The AMR challenge – Perspectives from the life science industry

Luka Srot, Manager, Health Security, International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), Geneva, Switzerland and **Diane Flayhart,** Global Program Leader, AMR, Becton Dickinson, USA


LUKA SROT


DIANE FLAYHART

Without action, we risk losing effective antibiotics which could undo decades of medical progress, including in cancer treatment and care, with significant potential impact on cancer patients. Industry leaders, through the AMR Industry Alliance, are actively contributing solutions to ensure antibiotics continue to be a powerful tool in our medical arsenal. This includes investing in research and development for AMR-relevant products, supporting access and stewardship efforts, and addressing the environmental risks from antibiotic manufacturing. No single actor can tackle this challenge on their own. A long-term, sustainable effort is needed from governments and other stakeholders to succeed. Advocacy and support from relevant communities, such as in cancer care, is essential to stimulate and maintain action by governments.

Antimicrobial resistance (AMR) is one of the leading, most pervasive health threats globally. At the end of 2020, the World Health Organization (WHO) designated it as one of 10 global health issues to track *(1)*, right as the deadliest pandemic of our lifetime was unfolding. This year, we were confronted with a reality check. New data revealed AMR to have been directly responsible in 2019 for 1.3 million deaths globally, with close to 5 million deaths associated with AMR *(2)*, much greater than was previously thought. This suggests the burden was previously grossly underestimated, or AMR has spread at a worrying pace in the last five years – or both. If no action is taken, the death toll could rise to 10 million annually by 2050, and result in a US$ 100 trillion global GDP loss *(3)*.

Antibiotics have been a staple in care ever since Alexander Fleming discovered penicillin in 1928. This was a watershed moment for modern medicine. In the decades that followed, we have seen significant innovation and new classes of antibiotics being developed. Further, diagnostic testing has evolved to help optimize the use of antibiotics by identifying the pathogen causing infection and providing susceptibility testing to ensure the right antibiotic is given at the right time.

However, the rules of evolution apply to every living organism on the planet, and bacteria have learned to adapt to our tools. Whenever an antibiotic is used, appropriately or not, resistance can develop. Today, multi-resistant infections pose an increased risk, where, in some cases, no appropriate treatment is available. Industry has been taking a leading role in contributing solutions to slow down the pace of resistance – for example, the use of diagnostics that rapidly identify a pathogen and determine suitable treatment options has helped minimize inappropriate use. Diagnostic tools also support the measurement of drug resistance in health care, providing a warning signal to epidemiologists of impending risks. That is how we have come to know the six leading pathogens responsible for deaths associated with resistance *(2)*.

Additionally, increasing the uptake of existing AMR-relevant vaccines and enabling the development of new ones is a crucial complementary effort in managing the spread of AMR and infectious disease more generally *(4)*. Preventing bacterial infections reduces the opportunities for AMR to develop and reduces antibiotic use, and vaccines against some viral diseases like influenza can also help reduce antibiotic use by reducing opportunities for inappropriate antibiotic prescriptions, as well as preventing potential secondary bacterial infections which would require antibiotic treatment. Collectively, these approaches form critical aspects of antimicrobial stewardship to ensure the antibiotics we have, and those industry is developing, remain viable tools for years to come.

We have come to rely on effective antibiotics being available, and often take them for granted. While the primary role of antibiotics is to treat individual bacterial infections, this is far from their only purpose. Antibiotics are the great enablers of modern medicine. Anything from the simplest procedures, like a tooth extraction, to more complex ones like hip replacement or cancer surgery, rely on antibiotics to prevent infections. This also applies to cancer care – as many as one in five cancer patients will be hospitalized due to an infection at some point during their treatment. However, a recent UK survey of 100 oncologists shows that 95% of them are concerned about the threat of resistant bacteria and the implications on cancer care *(5)*.

Figure 1: Global deaths (counts) attributable to and associated with bacterial resistance by pathogens, 2019

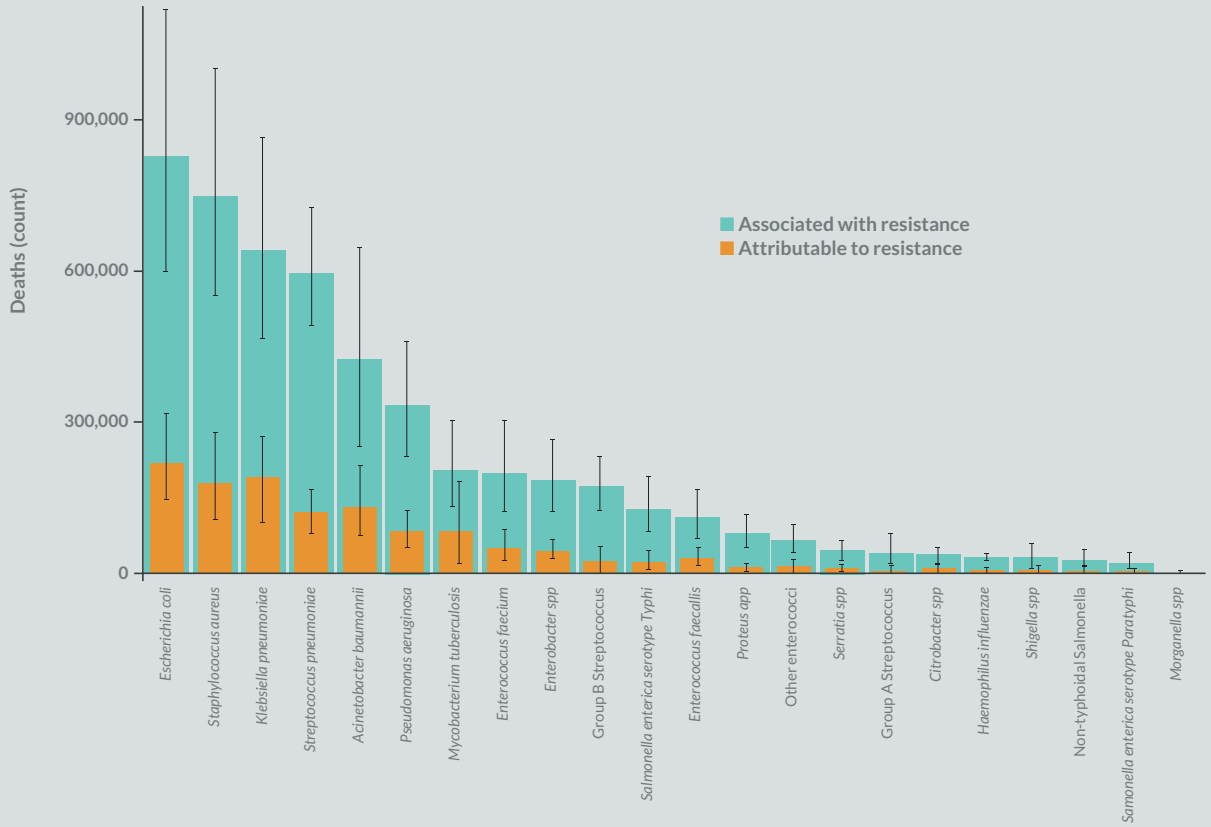

Figure taken from Murray, C., Ikuta, K., Sharara, F., Swetschinski, L., Robles Aguilar, G., & Gray, A. et al. (2022). Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. The Lancet, 399(10325), 629-655. doi: 10.1016/s0140-6736(21)02724-0. Used under CC BY 4.0 license.

Key challenges for developing new antibiotics

Unfortunately, this broad value of antibiotics is generally poorly recognized by health systems. Coupled with a challenging environment and long timelines for research and development (R&D), and prospects of successful innovation not being appropriately recognized, development of new antibiotics has slowed. New antibiotics need to be used extremely sparsely in order to preserve their effectiveness – the more they are used, the more bacteria can develop resistance. But just having them available gives us confidence we will be able to treat patients when necessary – in a way, they are like a fire extinguisher of modern medicine *(6)*. As a result, given the need for good stewardship, the total US sales of the 17 antibiotics approved by the US Food and Drug Administration (FDA) since 2010 was only US$ 714 million, with a median of ~US$ 16 million *(7)*. Even companies that successfully developed an antibiotic in the last few years have had their viability put to question *(8)*, which risks leaving a gap in terms of expertise, skills, and support to patients. Consequently, the pipeline is fragile and widely considered to be insufficient relative to the challenge *(9)*.

Despite these challenges, industry continues to invest in AMR-relevant R&D and has taken a leading role in proposing solutions that would allow a reinvigoration of the pipeline. Members of the AMR Industry Alliance collectively invested US$ 1.8–1.9 billion annually in 2019 and 2020, including in diagnostics *(10)*. Further stepping up to the challenge, in 2020 the biopharmaceutical industry led the establishment of a US$ 1 billion AMR Action Fund, with the aim to bring to market two to four new antibiotics by 2030 *(11)*. In April this year, the Fund announced its first two investments, with plans to commit over US$ 100 million in 2022 alone *(12)*. While the Fund can buy time by bridging the clinical funding gap, it will not solve the fundamental market challenges of antibiotic development. For that, sustainable market-based incentives are needed.

Similarly, the Alliance reported that industry investment levels are threatened if market conditions do not improve. On the other hand, Alliance companies reported plans to increase investment levels in AMR R&D if market conditions improved through the introduction of new policy reforms. In this respect, the most impactful solution would be so-called "pull incentives" *(10)* which reward successful antibiotic development beyond sales volumes. Pull incentives can take on several forms – some of the most commonly discussed ones include lump-sum market entry rewards, subscription-style rewards paid over a period of time, and transferable exclusivity extensions. A recent best estimate has put the globally required reward

at US$ 4.2 billion per antibiotic *(13)* on average, with the aim of providing the developer with an appropriate return on investment that could support further sustained investment into antimicrobial R&D.

Opportunities for new incentives

Pull incentives for antibiotics have been part of the global discussion for many years and have featured in virtually all G7 and G20 communiqués of the last several years, perhaps most notably under G7 UK in 2021 *(14)*. While no effective pull incentive has yet been implemented, some countries are leading the charge. One such intervention, the draft PASTEUR Act in the United States, which proposes a US$ 750 million to US$ 3 billion reward per antibiotic through a subscription model *(15)*, could move the needle significantly if implemented in its current form. The model is sometimes referred to as the "Netflix model", where subscribers pay a fixed annual sum and can watch content regardless of hours. In the case of PASTEUR, such a model would pay out a fixed annual fee over a certain period of years for all the government-procured antibiotics regardless of the volume (i.e. according to need), and based on additional determinants of a given antibiotic's value such as novelty, improving clinical outcomes, targeting priority pathogens, and others. The model is also able to support appropriate stewardship.

In the United Kingdom, a subscription model is already being piloted for two antibiotic products. The pilot is being implemented in England through National Health Service England and is capped at £10 million per product per year. The signing of contracts was announced in June, 2020 *(16)*. Although the pilot was capped, in April 2022, UK National Institute for Health and Care Excellence (NICE) published draft guidance for the two products, which specifically captured the additional societal value of these products, exceeding the initial cap *(17)*. This was achieved by recognizing the additional quality-adjusted life years (QALYs) for the products' incremental net health benefit, accounting for additional value which is captured as STEDI in the United Kingdom *(18)*. Although more work is needed to properly quantify and take into account the broader benefits antibiotics deliver beyond treating individual infections, this is an important first step. While these are positive developments, other countries need to follow suit if we are to be successful. Importantly, we need all of the G7 and the European Union to implement solutions of their own in the next few years. Given the potential impact on cancer care, we welcome a call from the cancer community for the implementation of sustainable solutions to revitalize the ecosystem and ensure that new antibiotics are available in the future. Further, there is a need for increased education and awareness among all key groups impacted.

Broad industry action and way forward

New antibiotics will always be needed and, collectively, we need to do more to ensure that they are developed. The industry is also cognizant that reinvigorating the antibiotic pipeline is not the only AMR-related challenge we face today, despite its utmost importance. Through the AMR Industry Alliance, the life sciences industry works to actively contribute to tackling the challenges of access, improving stewardship globally, and advancing manufacturing practices with respect to the environment, and has been reporting on industry progress since 2018.

To support global access, the Alliance is developing a framework for scaling access to antibiotics and diagnostics in low- and middle-income country (LMIC) hospital settings and developing a sustainability framework for off-patent antibiotics. By developing a set of best practices and clear implementation roadmaps, the Alliance, representing more than 100 biotech, large R&D pharmaceutical, generics, and diagnostics companies, can achieve significant impact.

To ensure that antibiotics are used appropriately, the Alliance has encouraged innovation in stewardship through the 2021 Stewardship Prize, which was again announced for 2022. This programme rewards stewardship programmes in LMICs that have demonstrated their ability to improve the appropriate use of antibiotics, and which can be adopted and scaled up elsewhere to further support stewardship principles. The Alliance is also supporting efforts to understand the barriers to diagnostic use in stewardship programmes in high-resource settings to encourage policy, payment, and product innovations in support of antimicrobial stewardship.

Another area of significant engagement of industry has been to encourage the responsible manufacturing of antimicrobials. Manufacturing is just one of many potential sources of antimicrobials in the environment (alongside normal human and agricultural use). In the production of these medicines, emissions in manufacturing waste streams can increase the selection pressure on bacteria in the environment to develop resistance to the antimicrobials they encounter. Since 2018, in the absence of international standards, the Alliance has been providing clear guidance to manufacturers in the global antibiotic supply chain to ensure that their antibiotics are made responsibly, helping to minimize the risk of the environmental dimension of antimicrobial resistance. In June 2022, the Alliance launched its Antibiotic Manufacturing Standard, which aims to formalize its work to date. An associated certification scheme in partnership with the British Standards Institute is set to follow in 2023 *(19)*.

Industry has an important role to play as a partner and solutions provider in the global fight against AMR. Working together to invest in R&D that meets the global health

needs with new innovative diagnostics and treatments, improving access to high-quality antibiotics and ensuring that new ones are available to all, and working to reduce the development of AMR through improved stewardship are the key commitments of the Alliance members. But, to truly solve the challenge, all stakeholders need to work jointly. While we have seen progress, it has so far been uneven both in terms of geography and policy areas, as shown by the 2021 AMR Preparedness Index *(20)*. Given the impact of AMR on all facets of health care, it is crucial that patients, including those suffering from cancer, health-care professionals and other affected communities have their voices heard. Only then can the full extent of the AMR challenge be properly understood, and action prioritized. ■

Luka Srot, MPharm works at the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA). At IFPMA, he manages the organization's policy and advocacy work on AMR, including maximizing the impact of vaccines in the fight against AMR. Previously, he also led the Secretariat of the AMR Industry Alliance, a broad life sciences industry coalition set up to identify sustainable solutions against AMR and to drive and measure industry progress.

Diane Flayhart works at Becton Dickinson & Co. (BD) and is a member of BD's Global Public Health Team. As the AMR Global Program Leader, Diane works to champion and support the development of new AMR programme initiatives in global awareness, infection prevention and control, and antimicrobial stewardship. She leads efforts for the Antimicrobial Resistance Fighter Coalition, a global organization that aspires to change behaviour across the globe that will maintain the effectiveness of antibiotics for future generations. BD is a board member of the AMR Industry Alliance.

References

1. 10 global health issues to track in 2021. WHO (2020). Accessed 25 July 2022, from https://www.who.int/news-room/spotlight/10-global-health-issues-to-track-in-2021
2. Murray C, Ikuta K, Sharara F, Swetschinski L, Robles Aguilar G, Gray A, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet*. 2021; 399(10325), 629-655. doi: 10.1016/s0140-6736(21)02724-0
3. O'Neill J. Tackling Drug-Resistant Infections Globally: Final Report and recommendations. *Review on Antimicrobial Resistance* (2016). London: HM Government. doi: 10.1016/j.jpha.2015.11.005 Accessed from: https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf
4. Leveraging Vaccines to Reduce Antibiotic Use and Prevent Antimicrobial Resistance: An Action Framework. WHO (2020). Accessed from: https://cdn.who.int/media/docs/default-source/immunization/product-and-delivery-research/action-framework-final.pdf
5. Effectiveness of Cancer Treatments Threatened by Rising Antibiotic Resistance. Longitude Prize. (2020). Accessed 25 July 2022, from https://longitudeprize.org/resources/effectiveness-of-cancer-treatments-threatened-by-rising-antibiotic-resistance/
6. Rex J. Fire Extinguishers of Medicine. AMR.Solutions. Accessed 25 July 2022, from https://amr.solutions/fire-extinguishers-of-medicine/
7. Outterson K, Orubu E, Rex J, Ardal C, Zaman M. Patient Access in 14 High-Income Countries to New Antibacterials Approved by the US Food and Drug Administration, European Medicines Agency, Japanese Pharmaceuticals and Medical Devices Agency, or Health Canada, 2010-2020 (2021). *Clinical Infectious Diseases* (2022), 74(7), 1183-1190. doi: https://doi.org/10.1093/cid/ciab612.
8. McKenna M. The antibiotic paradox: why companies can't afford to create life-saving drugs. *Nature* 2020. Accessed 26 July 2022, from https://www.nature.com/articles/d41586-020-02418-x
9. 2020 antibacterial agents in clinical and preclinical development: an overview and analysis. WHO (2021). Accessed from https://apps.who.int/iris/bitstream/handle/10665/340694/9789240021303-eng.pdf?sequence=1&isAllowed=y
10. Progress Report. AMR Industry Alliance (2022). Accessed 25 July 2022, from https://www.amrindustryalliance.org/progress-report/
11. Antimicrobial Resistance Research & Development. AMR Action Fund. Accessed 25 July 2022, from https://www.amractionfund.com/
12. AMR Action Fund Announces First Investments in Adaptive Phage Therapeutics and Venatorx Pharmaceuticals (2022). Accessed 25 July 2022, from https://www.prnewswire.com/news-releases/amr-action-fund-announces-first-investments-in-adaptive-phage-therapeutics-and-venatorx-pharmaceuticals-301514936.html
13. Outterson K. Estimating The Appropriate Size Of Global Pull Incentives For Antibacterial Medicines. *Health Affairs* (2021), 40(11), 1758-1765. doi: 10.1377/hlthaff.2021.00688
14. G7 Finance Ministers' Statement on Actions to Support Antibiotic Development. Gov.UK (2021). Accessed 25 July 2022, from https://www.gov.uk/government/publications/g7-finance-ministers-statement-on-actions-to-support-antibiotic-development
15. 117th Congress 1st Session-PASTEUR Act. Accessed from BON21821 (senate.gov)
16. NHS lands breakthrough in global battle against superbugs. NHS England (2022). Accessed 25 July 2022, from https://www.england.nhs.uk/2022/06/nhs-lands-breakthrough-in-global-battle-against-superbugs/
17. Models for the evaluation and purchase of antimicrobials. National Institute for Health and Care Excellence. Accessed 25 July 2022, from https://www.nice.org.uk/about/what-we-do/life-sciences/scientific-advice/models-for-the-evaluation-and-purchase-of-antimicrobials
18. Outterson K, Rex J. Evaluating for-profit public benefit corporations as an additional structure for antibiotic development and commercialization. *Translational Research* (2020), 220, 182-190. doi: 10.1016/j.trsl.2020.02.006
19. Responsible Manufacturing. AMR Industry Alliance (2022). Accessed 25 July 2022, from https://www.amrindustryalliance.org/shared-goals/common-antibiotic-manufacturing-framework/
20. 2021 AMR Preparedness Index. Global Coalition on Aging (2021). Accessed 25 July 2022, from https://globalcoalitiononaging.com/wp-content/uploads/2021/06/GCOA-AMR-Preparedness-Index_FINAL.pdf