;,
- Analyze and report global data on AMR on a regular basis,
- Detect emerging resistance and its international spread,
- Inform implementation of targeted prevention and control programs; and
- Assess the impact of interventions.

Different sectors of the Alliance contribute to surveillance in various ways, as illustrated in Figure 13. Biotechnology companies are excluded from this section as they are consumers, not generators, of surveillance data while they focus on developing new products.

Large research-based biopharmaceutical and generics companies conduct surveillance to monitor resistance patterns and trends over time to inform public health practice. Pfizer’s Antimicrobial Testing Leadership and Surveillance (ATLAS) database—one of the world’s largest AMR surveillance programs—is a fully searchable, interactive website with a mobile application enabling easy and rapid access. It provides physicians and the global health community with free access to data on bacterial sensitivity to various antibiotics and emerging resistance patterns in more than 75 countries. Source information is collected from more than 800 sites, with data encompassing more than 670,000 isolates. Resistance trends, along with other data, provide physicians and healthcare practitioners with information that can inform their work to address AMR in their hospital or region.

Diagnostics companies, as manufacturers of the systems and tools that generate resistance data, may participate in surveillance efforts by supporting independent programs or allowing their customers to more easily report surveillance results. BioMérieux funds the Global Point Prevalence Survey of Antimicrobial Consumption and Resistance, which collects global data on hospitalized patients. Goals include monitoring rates of antimicrobial prescribing and resistant bugs in hospitals; benchmarking among hospitals, countries, and regions; identifying targets to improve the quality of antimicrobial prescribing; designing and assessing hospital interventions to improve stewardship; and increasing public health capacity.



**FIGURE 13:** COMPANIES COLLECTING SURVEILLANCE DATA (TOTAL: 23 COMPANIES).

Among Alliance companies that collect surveillance data, 88% share them externally. Avenues include publication in peer-reviewed medical journals and presentations at medical conferences. Members also share data directly with healthcare practitioners, healthcare authorities, and researchers to inform decisions on appropriate patient treatment and strategies.

#### THE ALLIANCE IN ACTION: MSD SURVEILLANCE DATA SUPPORTS DEVELOPMENT OF RAPID DIAGNOSTICS

Early and appropriate antibiotic therapy can have a large impact on outcomes for critically ill patients with resistant infections. Yet, in many cases, no rapid diagnostics currently exist to detect resistance to novel antibiotics.

To help bridge this gap, MSD is harnessing data from its Study for Monitoring Antimicrobial Resistance Trends (SMART), one of the largest AMR surveillance programs. SMART enables researchers to monitor susceptibility of Gram-negative bacteria to 12 common antibiotics and identify resistance trends. Since 2002, the program has collected approximately 500,000 bacterial isolates from 217 sites in 63 countries.

MSD is working with OpGen, a precision medicine company specializing in molecular diagnostics and informatics, to turn these data into actionable strategies to treat AMR infections. Through access to the SMART isolates, OpGen is developing new rapid diagnostics that can predict pathogen susceptibility and improve patient outcomes.

#### THE ALLIANCE IN ACTION: ANTIBIOTIC ADJUVANT'S ELECTRONIC TOOL REDUCES ANTIBIOTIC MISUSE IN THE LONG-TERM CARE SECTOR

According to the U.S. CDC, up to 75% of antibiotic prescriptions in American nursing homes are given inappropriately or incorrectly, spurring resistance. To counter this trend, biotechnology company Antibiotic Adjuvant developed SmartSteward, an electronic tool designed to lower medication misuse and overuse through automated infection control and antibiotic stewardship.

The software provides real-time surveillance for possible outbreaks at long-term care facilities, and a decision support system to help physicians optimize antibiotic prescriptions. The tools also take into account physician feedback and real-time infection control reports and provide staff education.

Developed in collaboration with two skilled nursing facilities, SmartSteward is generating early results. One pilot facility saw a 59% decrease in infection rates, a 42% reduction in antibiotic starts, and an increase in sensitivity to Cefazolin, used to treat a wide variety of bacterial infections, from 58% to 100%.

## DEPLOYING DIAGNOSTICS FOR APPROPRIATE USE

Accurate diagnosis of infection is crucial to ensuring that the right patient receives the right drug for the right pathogen at the right time. This means knowing what pathogen is causing

the infection (identification), determining the best way to treat it (susceptibility), and doing so in the fastest possible time. Diagnostic tools are crucial to getting both identification and susceptibility testing done accurately and quickly, ensuring that the use of antimicrobials can achieve the best patient and public health outcomes, including reducing the incidence of sepsis and decreasing the inappropriate prescription of antimicrobials. Diagnostic results are also an integral part of supporting surveillance of drug-resistant infections by identifying emerging resistant infections and their transmission.

Diagnostic companies within the Alliance are at the forefront of these efforts. They develop and deploy tools for the diagnosis of infection around the world. They are engaged in the generation of evidence that supports diagnostics' clinical utility and the economic and medical value of their use, including in the improved use of antimicrobials.

Other Alliance member companies are also involved in activities related to diagnosis. Alliance members report partnering with diagnostics companies to support research and development of new tools and tests to support appropriate use.

#### THE ALLIANCE IN ACTION: MOBIDIAG'S FAST SCREENING TEST IDENTIFIES RESISTANT BACTERIA, ASSESSES PATIENT CONDITION

Carbapenemase-Producing *Enterobacteriaceae* are responsible for a wide range of common medical conditions, including urinary tract infections, diarrhea, peritonitis, and bloodstream infections. They are also extremely resistant to the carbapenem class of antibiotics often used for high-risk and multidrug-resistant bacterial infections. To implement proper infection control measures in hospitals, simple, rapid, and accurate methods are needed to detect all carbapenemase producers and differentiate between them and other bacteria.

Global diagnostics company Mobidiag is offering in Europe a fast screening assay that can rapidly and automatically identify clinically relevant carbapenemase resistance and assess the patient's condition. The goal is to enable healthcare providers to act quickly to reduce the risk of infection spread in hospitals, and avoid related costs such as unnecessary bed days in isolation. The assay will be substitutable for slower and more labor-intensive culture-based tests as well as an adjunct to antimicrobial resistance testing.

## VACCINES SUPPORT APPROPRIATE USE

The successful development of new vaccines and achievement of universal vaccination will be important milestones in curbing AMR. Vaccines offer the potential for sustained protection against life-threatening infections and their associated consequences. By helping to prevent infections in the first place, vaccines can reduce the need for antibiotic prescriptions and help prevent potential overuse of common antibiotics—which may result in resistant strains.<sup>128</sup> This in turn helps prolong the effectiveness of antimicrobials when they need to be used to treat infections.<sup>129</sup>

Research has demonstrated the positive role some existing vaccines already play.<sup>130</sup> Nearly all individuals with a healthy immune system may develop resistance to the pathogen for which a vaccine is given.<sup>131</sup> Vaccines can preemptively reduce the burden of infectious diseases and reduce the prevalence of resistance by reducing antibiotic use.<sup>132</sup>

Vaccination can play multiple roles in antimicrobial stewardship strategies, including:

- Reducing the use of antibiotics by preventing bacterial infections, including those that may carry resistance;
- Reducing the use of antibiotics by preventing viral diseases that lead to secondary bacterial infections requiring antibiotic treatment;
- Reducing the use of antibiotics by preventing viral diseases for which antibiotics are inappropriately prescribed; and
- Preventing antimicrobial-resistant infections from spreading.

Moving forward, the impact of vaccinations on AMR is likely to be highest for diseases with a high burden, such as TB or typhoid, where antibiotics are the primary treatment employed by physicians and where resistance is high and increasing.

## RESPONSIBLE ANIMAL USE

The AMR Industry Alliance recognizes the importance of improving antibiotic use in animals. In some countries, an estimated 80% of medically important antibiotics are used in the animal sector.<sup>133</sup> The Alliance is focused on human health, but encourages members with animal health portfolios to align to the Antibiotic Commitments<sup>134</sup> issued by Health for Animals, the global animal health industry association. This framework is supported by organizations representing more than 200 companies and 700,000 veterinarians worldwide.

Six Alliance members reported developing or commercializing products licensed for animal use. These companies span the large research-based biopharmaceutical, generics, and diagnostics sectors, and are promoting responsible and judicious antimicrobial use in animals by:

- Setting corporate policies on animal welfare, which can include the appropriate use of antibiotics in animals;
- Commercializing susceptibility tests for veterinary animal use;
- Developing vaccinations in line with a One Health approach<sup>xxii</sup> that can minimize the need for antibiotics;
- Partnering with farmers and veterinarians to promote vaccination and the appropriate use of antibiotics; and
- Collaborating with animal health and environmental organizations.

<sup>xxii</sup> An approach that recognizes the links among the health of humans, animals, and ecosystems, and involves applying coordinated, collaborative, cross-sectoral approaches to manage health risks, such as AMR.

## NEXT STEPS

### APPROPRIATE USE

- Continue to engage stakeholders, including the general public, to raise awareness on AMR and appropriate use. This includes scaling up educational activities and promoting the use of smarter prescription tools that are adapted to local contexts. It also includes providing timely and accurate microbiological data.
- Increase sharing of AMR surveillance data by Alliance members and support initiatives to increase public reporting of infection rates, antimicrobial resistance patterns, and antibiotic use.
- Encourage Alliance members to share best practice and align product-related promotional activities with the goal of supporting appropriate use.
- Strengthen external stakeholders' awareness of the critical role that diagnostics and vaccines have in supporting antimicrobial stewardship.
- Encourage Alliance members to engage in more activities for appropriate use, including increased work on IPC and WASH. This includes sharing best practices, for example, through independent educational webinars and research grants.

# MANUFACTURING

## THE ALLIANCE'S MANUFACTURING ENVIRONMENTAL COMMITMENTS

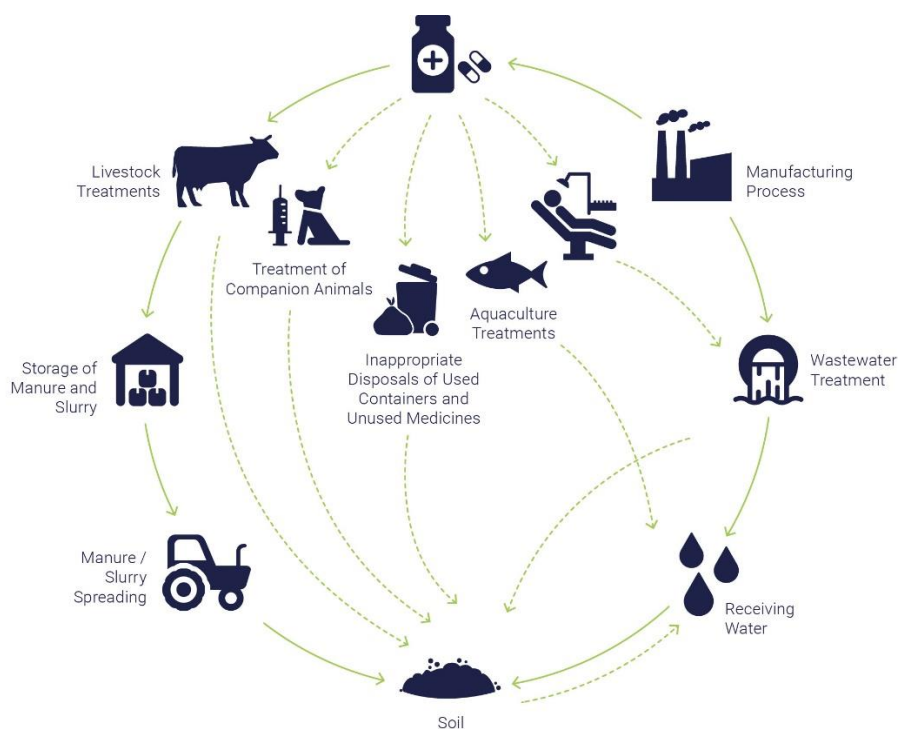
- Review Alliance members' own manufacturing and supply chains to assess good practice in controlling releases of antibiotics into the environment.
- Establish a common framework for managing antibiotic discharge, and start to apply it across their own manufacturing and supply chains by 2018.
- Work with stakeholders to develop a practical mechanism to transparently show that Alliance member supply chains meet the framework's standards.
- Work with independent technical experts to establish science-driven, risk-based targets for discharge concentrations of antibiotics and develop good practice methods to reduce environmental impacts of manufacturing discharges by 2020.

Antibiotics may enter the environment through several sources, including from agriculture, aquaculture, hospital effluent, and human and animal waste<sup>135</sup> (see Figure 14). Discharges from antibiotic manufacturing can be another source of environmental emissions, especially where discharges are not well controlled. The AMR Industry Alliance is firmly committed to minimizing antibiotic residues in manufacturing discharges, especially by improving environmental management systems and wastewater management.

To that end, all Alliance manufacturing members (see box) in the large research-based biopharmaceutical and generics sectors are acting on the AMR Industry Roadmap commitments related to antibiotic production. Together, these 18 companies represent around a third of global antibiotics sales.<sup>xxiii</sup>

Alliance member supply chains for producing antibiotics are global, with production performed in-house (at "owned sites") and through third-party manufacturers (at "supplier sites"). As such, Alliance members are well positioned to promote responsible antibiotic manufacturing throughout their supply chains, building on the baseline expectation of compliance with local environmental regulations and, in many cases, corporate environmental requirements.

<sup>xxiii</sup> Calculation based on 2018 sales data from IMS Padds. The data are based on sales in 67 countries, excluding India; they cover 300 molecules and concern antibiotics for human use only.



**FIGURE 14:** SOURCES OF ANTIMICROBIALS IN THE ENVIRONMENT. (ADAPTED FROM BOXALL, ALISTAIR B.A., ‘THE ENVIRONMENTAL SIDE EFFECTS OF MEDICATION’, EUROPEAN MOLECULAR BIOLOGY ORGANIZATION REPORTS, VOL. 5, NO. 12, 2004.)

Alliance members have made excellent progress in delivering against the manufacturing environmental commitments during the period of this report. In 2018 manufacturing members of the Alliance developed *The Common Antibiotic Manufacturing Framework* (“the framework”), for environmental management of antibiotic manufacturing. The framework offers companies a methodology for doing risk assessments, and sets out the minimum site requirements to meet environmental standards.

Together, manufacturing members of the Alliance are driving the framework’s implementation at both owned and supplier manufacturing sites. By June 2019, 83% of Alliance manufacturing members had assessed all of their owned sites against the framework. Other organizations have begun adopting the Alliance’s standards too. For example, Medicines for Europe, a trade association for European generics companies, has now made commitment to the framework and predicted no-effect concentration targets (described below) a condition of its membership.

In addition, manufacturing members of the Alliance shared scientific data to support the development of science-based targets for receiving waters impacted by antibiotic manufacturing for around 120 antibiotics. These targets, which are expressed as predicted no-effect concentrations (PNECs), were established two years ahead of schedule, in September 2018, and published in peer-reviewed literature. All relevant Alliance members are now committed to meeting these very low discharge targets over time across their supply chains.

## ALLIANCE MANUFACTURING MEMBERS

The following companies provided data for the manufacturing section:

- Aurobindo
- Boehringer Ingelheim
- Centrient Pharmaceuticals
- Cipla Ltd.
- F. Hoffmann-La Roche AG
- GlaxoSmithKline plc
- Johnson & Johnson
- Merck KGaA
- MSD
- Mylan
- NGB Laboratories
- Novartis
- Otsuka
- Pfizer Inc.
- Sanofi S.A.
- Shionogi & Co. Ltd.
- Sumitomo Dainippon Pharma
- Teva

This progress represents a major achievement by the Alliance in a short timeframe. The latest member survey also reveals a 40% increase in the number of manufacturers (particularly generics companies) committed to meeting the Alliance's environmental commitments (to reduce concentrations of antibiotics manufacturing waste discharges in alignment with the Common Antibiotic Manufacturing Framework and PNECs), with 100% of relevant companies reporting their performance, up from 77% in 2018.

**2 years ahead of schedule**, the Alliance published predicted no-effect concentrations (PNECs), which can be used to establish **discharge targets** for antibiotic manufacturing sites

**83%** of manufacturing company members have assessed all of their own antibiotics manufacturing sites against the Alliance's new manufacturing **framework**

**82%** of owned sites **meet the framework's requirements** wholly or in part

**56%** of products made at member-owned sites are expected to be made in accordance with discharge targets **within 3 years** and **88%** of member products are expected to be manufactured to discharge targets within a **7-year timeframe**

**24%** of products made at supplier sites are expected to be made in accordance with discharge targets **within 3 years** and a further **70%** of products made at supplier sites are expected to be made in accordance with these targets **within 4-7 years**



## STAKEHOLDER COMMENTARY

Antibiotic contamination of the natural environment is thought to contribute to the AMR crisis. Manufacturing makes up a small proportion of all antibiotic emissions to the environment but, where discharges are poorly controlled, can lead to high levels of active residues in the waters, soils, and sediments around antibiotic factories resulting in hotspots of AMR. Better management of manufacturing emissions is critical if we are going to curb the AMR problem.

The Alliance's manufacturing framework and discharge targets mark a significant step forward in reducing antibiotic impacts in the environment. These initiatives, developed considering current scientific understanding, are already having an impact: 34% of owned and supplier sites now meet or partially meet framework requirements; and production processes for 92% of products across all sites are expected to meet the discharge targets within the next seven years.

There is still work to do to ensure full adherence to the framework within this timeframe. Alliance members must continue to refine and update the framework and targets as new scientific knowledge becomes available; and should work to encourage non-member manufacturers to adopt the new standards.

*Alistair Boxall, Professor of Environmental Science, University of York, United Kingdom*

## ADVANCING THE MANUFACTURING FRAMEWORK

The Common Antibiotic Manufacturing Framework applies to all owned and supplier sites that produce antibiotic APIs and/or formulate them into medicines.<sup>xxiv</sup> Its minimum requirements cover five areas:

- Regulatory compliance
- Environment, health, and safety (EHS) management systems
- Training
- Waste and emissions
- Site audits

Responsible manufacturing plays an important role in reducing the potential environmental risk arising from antibiotic production. Poorly controlled discharges from the production of APIs and formulated medicines can generate environmental emissions which, if not carefully managed, may contribute to the development of resistant bacteria in local waterways and soils. In some countries, including China<sup>136</sup> and India<sup>137</sup>, studies have identified very high concentrations of antibiotics in the discharge vicinities of antibiotic production facilities.

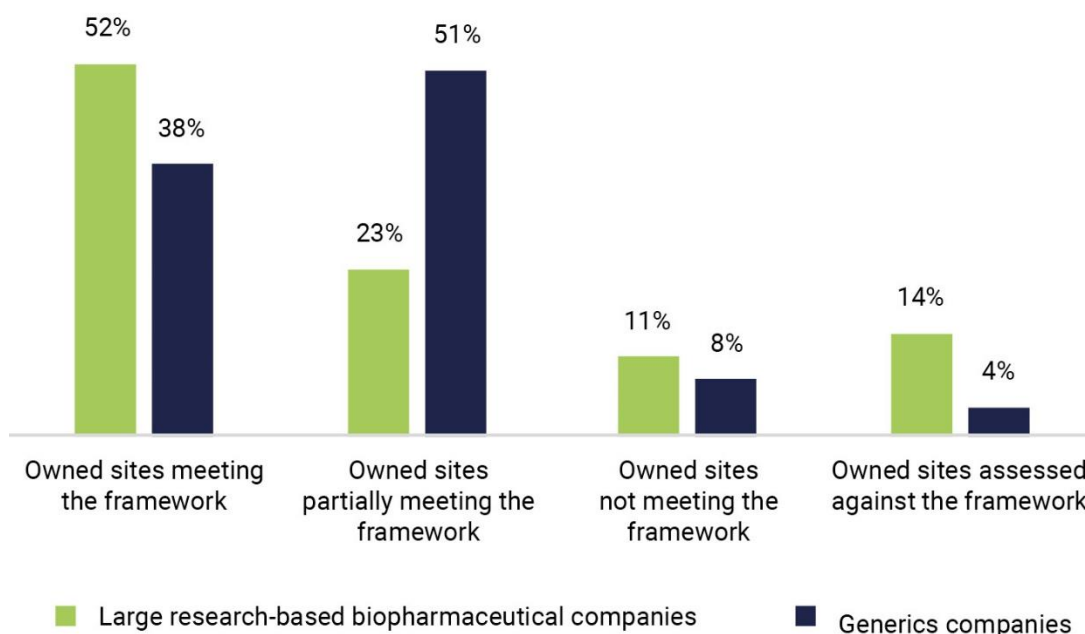
This section reports on Alliance members' progress in aligning their owned and supplier sites against the Common Antibiotic Manufacturing Framework and PNEC targets established in 2018. Companies are at different stages in meeting these commitments, with those involved in the Alliance's

<sup>xxiv</sup> This section refers to commercialized products and sites that make commercialized products only. Clinical trials manufacturing is not included.

Manufacturing Working Group from the outset making the most progress. Companies that are earlier in their journey predict strong progress as they turn commitments into action. Overall, most members anticipate meeting PNEC targets across their operations and supply chains within seven years.

The rapid progress recorded in this report reflects companies' commitment to fully implement the framework across their supply chains. Recognizing the scale of the task, the Alliance will foster cross-member collaboration on best practice to ensure the journey to adherence with the framework across members' supply chains (own sites and supplier sites) is fully achieved (with 100% of owned sites and supplier adhering to the framework over the time lines indicated in this report, or sooner, where reasonably practicable).

## PROGRESS AT COMPANY-OWNED SITES



**FIGURE 15: OWNED MANUFACTURING SITE PERFORMANCE AGAINST THE COMMON ANTIBIOTIC MANUFACTURING FRAMEWORK, BY SECTOR (TOTAL: 208 OWNED SITES).<sup>xxv</sup>**

Figure 15 shows members' current performance, by sector. Overall, companies reported that 44% of owned sites already meet the framework requirements, 38% partially meet them, and only 9% fail to meet them.

As companies often prioritize assessments on potentially higher-risk sites, cases where sites have not yet been assessed should not be assumed to correlate with likely poor performance.

Looking ahead, reporting companies forecast that 77% of their 208 manufacturing facilities will meet the framework's requirements within three years. A further 15%, all owned by generics companies, will meet these requirements within four to seven years. The Alliance will work with members to promote efforts to achieve adherence with the framework at the 8% of sites for which no adherence time line was projected. Among early members of the Alliance's Manufacturing Working Group, 52% of sites already meet the requirements and 90% are projected to do so within three years.

<sup>xxv</sup> Percentages presented in graphs may not add up exactly to 100% due to rounding to the nearest whole number.

Alliance members are working around the world to meet the framework requirements alongside local environmental regulations. For example, Aurobindo Pharma, which joined in 2019, has enhanced its application of zero liquid discharge (a regulatory requirement for API manufacturers in India) to provide better assurance of adherence to the Alliance framework requirements (see case study).

## ALLIANCE IN ACTION: AUROBINDO PHARMA MODELS ZERO WASTE DISCHARGE ANTIBIOTIC FACTORY

Indian pharmaceutical manufacturer Aurobindo Pharma is using the Alliance's manufacturing framework to build on its longstanding efforts to curb environmental impacts. The company has invested heavily in environmental infrastructure to improve wastewater and solid waste management.

At the facility that makes the cephalosporin group of antibiotics and beta-Lactam antibiotic APIs, Aurobindo developed and then implemented a procedure to deactivate traces of these products in wastewater and dispose of it responsibly, at an off-site common effluent treatment plant. This action was taken even though India does not set environmental discharge standards for individual or group API residues.

The company then introduced an integrated wastewater treatment process at the same facility. This further treats deactivated wastewater, in line with local regulations, to achieve zero liquid discharge, enabling the treated wastewater to be reused. The thorough integrated wastewater treatment process consists of a stripper, multi-effect evaporator, drier, biological wastewater treatment, and reverse osmosis. Treated wastewater is reused in utility services such as cooling towers as well as in cleaning and maintenance activities for treatment systems, and preparation of dosing solutions for treatment, among other uses.

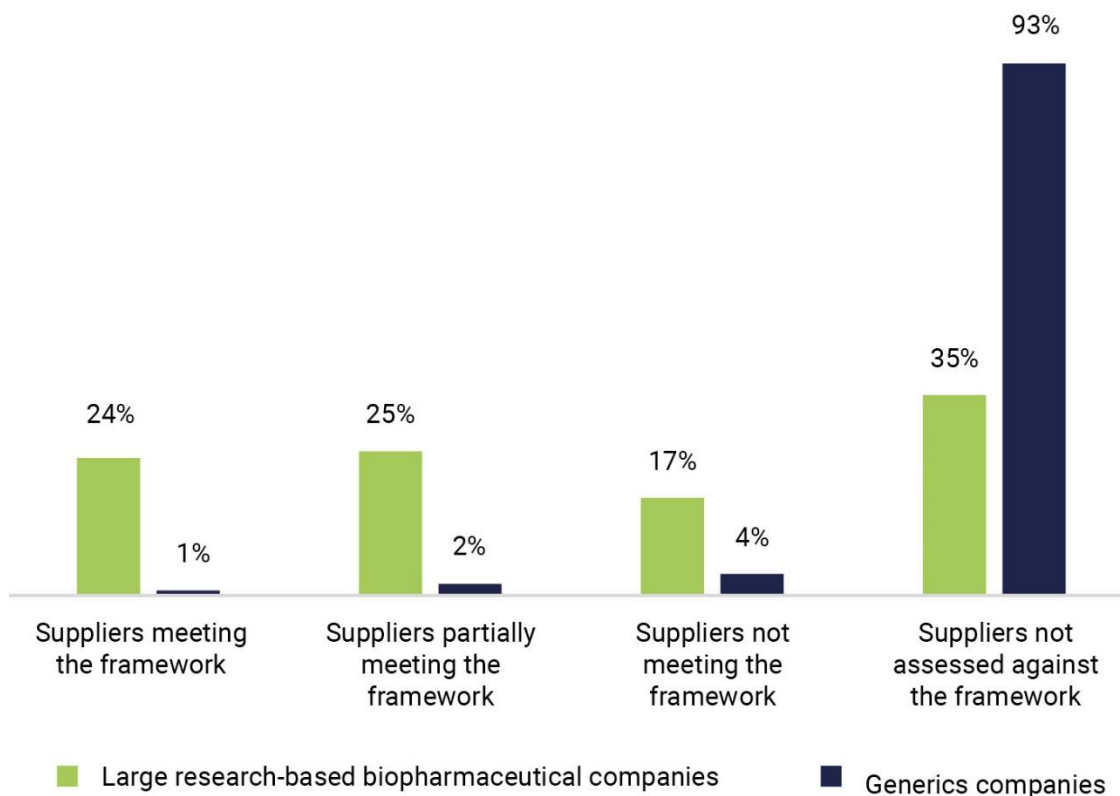
Most recently, the facility introduced continuous on-line monitoring systems for its wastewater treatment process. This helps monitor the volume of treated wastewater being routed for reuse on a continuous basis.

## PROGRESS AT SUPPLIER SITES

Globally, significantly more antibiotic products are made at supplier sites compared with those owned by biopharmaceutical and generics companies. Some suppliers—particularly those in emerging markets or countries with less rigorous environmental regulation and enforcement—may require expert help to meet the requirements of the Alliance framework.

Collectively, Alliance manufacturing members have conveyed the framework requirements to slightly more than half of the 926 total suppliers<sup>xxvi</sup> they use. They have assessed around a third (32%) of suppliers against the requirements of the framework. To drive supplier adherence companies are including framework requirements in new contracts, informing suppliers with older contracts of the new requirements, and conducting audits. Some members also provided training, either directly or through other organizations, such as the Pharmaceutical Supply Chain Initiative (PSCI). Training to date has focused mainly on technical aspects such as calculating antibiotic concentrations in wastewater.

<sup>xxvi</sup> The data were analyzed assuming that each supplier is unique, although Alliance members may share the same supplier, or indeed one Alliance member can be the supplier to another.



**FIGURE 16: SUPPLIER PERFORMANCE AGAINST THE COMMON ANTIBIOTIC MANUFACTURING FRAMEWORK, BY SECTOR (TOTAL: 926 SUPPLIERS).**<sup>xxvii</sup>

Large research-based biopharmaceutical companies have made more progress assessing their supply chains, in large part because they adopted the framework first, in early 2018. More generics companies have since joined the Alliance, which explains the higher proportion of suppliers from that sector awaiting assessment.

Member companies reported that it would take time for suppliers who are not yet meeting or partially meeting framework requirements to change. Quantifying the concentration of antibiotics in wastewater was cited as particularly challenging for many suppliers.

Across sectors, companies predicted that 47% of suppliers would meet the framework requirements within three years, and a further 35% would do so within four to seven years. Shorter timeframes typically represent cases where simple operational changes may minimize the release of antibiotics from production processes. Longer timeframes anticipate the possible need for more significant or complex solutions, e.g.: capital investment to enhance waste management capabilities; identification and securing regulatory qualification of alternative suppliers.

Overall, the survey results show that Alliance members are working across the supply chain to reduce antibiotic-related discharges, with a strong initial focus on their own operations where they exercise more control.

<sup>xxvii</sup> Percentages presented in graphs may not add up to exactly 100% due to rounding to the nearest whole number.

## THE ALLIANCE IN ACTION: BOEHRINGER INGELHEIM WORKS WITH SUPPLIERS TO END USE OF BIOMASS WASTE AS FERTILIZER

Boehringer Ingelheim, which joined the Alliance in 2019, has an antibiotics portfolio mainly focused on animal health. The pharmaceutical company engages closely with manufacturing suppliers of the active pharmaceutical ingredient used in its products.

Through its audit program, which is linked to the PSCI, the company has assessed and reduced the risk of increasing AMR through biomass waste management. One common practice that came under scrutiny was the sale of sludge containing antibiotic residues from waste treatment plants, by suppliers in China and other countries, for use as fertilizer.

Where it identifies such risks, Boehringer Ingelheim works with suppliers to develop safe alternative methods of waste disposal. As a result, one of its main manufacturing suppliers in China switched its sludge waste disposal method from fertilizer to incineration. This kills the antibiotic content while creating a material that can be used in cement, paving, and roads, so retaining the waste's economic value.

## REDUCING AMR RISKS WITH DISCHARGE TARGETS

Industry is committed to adopting good practice methods to reduce environmental emissions from antibiotic manufacturing.

In September 2016, the AMR Industry Alliance committed to establish, science-driven, risk-based targets for use in environmental risk assessments of site discharge concentrations of antibiotics by 2020. This goal was achieved two years early, in September 2018, when Manufacturing Working Group members published an agreed set of PNECs for companies and suppliers to use.

These PNEC targets cover around 120 APIs used in antibiotic manufacturing. Calculated using the best available science, they draw on both industry data and peer-reviewed literature, marking the first-time pharmaceutical companies have shared, analyzed, and published antibiotic data related to antimicrobial resistance and eco-toxicity. The targets represent significant progress in building a quantitative foundation for good practice methods to reduce the environmental risk of manufacturing emissions.<sup>xxviii</sup>

In March 2019, Alliance members published "Science-based Targets for Antibiotics in Receiving Waters from Pharmaceutical Manufacturing Operations" in *Integrated Environmental Assessment and Management*, a peer-reviewed journal.<sup>138</sup> The paper summarizes current science, explains the rationale for the approach taken, and sets out specific concentration water discharge targets for APIs in receiving waters. The Alliance expects these targets to evolve (to increase or decrease) as new data become available and as scientific understanding of AMR and of the environmental contribution to clinically relevant resistance continues to advance.

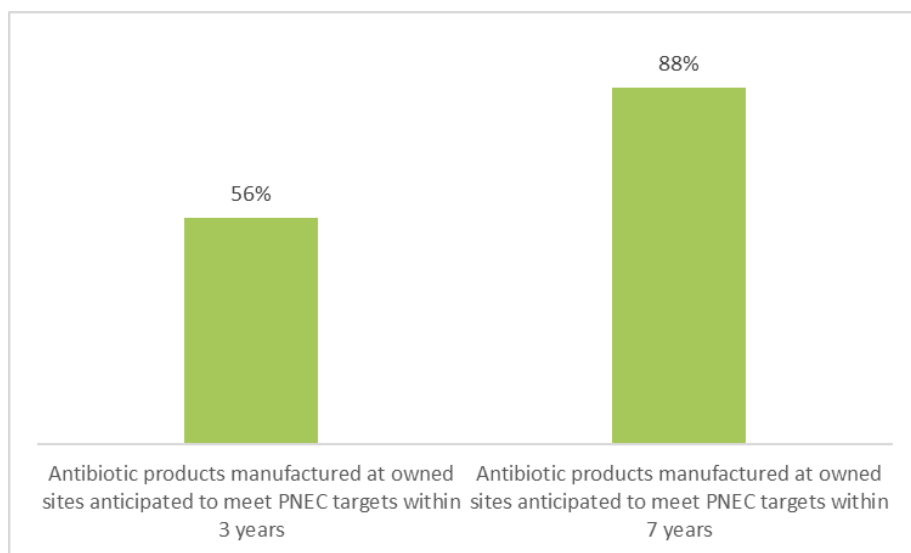
The Alliance is committed to driving PNEC adherence and will review anticipated adherence (at both owned sites and supplier sites) in more detail to better understand members' projections and, where

<sup>xxviii</sup> The Alliance's PNEC targets have also been used to evaluate impacts from publicly owned wastewater treatment plants.

appropriate, will encourage acceleration of member companies' efforts to ensure products are manufactured meeting the relevant PNEC.

## PROGRESS AT COMPANY-OWNED SITES

Companies have had just over a year to consider what to do to ensure they meet the PNEC targets at their owned and supplier facilities. The Alliance is encouraged by members' rapid timelines for action, summarized below.



**FIGURE 17: PROJECTED ADHERENCE TO PNEC TARGETS AT OWNED MANUFACTURING SITES (TOTAL: 624 ANTIBIOTIC PRODUCTS).<sup>xxix</sup>**

Collectively, 18 manufacturing members reported manufacturing 624 antibiotic products at owned sites.<sup>xxx</sup> Members expect more than half of these products to meet the PNEC targets in less than three years; 88% of products are expected to meet PNEC targets within seven years.

It is important to note that PNECs represent exceedingly low concentrations of antibiotics. To give some context PNECs are typically established at the microgram/liter level (parts per billion). For a factory supplying one million antibiotic tablets per year, with the concentration of antibiotic in the collected waste water equalling the PNEC of 1 microgram per liter, collecting all the waste water produced during the year would not contain enough antibiotic to extract to make one tablet.<sup>xxxi</sup>

For some companies, achieving these targets may require complex long-term solutions, such as capital-intensive investments to upgrade wastewater treatment infrastructure.

<sup>xxix</sup> As the data does not add up to 100% of products manufactured at owned sites, it is assumed that at the time of the Alliance survey, that either companies did not have enough information to anticipate when certain products would be made in adherence with the relevant PNEC, or, that companies felt based on information they had, it may take longer than seven years for such products to be made in adherence with the relevant PNEC.

<sup>xxx</sup> Some products will be made by one member company at more than one site, and/or by more than one member company.

<sup>xxxi</sup> Calculation basis: 100 tonne/yr API factory (equivalent to 200 million tablets) producing 100M3/day effluent at PNEC 1ug/l Yields 0.35 tablets in effluent per 1 million tablets produced.

## THE ALLIANCE IN ACTION: CENTRIENT ACTS ON DISCHARGES

High concentrations of antibiotic residues in factory wastewater may increase the selection pressure on environmental bacteria to develop resistance. As one of the largest producers of penicillin antibiotics, Centrient Pharmaceuticals strives to be a responsible manufacturer and avoid the risk of contributing to AMR.

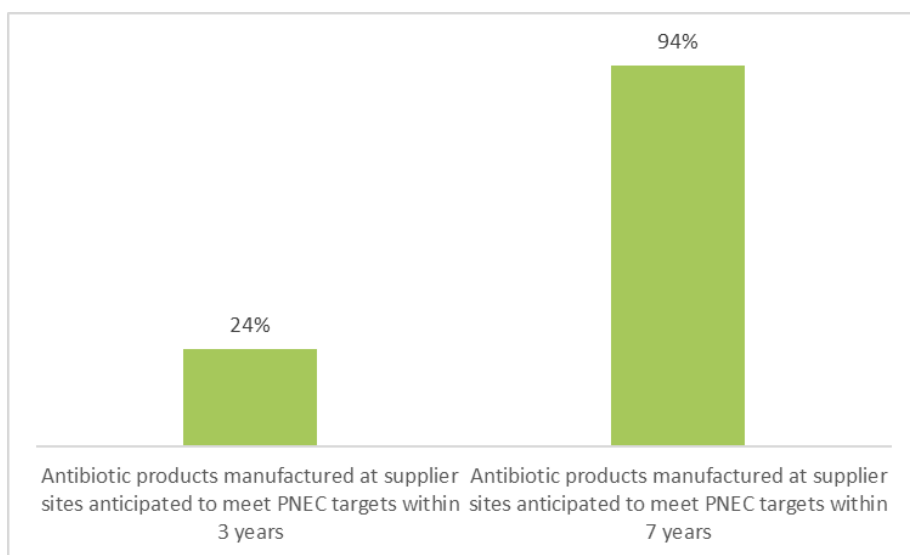
The company has invested heavily in state-of-the-art wastewater technologies. Its Sustainable Antibiotics Program developed an innovative method of detecting antibiotic activity levels in treated wastewater as low as 50 parts per billion (equivalent to 50 micrograms/liter). The company has used this rigorous method at all sites since 2016.

Building on this record, Centrient has recently launched Project PNEC, designed to meet the Alliance PNEC target values for all wastewater streams, including at supplier sites, by 2021. The Semi-Synthetic Penicillin API range (Centrient's largest portfolio) has already reached PNEC targets. Centrient has invested EUR 120,000 to analyze and test treated wastewater against the targets in addition to its proprietary technology.

The measurement of residual antibiotics at such low concentrations requires sophisticated instruments as well as deep analytical knowledge and experience: Centrient has partnered with a third party laboratory in the Netherlands to assist with this.

## PROGRESS AT SUPPLIER SITES

Seventeen companies reported manufacturing 1,035 antibiotic products.<sup>xxxii</sup> Their forecasts for meeting the PNEC targets for these products are summarized below, with 94% of products anticipated to be doing so within seven years.



**FIGURE 18: PROJECTED ADHERENCE TO PNEC TARGETS AT SUPPLIER MANUFACTURING SITES (TOTAL: 1035 ANTIBIOTIC PRODUCTS).**<sup>xxxiii</sup>

<sup>xxxii</sup> Some products will be made by one member's supplier at more than one site, and/or by more than one member's supplier.

<sup>xxxiii</sup> As the data does not add up to 100% of products manufactured at supplier sites, it is assumed that at the time of the Alliance survey, that either companies did not have enough information to anticipate when certain products would be made in

The survey results revealed a difference in the expected timelines for achieving PNECs at owned and supplier sites. Meeting PNEC targets at supplier sites is expected to take longer as companies have less influence over supplier operations than over their own production facilities. Also, as a lower percentage of fewer supplier sites (compared to owned sites) have been assessed against the framework, less is known about potential investment needs to meet the discharge PNEC targets. This means that companies are more cautious in their estimates for meeting PNECs and so project longer timelines for meeting PNECs at non-owned sites.

While making improvements across complex and global supply chains is challenging, the Alliance calls on members to accelerate engagement with, and support for, their suppliers on meeting PNEC targets. Some members are already doing so. For example, GSK is using a proactive approach to drive supplier action toward meeting Alliance requirements (see box).

### THE ALLIANCE IN ACTION: GSK DRIVES MANUFACTURING ENVIRONMENTAL STANDARDS

GSK is implementing both the PNEC targets and the Common Antibiotic Manufacturing Framework across its own operations and rolling out the requirements to suppliers. The large research-based pharmaceutical company is committed to ensuring that discharges of active antibiotics are at or below science-driven acceptable targets by the end of 2020.

In auditing and assessing its antibiotics suppliers, GSK prioritizes countries like China and India where significant work will likely be needed for manufacturers to meet the Alliance standards. The company takes a carrot and stick approach; working with suppliers on remedial action while warning that continued non-compliance may result in the non-renewal of contracts.

This strategy is bearing results. One Indian supplier moved from non-compliance with the standards to full compliance in less than two months. The manufacturer's actions have minimized the amount of antibiotic entering wastewater before treatment, substantially reducing environmental discharges afterwards.

GSK with Centrient and the Alliance also supports local antibiotic manufacturers in China, India and elsewhere through a public-private partnership, Reducing AMR through Sustainable Manufacturing (RATSAM), which acts as a best practice forum to agree actions to improve local manufacturing standards. In addition, the company is starting to work with governments on economic incentives to reward manufacturers who have adopted best manufacturing practice.

adherence with the relevant PNEC, or, that companies felt based on information they had, it may take longer than seven years for such products to be made in adherence with the relevant PNEC.



## NEXT STEPS

### MANUFACTURING & ENVIRONMENT

- Accelerate implementation of the common manufacturing framework across members' supply chains, and encourage Alliance members to take appropriate action to address facilities that do not meet expectations.
- Periodically update PNECs as new data becomes available and in light of relevant scientific advances, and consider developing further technical guidance to support broader risk assessments (e.g., for solid wastes and other antimicrobials).
- Review anticipated PNEC adherence to better understand members' projections and, where appropriate, explore mechanisms to encourage faster progress.
- Determine the relative merits of self-assessment compared with independent third-party assessment against Alliance standards.
- Leverage the Alliance's expertise to engage and inform regulators as a means to support appropriate oversight of antimicrobial manufacturing.

# APPENDICES

## APPENDIX 1: AMR INDUSTRY ALLIANCE MEMBERS

As of September 2019, the organizations listed below were members of the AMR Industry Alliance. Those marked with an asterisk (\*) responded to part or all of the second AMR Industry Alliance survey on progress, conducted in 2019. Those marked with an obelisk (†) responded to part or all of the first AMR Industry Alliance survey on progress, conducted in 2017.

### Biotechnology companies/SMEs

Allegra Therapeutics, Germany	*Moderna, United States
*†Aequor Inc., United States	*Motif Bio, France
*Agile Sciences, United States	Mutabilis, France
*AiCuris Anti-infective Cures GmbH, Germany	†Nabriva Therapeutics AG, Austria
*†Alaxia Pharma, France	NAICONS, Italy
*Amplyx, United States	Northern Antibiotics Ltd., Finland
*Antabio, France	*†Nosopharm, France
*Antibiotic Adjuvant, United States	*NovaBiotics, United Kingdom
*BioVersys AG, Switzerland	†NovaDigm Therapeutics Inc., United States
*Bugworks Research, India	OJBio Ltd., United Kingdom
Cardeas Pharma, United States	*Paratek, United States
*Combioxin, Switzerland	*†Peptilogics Inc., United States
*Curza, United States	Pherecydes Pharma, France
*†Da Volterra, France	*Rebiotix, United States
Deinove, France	*Scynexis, United States
Destiny Pharma Ltd., United Kingdom	*SetLance, Italy
Eligo Bioscience, France	*SinSa Labs, Sweden
*†Entasis Therapeutics, United States	*Soligenix, United States
*Fedora Pharmaceuticals Inc., Canada	*Spero Therapeutics LLC, United States
Fastinov, Portugal	*Stochos Therapeutics, United States
*Forge Therapeutics, United States	*Summit Therapeutics, United Kingdom
*Meiji Seika Pharma Co., Japan	Synthetic Genomics, United States
Helperby Therapeutics plc, United Kingdom	Sysmex, United Kingdom
†iNtRON Biotechnology Inc., Korea	TAXISpharma, United Statesparig
MaaT Pharma, France	*†Tetraphase Pharmaceuticals, United States
Macrolide Pharmaceuticals Inc., United States	*VenatoRx Pharmaceuticals Inc., United States
*Melinta Therapeutics Inc., United States	VibioSpheN, France
Microbion Corporation, United States	Vitas Pharma Ltd., India
MicuRx Pharmaceuticals Inc., China and United States	*Xellia, Denmark

## Large research-based biopharmaceutical companies

- \*† AstraZeneca plc, United Kingdom
- \*Boehringer Ingelheim, Germany
- \*Evotec, Germany
- \*† F. Hoffmann-La Roche AG.
- \*† GlaxoSmithKline plc, United Kingdom
- \*† Johnson & Johnson, United States
- \*† Merck KGaA, Germany
- \*† MSD (known as Merck and Co., Inc. in the U.S. and Canada), United States
- \*† Otsuka, Japan
- \*† Pfizer Inc., United States
- \*† Sanofi S.A., France
- \*† Shionogi & Co. Ltd., Japan
- \*Sumitomo Dainippon Pharma, Japan

### Generics

- \*Aurobindo, India
- \*Centrient Pharmaceuticals, The Netherlands
- \*Cipla Ltd., India
- \*† Mylan, United States
- \*NGB Laboratories, India
- \*† Novartis AG<sup>xxxiv</sup>, Switzerland
- \*† Teva Pharmaceuticals, Ltd. Israel

### Diagnostics

- \*† BD, United States
- \*† bioMérieux SA, France
- Cepheid, United States
- \*† Curetis AG, Germany
- \*HemoCue AB, Sweden
- \*Luminex B.V., The Netherlands
- \*MeMed, Israel
- \*Mobidiag Oy Ltd., Finland
- \*Momentum Bioscience Ltd., United Kingdom
- \*Nemis Technologies, Germany
- \*Qiagen, Germany
- QuantuMDx Ltd. United Kingdom
- Spectromics, United Kingdom

### Industry Associations<sup>xxxv</sup>

- AdvaMedDx
- Alliance of Biotech companies in Europe combating Anti-Microbial resistance (BEAM Alliance)
- Antimicrobial Innovation Alliance (AIA)
- Association Innovative Medicines, The Netherlands
- Association of the British Pharmaceutical Industry (ABPI)
- Biotechnology Innovation Organization (BIO)
- British Generic Manufacturers Association (BGMA)
- British In Vitro Diagnostics Association (BIVDA)
- European Federation of Pharmaceutical Industries and Associations (EFPIA)
- German Association of Research-Based Pharmaceutical Companies (VFA)
- International Federation of Pharmaceutical Manufacturers & Association (IFPMA)
- Japan Pharmaceutical Manufacturers Association (JPMA)
- Medicines for Europe
- UK BioIndustry Association (BIA)

<sup>xxxiv</sup> For the purposes of this report, and due to the predominant nature of its AMR-relevant business, where a sector breakdown is provided, data submitted by Novartis were included under the generics sector, rather than the large research-based biopharmaceutical sector.

<sup>xxxv</sup> Industry associations were not asked to participate in the survey, as it focuses specifically on company activity.

## APPENDIX 2: METHODOLOGY

### REPORT SCOPE

SCOPE	DESCRIPTION
Company Scope	Completion of the survey is a mandatory requirement of Alliance membership, which enables the Alliance to report more comprehensively on its progress and the shared challenges in tackling AMR.
Disease Scope	All infectious diseases caused by bacterial pathogens. This includes but is not limited to tuberculosis, pneumonia, gonorrhea, skin/soft tissue infections. Some metrics refer to public health priorities as specific pathogen-drug combinations that are in most need of therapeutic alternatives (e.g. CDC Biggest Threats <sup>cxix</sup> , WHO Priority Pathogens <sup>cxl</sup> ).
Product Scope	Any technology that has the potential to positively impact bacterial infections and/or resistance including but not limited to antibiotics, antifungals, vaccines, alternative technologies (e.g. biologics) and diagnostics.
Geographic Scope	Metrics are relevant to the global population where patients in need may reside independently of country GDP/wealth.
Survey Scope	A broad product definition has been adopted for R&D to allow for as yet ‘unknown’ solutions to AMR-challenges. Some metrics pertain only to post-launch activities and hence may not be relevant to members without activity in this space.

### SECTOR CATEGORIZATION

The final breakdown figures for life sciences company sectors are based on simple categorizations. For those companies that categorized themselves as hybrid given the nature of their businesses (biotechnology/large research-based biopharmaceutical; large research-based biopharmaceutical/diagnostics, etc.), we have selected the sector according to the Alliance’s records and groupings.





### METRICS FRAMEWORK

The Alliance’s metrics on combating AMR have been developed across four areas: Research and Science, Access, Appropriate Use, and Manufacturing. The following section shows each metric, sub-metric(s) and





sectors it is applicable to. These metrics formed the basis of the survey used to gather the data presented in this report.

## RESEARCH AND SCIENCE

### 1.1 FINANCIAL R&D INVESTMENT DEDICATED TO AMR-RELEVANT PRODUCTS

Applicable to	 R&D companies	 Generics Companies	 Biotech (SMEs)	 Diagnostics companies
	✓		✓	✓
<b>Metric</b>	1.1 The percentage and absolute number of companies that have made financial research and development (R&D) investment, excluding public funds, dedicated to AMR-relevant products/platforms either in-house or in collaboration in the reporting period			
<b>Sub-metric 1</b>	<p>The amount of financial investment in R&amp;D, excluding public funds, that your company dedicated to AMR-relevant products/platforms in the reporting period.</p> <ul style="list-style-type: none"> <li>a) USD 1-5m</li> <li>b) USD 6-10m</li> <li>c) USD 11-15m</li> <li>d) USD 16-20m</li> </ul> <p>If your investment is above 20m, please provide the specific figure.</p>			

### 1.2 IMPACT OF POLICIES ADDRESSING MARKET CHALLENGES ON R&D INVESTMENT





Applicable to	 R&D companies	 Generics Companies	 Biotech (SMEs)	 Diagnostics companies
	✓		✓	✓
<b>Metric</b>	1.2 The likely impact of policies addressing market challenges (e.g. reimbursement, valuation mechanisms, new commercial models) on company investment in AMR-relevant R&D			
<b>Sub-metric 1</b>	What factors have influenced your company's investment decisions in the reporting period?			
<b>Sub-metric 2</b>	What else do you believe is required to enable sustainable investment to combat AMR?			

### 1.3 THE LEVEL OF AMR-RELATED INVESTMENT





Applicable to	 R&D companies	 Generics Companies	 Biotech (SMEs)	 Diagnostics companies
	✓		✓	✓

<b>Metric</b>	1.3 The percentage and absolute number of companies whose AMR-related investment has increased, decreased or remained the same
<b>Sub-metric 1</b>	Has your company increased, decreased or maintained levels of investment in AMR-relevant R&D since the last reporting period?
<b>Sub-metric 2</b>	Would your company increase, decrease or maintain current levels of investment in AMR-relevant R&D under different market scenarios: <ul style="list-style-type: none"> <li>• The market remains unchanged</li> <li>• The market improves</li> <li>• The market worsens</li> </ul>
<b>Sub-metric 3</b>	How is your company involved in efforts to create a market that supports sustainable investment in AMR-relevant R&D?

#### 1.4 PRE-CLINICAL R&D TO ADDRESS AMR





Applicable to	 R&D companies	 Generics Companies	 Biotechs (SMEs)	 Diagnostics companies
	✓		✓	✓
<b>Metric</b>	1.4 The percentage and absolute number of companies that have pre-clinical R&D to address AMR (including the number of products that have the potential or are likely to address a CDC Biggest Threat or WHO Priority Pathogen) in the reporting period			
<b>Sub-metric 1</b>	Does your company have pre-clinical research and development to address AMR?			
<b>Sub-metric 2</b>	Does any of your pre-clinical research and development have the potential or is likely to addresses a CDC Biggest Threat or WHO Priority Pathogen?			

#### 1.5 AMR-RELEVANT PRODUCTS/PLATFORMS IN CLINICAL STAGE R&D





Applicable to	 R&D companies	 Generics Companies	 Biotechs (SMEs)	 Diagnostics companies
	✓		✓	✓
<b>Metric</b>	1.5 The percentage and absolute number of companies that have had AMR-relevant products/platforms in clinical stage R&D (including the number of products that address a CDC Biggest Threat or WHO Priority Pathogen) in the reporting period			

<b>Sub-metric 1</b>	<p>Provide the number and name* of AMR-relevant products/platforms in development including for example:</p> <ul style="list-style-type: none"> <li>• Antibiotic(s)</li> <li>• AMR-relevant vaccines</li> <li>• AMR-relevant novel approaches or technologies (e.g. biologics, microbiome, phage, biofilm)</li> <li>• AMR-relevant diagnostic platforms or assays</li> <li>• Other (please state)</li> </ul> <p><i>*NB providing the name is optional for diagnostics companies</i></p>
<b>Sub-metric 2</b>	Which, if any, of these products/platforms address a CDC Biggest Threat or WHO Priority Pathogen
<b>Sub-metric 3</b>	Were any of your AMR-relevant products/platforms discontinued since the last time of reporting? Please share the number and name.

## 1.6 DATA EXCHANGE ON OFF-PROTECTION ANTIBIOTICS





Applicable to	 <b>R&amp;D companies</b>	 <b>Generics Companies</b>	 <b>Biotechs (SMEs)</b>	 <b>Diagnostics companies</b>
	✓			
<b>Metric</b>	1.6 The percentage and absolute number of companies that have facilitated data exchange on off-protection antibiotics in the reporting period			
<b>Sub-metric 1</b>	<p>How has your company facilitated data exchange?</p> <ul style="list-style-type: none"> <li>- Through publication</li> <li>- With other companies, and/or industry initiatives - With Product Development Partnerships (PDPs)</li> <li>- With academia</li> <li>- Other (please state)</li> </ul>			
<b>Sub-metric 2</b>	<p>Has your company contributed to advancing the evidence base through scientific publication?</p> <ul style="list-style-type: none"> <li>- Clinical trials results</li> <li>- Regulatory science</li> <li>- Stewardship</li> <li>- Manufacturing</li> <li>- Environmental science, including surveillance</li> <li>- Other (please state)</li> </ul>			

## 1.7 COLLABORATIVE WAYS OF WORKING, INCLUDING BUT NOT LIMITED TO PUBLIC-PRIVATE PARTNERSHIPS, IN R&D DEDICATED TO AMR-RELEVANT PRODUCTS/PLATFORMS

Applicable to	 R&D companies	 Generics Companies	 Biotechs (SMEs)	 Diagnostics companies
	✓		✓	✓
<b>Metric</b>	1.7 The percentage and absolute number of companies that have pursued collaborative ways of working, including but not limited to public-private partnerships, in R&D dedicated to AMR-relevant products/platforms in the reporting period			
<b>Sub-metric 1</b>	Please share the type of collaborative R&D your company is engaged in.			
<b>Sub-metric 2</b>	Please share the kinds of R&D partners collaborated with.			

## ACCESS





### 2.1 IMPROVING AVAILABILITY, AFFORDABILITY AND ACCESSIBILITY

Applicable to	 R&D companies	 Generics Companies	 Biotechs (SMEs)	 Diagnostics companies
	✓	✓	✓	✓
<b>Metric</b>	2.1 The percentage and absolute number of companies that support efforts to improve the availability, affordability and accessibility to patients of the company's AMR-relevant products in the reporting period			
<b>Sub-metric 1</b>	How does your company support access to AMR-relevant products/platforms - from making diagnostics and vaccines more widely available and used through to therapies (e.g. antibiotics)?			
<b>Sub-metric 2</b>	Do you have an access plan addressing AMR-relevant products in: <ul style="list-style-type: none"> <li>• High income countries</li> <li>• Middle income countries</li> <li>• Low income countries</li> </ul>			
<b>Sub-metric 3</b>	Does the plan address the following aspects: <ul style="list-style-type: none"> <li>• Registration</li> <li>• Affordability</li> <li>• Health system capacity and appropriate use</li> <li>• Partnerships/collaborative access mechanisms</li> <li>• Other (please state)</li> </ul>			







<b>Sub-metric 4</b>	Is this plan public?
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## 2.2 COLLABORATING AND PARTNERING WITH EXTERNAL STAKEHOLDERS REGARDING ACCESS TO AMR

Applicable to	 R&D companies	 Generics Companies	 Biotechs (SMEs)	 Diagnostics companies
		✓	✓	
<b>Metric</b>	2.2 The percentage and absolute number of companies that have collaborated or partnered with external stakeholders regarding access to AMR-relevant products in the reporting period			
<b>Sub-metric 1</b>	Have you collaborated or partnered with external stakeholders to support access to your AMR-relevant products/platforms? Please describe (e.g. details of the engagement, the area/issue addressed, and any outcomes).			

## 2.3 ADDRESSING SUSTAINABLE SUPPLY CHALLENGES FOR AMR-RELEVANT PRODUCTS





Applicable to	 R&D companies	 Generics Companies	 Biotechs (SMEs)	 Diagnostics companies
		✓	✓	
<b>Metric</b>	2.3 The percentage and absolute number of companies that work with relevant stakeholders to identify and address specific sustainable supply challenges for AMR-relevant products in the reporting period			
<b>Sub-metric 1</b>	What are the barriers to ensuring the sustainable supply of AMR-relevant products? Please describe.			
<b>Sub-metric 2</b>	<p>Do you work with relevant stakeholders to proactively identify and address sustainable supply challenges for AMR-relevant products through:</p> <ul style="list-style-type: none"> <li>• Buffer stocks</li> <li>• Supplier diversity</li> <li>• Tools/information systems to forecast need and API shortages</li> <li>• Capacity building</li> <li>• Other (please state)</li> </ul>			
<b>Sub-metric 3</b>	Has your company experienced one or more disruptions in the supply chain of AMR-relevant products in the last two years? Please describe the reasons for disruption and any actions taken to ensure uninterrupted supply and mitigate disruptions in the supply chain.			

## 2.4 REDUCING THE PREVALENCE OF SUBSTANDARD AND FALSIFIED AMR-RELEVANT PRODUCTS

Applicable to	 R&D companies	 Generics Companies	 Biotechs (SMEs)	 Diagnostics companies
	✓	✓		
<b>Metric</b>	2.4 The percentage and absolute number of companies that have measures in place to help reduce the prevalence of substandard and falsified AMR-relevant products in the reporting period			
<b>Sub-metric 1</b>	Do you have any measures in place to help reduce the prevalence of substandard and falsified AMR-relevant products? Please describe.			





## APPROPRIATE USE

### 3.1 SUPPORTING APPROPRIATE USE AND STEWARDSHIP





Applicable to	 R&D companies	 Generics Companies	 Biotechs (SMEs)	 Diagnostics companies
	✓	✓	✓	✓*
<b>Metric</b>	3.1 The percentage and absolute number of companies that support appropriate use and stewardship for AMR-relevant products in the reporting period			
<b>Sub-metric 1</b>	How does your company support appropriate use and stewardship of antibiotics (including through the use of diagnostics)? Please describe.			
<b>Sub-metric 2</b>	Does your company have an appropriate use and stewardship plan for AMR-relevant products? Please describe, if relevant, to which of your products it applies and at which stage of development appropriate use considerations were made. * NB This sub-metric does not apply to diagnostics companies			

<b>Sub-metric 3</b>	<p>Does this plan address:</p> <ul style="list-style-type: none"> <li>• IPC/hygiene</li> <li>• Prevention through vaccines</li> <li>• Early and appropriate diagnosis</li> <li>• Generation of evidence to support appropriate use</li> <li>• Surveillance</li> <li>• Education</li> <li>• Promotion</li> <li>• Reducing uncontrolled use (including over the counter and non-prescription internet sales)</li> <li>• Other area (please state)</li> <li>• Not applicable</li> </ul>
<b>Sub-metric 4</b>	<p>Does your company measure the outcomes or impact of its appropriate use and stewardship plan (all or in part)</p> <p>* NB This sub-metric does not apply to diagnostics companies</p>

### 3.2 COLLECTING OF SURVEILLANCE DATA IN THE REPORTING PERIOD





Applicable to	 <b>R&amp;D companies</b>	 <b>Generics Companies</b>	 <b>Biotechs (SMEs)</b>	 <b>Diagnostics companies</b>
	✓	✓		✓
<b>Metric</b>	3.2 The percentage and absolute number of companies that collect or support the collection of surveillance data in the reporting period			
<b>Sub-metric 1</b>	Does your company collect surveillance data?			
<b>Sub-metric 2</b>	Do you take steps to share these data externally? Please describe.			

### 3.3 PROMOTING STEWARDSHIP, EITHER DIRECTLY OR COLLABORATIVELY





Applicable to	 <b>R&amp;D companies</b>	 <b>Generics Companies</b>	 <b>Biotechs (SMEs)</b>	 <b>Diagnostics companies</b>
	✓	✓		✓
<b>Metric</b>	3.3 The percentage and absolute number of companies that engage in activities promoting stewardship, either directly or collaboratively, in the reporting period			

<b>Sub-metric 1</b>	<p>Are you engaged in initiatives that directly or indirectly help to educate the following stakeholders on promoting stewardship:</p> <ul style="list-style-type: none"> <li>• HCPs</li> <li>• Health care workers</li> <li>• Patients</li> <li>• General public</li> <li>• Other stakeholders (please state)</li> </ul> <p>Please describe, including any efforts to mitigate conflict of interest.</p>
<b>Sub-metric 2</b>	Are any educational materials for stewardship peer-reviewed? Please describe.

### 3.4 PROMOTIONAL ACTIVITIES TO ADVANCE STEWARDSHIP





Applicable to	 R&D companies	 Generics Companies	 Biotechs (SMEs)	 Diagnostics companies
	✓	✓		✓
<b>Metric</b>	3.4 The percentage and absolute number of companies that examine their promotional activities to ensure they are consistent with the goal of advancing stewardship in the reporting period			
<b>Sub-metric 1</b>	Are your promotional practices consistent with the goal of advancing stewardship? Please describe any initiatives or plans.			

### 3.5 PROMOTE RESPONSIBLE ANIMAL USE OF AMR-RELATED PRODUCTS

Applicable to	 R&D companies	 Generics Companies	 Biotechs (SMEs)	 Diagnostics companies
	✓	✓		✓
<b>Metric</b>	3.5 The percentage and absolute number of companies that have products licensed for animal use and how they promote responsible and judicious use in animals in the reporting period			
<b>Sub-metric 1</b>	I. Does your company develop or commercialize products that are licensed for animal use? If so, how is your company promoting responsible and judicious use in animals?			

## ENVIRONMENT AND MANUFACTURING

#### 4.1 ASSESSING OWN SITES AND PRODUCTS AGAINST THE CRITERIA IN THE COMMON ANTIBIOTIC MANUFACTURING FRAMEWORK AND THE LIST OF PREDICTED NO-EFFECT CONCENTRATION TARGETS





Applicable to	 R&D companies	 Generics Companies	 Biotechs (SMEs)	 Diagnostics companies
	✓	✓		
<b>Metric</b>	4.1 The percentage of sites assessed against and meeting the criteria in the Common Antibiotic Manufacturing Framework and number of products manufactured at your sites meeting the List of Predicted No-effect Concentration (PNEC) targets			
<b>Sub-metric 1</b>	How many of your own antibiotic manufacturing sites do you have? How many of your own antibiotic manufacturing sites have been assessed against the criteria in the Common Antibiotic Manufacturing Framework?			
<b>Sub-metric 2</b>	How many of your own antibiotic manufacturing sites meet the Common Antibiotic Manufacturing Framework requirements?			
<b>Sub-metric 3</b>	How many of your own antibiotic manufacturing sites partially meet the Common Antibiotic Manufacturing Framework requirements?			
<b>Sub-metric 4</b>	How many of your own antibiotic manufacturing sites do not meet the Common Antibiotic Manufacturing Framework requirements?			
<b>Sub-metric 6</b>	How many of your own antibiotic manufacturing sites do you anticipate meeting Common Antibiotic Manufacturing Framework requirements in: - 0-3 years - 4-7 years			
<b>Sub-metric 7</b>	How many of your antibiotic products manufactured at your own sites do you anticipate meeting the PNEC targets in: - 0-3 years - 4-7 years			

#### 4.2 CONVEYING EXPECTATIONS OF THE COMMON ANTIBIOTIC MANUFACTURING FRAMEWORK TO SUPPLIERS

Applicable to	 R&D companies	 Generics Companies	 Biotechs (SMEs)	 Diagnostics companies
	✓	✓		
<b>Metric</b>	4.2 The percentage of suppliers that have had expectations of the Common Antibiotic Manufacturing Framework conveyed to them			

<b>Sub-metric 1</b>	How many antibiotic manufacturing suppliers do you have? How many of your antibiotic manufacturing suppliers have had the expectations of the Common Antibiotic Manufacturing Framework conveyed to them?
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#### 4.3 ASSESSING SUPPLIER SITES AND PRODUCTS AGAINST THE CRITERIA IN THE COMMON ANTIBIOTIC MANUFACTURING FRAMEWORK AND THE LIST OF PREDICTED NO-EFFECT CONCENTRATION TARGETS

Applicable to	 R&D companies	 Generics Companies	 Biotechs (SMEs)	 Diagnostics companies
	✓	✓		
<b>Metric</b>	4.3 The percentage of antibiotic manufacturing suppliers assessed against and meeting the criteria in the Common Antibiotic Manufacturing Framework and number of products manufactured at supplier sites meeting the List of Predicted No-effect Concentration targets			
<b>Sub-metric 1</b>	How many of your antibiotic manufacturing suppliers have been assessed against the criteria in the Common Antibiotic Manufacturing Framework?			
<b>Sub-metric 2</b>	How many of your antibiotic manufacturing suppliers meet Common Antibiotic Manufacturing Framework requirements?			
<b>Sub-metric 3</b>	How many of your antibiotic manufacturing suppliers partially meet the Common Antibiotic Manufacturing Framework requirements?			
<b>Sub-metric 4</b>	How many of your antibiotic manufacturing suppliers do not meet the Common Antibiotic Manufacturing Framework requirements?			
<b>Sub-metric 5</b>	How many of your supplier antibiotic manufacturing sites do you anticipate meeting Common Antibiotic Manufacturing Framework requirements in: - 0-3 years - 4-7 years			
<b>Sub-metric 6</b>	How many of your antibiotic products manufactured at your supplier sites do you anticipate meeting the PNEC targets in: - 0-3 years - 4-7 years			

## APPENDIX 3: DEFINITIONS

TERM	DEFINITION
Access	Having medicines, diagnostics and alternative technologies available and affordable at public or private health facilities or medicine outlets.
AMR-related education programs	Product-independent materials or activities that aim to increase the knowledge of healthcare professionals, internal company staff and/or the general public on the issue of antibiotic resistance and the importance of the appropriate use of AMR-related products.
Animal health	See Health for Animals for more information on the responsible use of antibiotics to protect and treat animals.
Antibiotic (AB)	An agent that kills or inhibits the growth of a bacterial microorganism.
Antimicrobial	An agent that kills or inhibits the growth of microorganisms, such as antibiotics, antifungals, antivirals or antiparasitics.
Antibiotic resistance	The process whereby the ability of a given antibiotic to kill or inhibit a bacterium progressively wanes over time, making those antibiotics less able or effective in treating infections caused by that bacteria.
Antimicrobial resistance (AMR)	Broader than antibiotic resistance also encompassing resistance development to other microorganisms such as viruses and protozoa. Many global initiatives use this term.
Appropriate Use	The right patient receiving the right drug at the right dose in the right formulation at the right time for the right duration for the right pathogen and site of infection.
Barriers	Challenges in healthcare markets that may inhibit the development, manufacturing or distribution of a product to patients for example low prices, inefficient reimbursement or formulary mechanisms.
CDC Biggest Threat	The top 18 antibiotic-resistant threats in the United States, outlined in the Antibiotic Resistance Threats in the United States, 2013 (AR Threats Report).

TERM	DEFINITION
Commercial models	Processes or mechanisms whereby companies receive a return from an upfront investment. The traditional commercial model of these sectors is based on monopoly market conditions for a defined time but could include patent-independent lump-sum payments or public subsidy.
Data exchange on off-protection antibiotics	Making data (e.g. regulatory dossier or information related to dosing and manufacturing processes) on off-protection antibiotics available to external stakeholders, where off-protection is when a product is no longer protected from competition due to expiry of proprietary protections (such as patents, data exclusivity, etc.).
Falsified medical products	Products that deliberately/fraudulently misrepresent their identity, composition or source.
Financial R&D investments	Investments in early through to late-stage R&D measured as full-time-employees and direct project costs only (in 2018 USD).
Healthcare professional (HCP)	Any individual employed within a health system with the potential to impact patient care.
Incentive	Additional resources being released or made available to redress market value challenges.
Off-protection	When a product is no longer protected from competition due to expiry of proprietary protections (such as patents, data exclusivity etc.)
Operations under the participating company's direct control	Refers to operations of: <ul style="list-style-type: none"> <li>○ The reporting organization</li> <li>○ Subsidiary where the reporting organization owns, directly or indirectly, more than 50% of the voting power regardless of their public listing status</li> <li>○ Joint venture of which the reporting organization owns, directly or indirectly through subsidiaries, 50% or more of the voting power</li> <li>○ Other entities that the reporting organization has control over based on the principle of "substance over form".</li> </ul>
Own/internal manufacturing and products	Production sites and products manufactured under direct control or ownership of the company.



TERM	DEFINITION
Platforms	The system and tests (made up of instruments, reagents, and software) that can be used to diagnose infections.
Prevention	All measures taken which may stop new or repeat infections occurring in the first place, i.e. infection prevention and control measures, water and sanitation or vaccination.
Product Development Partnerships	Public-private partnerships that reduce industry and donor risks for investment in neglected disease research by leveraging funding and employing strict portfolio management strategies.
Promotional practices	Ethical, accurate, balanced and not misleading promotional practices; the information in promotional materials must support proper assessment of a product's risks and benefits and its appropriate use.
Public funds	Government/public funding towards research to reduce the burden of AMR.
Public-private partnerships	Partnerships that involve collaboration between a government agency and a private-sector company that can be used to finance, build, and operate projects.
Regulatory barriers	Refers to challenges in regulated healthcare markets that may inhibit the development or diffusion of products to patients i.e. slow, unclear, complex/expensive regulatory preconditions for marketing approval.
Regulatory science	The science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA-regulated products.
Reimbursement	The systems, processes and decision making in the payment of healthcare providers for services provided to patients, typically by governments or health insurance organizations.
Stakeholder	Individuals or groups that have an interest or potential impact on an issue.
Stewardship	Multidisciplinary measures to systematically ensure appropriate use of products that may be taken at all levels of the global system.
Substandard medical products	Authorized medical products that fail to meet either their quality standards or their specifications, or both.

TERM	DEFINITION
Supplier manufacturing	Production sites and products manufactured outside of the direct control or ownership of the company.
Surveillance data	Any data that has the potential to improve understanding of product consumption, use, and resistance development.
Valuation mechanisms	Refers to processes for determining the value of a product to a health system or society beyond its market-determined value.
WHO Priority Pathogen	Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics.

## APPENDIX 4: AMR-RELEVANT ANTIBIOTICS AND ANTIFUNGALS IN CLINICAL DEVELOPMENT DURING REPORTING PERIOD

COMPANY	ANTIBIOTICS IN CLINICAL STAGE DEVELOPMENT	PATHOGEN RELEVANT TO	WHO PRIORITY PATHOGENS LIST <sup>xxxvi</sup>	CDC BIGGEST THREAT LIST <sup>xxxvii</sup>
Entasis	ETX2514SUL	<i>Acinetobacter baumannii</i>	Critical	Urgent
Entasis	Zoliflodacin	<i>Neisseria gonorrhoeae</i>	High	Urgent
Entasis	ETX0282CPDP	<i>Enterobacteriaceae</i>	Critical	Serious
F. Hoffmann-La Roche AG.	Name not provided	<i>Staphylococcus Aureus</i>	High	Serious
GSK	Gepotidacin (2140944)	<i>Neisseria gonorrhoeae</i>	High	Urgent
		<i>Enterobacteriaceae (Escherichia coli)</i>	Critical	Serious
Meiji Seika/ Fedora	Nacubactam (RO7079901)	<i>Enterobacteriaceae</i>	Critical	Serious
Melinta Therapeutics Inc.	Solithromycin	<i>Streptococcus Pneumoniae</i>	Medium	Serious
MSD	Imipenem cilastatin - relebactam	<i>Enterobacter cloacae</i>	N/A	N/A
		<i>Escherichia coli</i>	Critical	Serious
		<i>Klebsiella Aerogenes</i>	N/A	N/A
		<i>Klebsiella pneumoniae</i>	Critical	N/A
		<i>Pseudomonas aeruginosa</i>	Priority	Serious
Motif Bio	Iclaprim	<i>Staphylococcus aureus</i>	High	Serious
Otsuka	OPC-167832	<i>Tuberculosis</i>	N/A	Serious

<sup>xxxvi</sup> As of December 2019

<sup>xxxvii</sup> As of December 2019

Paratek	Omadacycline	<i>Staphylococcus aureus</i>	High	Serious
		<i>Streptococcus pneumoniae</i>	Medium	Serious
		<i>Vancomycin-resistant Enterococci (VRE)</i>	N/A	Serious
		<i>Legionella</i>	N/A	N/A
		<i>Chlamydia</i>	N/A	N/A
Pfizer Inc.	Aztreonam-avibactam (PF-06947387)	<i>Enterobacteriaceae</i>	Critical	Serious
		<i>Pseudomonas aeruginosa</i>	Priority	Serious
		<i>Stenotrophomonas maltophilia</i>	N/A	N/A
Shionogi & Co. Ltd.	Cefiderocol	<i>Enterobacteriaceae</i>	Critical	Serious
		<i>Acinetobacter baumannii</i>	Critical	Urgent
		<i>Klebsiella pneumoniae</i>	Critical	N/A
		<i>Pseudomonas aeruginosa</i>	Priority	Serious
		<i>Stenotrophomonas maltophilia</i>	N/A	N/A
Shionogi & Co. Ltd.	S-004992	<i>Tuberculosis</i>	N/A	Serious
Spero Therapeutics	SPR994	<i>Enterobacteriaceae (Escherichia coli)</i>	Critical	Serious
		<i>Klebsiella pneumoniae</i>	Critical	N/A
Spero Therapeutics	SPR206	<i>Enterobacteriaceae</i>	Critical	Serious
		<i>Acinetobacter baumannii</i>	Critical	Urgent
		<i>Pseudomonas aeruginosa</i>	Priority	Serious
Spero Therapeutics	SPR720-NTM	<i>Staphylococcus aureus</i>	High	Serious
		<i>Neisseria gonorrhoeae</i>	High	Urgent
		<i>Tuberculosis</i>	N/A	Serious
Spero Therapeutics	SPR741	<i>Enterobacteriaceae (inc. Escherichia Coli)</i>	Critical	Serious
		<i>Klebsiella pneumoniae</i>	Critical	N/A
Summit Therapeutics	Ridinilazole	<i>Clostridioides Difficile</i>	N/A	Urgent
VenatoRx	Taniborbactam + Cefepime	<i>Enterobacteriaceae</i>	Critical	Serious
		<i>Pseudomonas aeruginosa</i>	Priority	Serious

VenatoRx	VNRX-7145 + ceftibuten	<i>Enterobacteriaceae</i>	Critical	Serious
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COMPANY	ANTIFUNGALS IN CLINICAL STAGE DEVELOPMENT	PATHOGEN RELEVANT TO	WHO PRIORITY PATHOGENS LIST <sup>xxxviii</sup>	CDC BIGGEST THREAT LIST <sup>xxxix</sup>
NovaBiotics	Novexatin	Non-metabolising and metabolically active nail fungal pathogens. This includes both dermatophyte and non-dermatophyte fungi associated with onychomycosis.	N/A	N/A
Scynexis	Ibrexafungerp	<i>Aspergillus</i>	N/A	N/A
		<i>Candida Auris</i>	N/A	Urgent
Amplix	Fosmanogepix	<i>Candida Auris</i>	N/A	Urgent

<sup>xxxviii</sup> As of December 2019

<sup>xxxix</sup> As of December 2019

## APPENDIX 5: AMR-RELEVANT VACCINES IN CLINICAL DEVELOPMENT DURING REPORTING PERIOD

COMPANY	AMR-RELEVANT VACCINES IN CLINICAL STAGE DEVELOPMENT	PATHOGEN RELEVANT TO	WHO PRIORITY PATHOGENS LIST <sup>xi</sup>	CDC BIGGEST THREAT LIST <sup>xli</sup>
GSK	1790GAHB Monovalent GMMA-based <i>S. sonnei</i>	<i>Shigella</i>	Medium	Serious
	GSK3536852A <i>Shigella</i> multivalent bioconjugate vaccine	<i>Shigella</i>	Medium	Serious
	SB692342: Tuberculosis Prophylactic Vaccine	<i>Tuberculosis</i>	N/A	Serious
	Invasive nontyphoidal <i>Salmonella</i> (iNTS; Bi-valent GMMA for <i>S. enterica</i> serovars Typhimurium + Enteritidis)	<i>Salmonella</i>	High	Serious
	Enteric fever (Bi- valent conjugate for <i>S. enterica</i> serovars Typhi+ Paratyphi A)	<i>Salmonella</i>	High	Serious
Johnson & Johnson	ExPEC vaccine	<i>Enterobacteriaceae</i> ( <i>Escherichia Coli</i> )	Critical	Urgent and Serious
MSD	V114	<i>Streptococcus</i> <i>Pneumoniae</i>	Medium	Serious
Pfizer	NCT03170609: Group B	<i>Streptococcus</i>	N/A	Concerning

<sup>xi</sup> As of December 2019

<sup>xli</sup> As of December 2019

	Streptococcus vaccine			
	PF-06842433: Pneumococcal vaccine	<i>Streptococcus Pneumoniae</i>	Medium	Serious
	PF-06425090: Clostridioides difficile vaccine	<i>Clostridioides difficile</i>	N/A	Urgent
	Respiratory Syncytial Virus Infection Vaccine	<i>RSV</i>	N/A	N/A

## APPENDIX 6: AMR-RELEVANT DIAGNOSTIC PLATFORMS AND ASSAYS IN CLINICAL DEVELOPMENT DURING REPORTING PERIOD

Diagnostics companies were not required to disclose the names of their platforms and assays in clinical development through the survey. As such the below list is not exhaustive, providing only some examples of companies with products in clinical development.

COMPANY	DIAGNOSTICS IN CLINICAL STAGE DEVELOPMENT	PATHOGEN RELEVANT TO	WHO PRIORITY PATHOGENS LIST <sup>xlii</sup>	CDC BIGGEST THREAT LIST <sup>xliii</sup>
bioMérieux SA	VITEK 2 AST panels and ID cards	<i>Tests for a variety of antimicrobial resistance genes.</i>	Some of the pathogens tested for are included in the WHO PPL	Some of the pathogens tested for are included in the CDC BTL
	VITEK MS bacterial ID	<i>Tests for a variety of antimicrobial resistance genes.</i>	Some of the pathogens tested for are	Some of the pathogens tested for are

<sup>xlii</sup> As of December 2019

<sup>xliii</sup> As of December 2019

			included in the WHO PPL	included in the CDC BTL
	BioFire Film Array panels	<i>Tests for a variety of antimicrobial resistance genes.</i>	Some of the pathogens tested for are included in the WHO PPL	Some of the pathogens tested for are included in the CDC BTL
	ChromID media for MDRO organisms	<i>Tests for a variety of antimicrobial resistance genes.</i>	Some of the pathogens tested for are included in the WHO PPL	Some of the pathogens tested for are included in the CDC BTL
	BioNexia Rapid Panels	<i>Streptococcus A</i>	N/A	N/A
	ETest ID strips	<i>Tests for a variety of antimicrobial resistance genes.</i>	N/A	One of the pathogens tested for is included in the CDC BTL
Qiagen	QuantiFERON Access	Tuberculosis	N/A	Serious
Qiagen	QIAStat-Dx	<i>Tests for a variety of antimicrobial resistance genes.</i>	Some of the pathogens tested for are included in the WHO PPL	Some of the pathogens tested for are included in the CDC BTL



## APPENDIX 7: AMR-RELEVANT NOVEL APPROACHES AND TECHNOLOGIES IN CLINICAL DEVELOPMENT DURING REPORTING PERIOD

COMPANY	NOVEL APPROACHES AND TECHNOLOGIES IN CLINICAL STAGE DEVELOPMENT	PATHOGEN RELEVANT TO	WHO PRIORITY PATHOGENS LIST <sup>xliv</sup>	CDC BIGGEST THREAT LIST <sup>xlv</sup>
AstraZeneca	MEDI3902: Suvratoxumab	<i>Pseudomonas aeruginosa</i>	Priority	Serious
	MEDI4893	<i>Staphylococcus aureus</i>	High	Serious
Combioxin	CL02	<i>Streptococcus Pneumoniae</i>	Medium	Serius
Da Volterra	DAV132	<i>Clostridioides difficile</i>	N/A	Urgent
Novabiotics	Lynovex oral	<i>Pseudomonas aeruginosa</i> and MDR <i>Pseudomonas aeruginosa</i>	Priority	Serious
Peptilogics	PLG0206	<i>Staphylococcus aureus</i>	High	Serious
Rebiotix	RBX7455	<i>Clostridioides difficile</i>	N/A	Urgent
Shionogi & Co. Ltd.	COT-143 <sup>xlvi</sup>	<i>Pseudomonas aeruginosa</i>	Priority	Serious
Soligenix	SGX942; SGX943 <sup>xlvii</sup>	<i>Oral Mucositis</i>	N/A	N/A

<sup>xliv</sup> As of December 2019

<sup>xlv</sup> As of December 2019

<sup>xlvi</sup> Shionogi entered into an out-licensing agreement with the AMR Center in the UK. The AMR Centre will hold the exclusive worldwide right of research, development and manufacturing of COT-143.

<sup>xlvii</sup> SGX942 is in development with a concurrent clinical development program with SGX943 supporting an antibacterial indication

## APPENDIX 8: OTHER AMR-RELEVANT PRODUCTS IN CLINICAL DEVELOPMENT DURING REPORTING PERIOD

COMPANY	OTHER PRODUCTS IN CLINICAL STAGE DEVELOPMENT	PATHOGEN RELEVANT TO	WHO PRIORITY PATHOGENS LIST <sup>xlvi</sup>	CDC BIGGEST THREAT LIST <sup>xli</sup>
GSK	GSK-3036656	<i>Mycobacterium Tuberculosis</i>	N/A	Serious

<sup>xlvi</sup> As of December 2019

<sup>xli</sup> As of December 2019

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