

ANTIMICROBIAL RESISTANCE (AMR)

INTRODUCTION

Antimicrobials are essential in the treatment of life-threatening infections and vital to the success of most common surgical procedures and many treatments, such as chemotherapy, HIV and transplant medicines. They also play a crucial role in maintaining the health of animals. However, bacterial resistance to antimicrobials has become a major problem.

Although resistance to antimicrobials is a naturally-occurring phenomenon among bacteria, inappropriate antimicrobial treatment and overuse of antibiotics in humans and animals have contributed to the growing emergence of drug-resistant bacteria.

Patients with infections caused by drug-resistant bacteria are at increased risk of worse clinical outcomes and death, and consume more health-care resources than patients infected with non-resistant strains of the same bacteria¹. The gravity of the situation is illustrated by the number of AMR-related deaths where serious infections cannot be treated, including estimates of 25,000 deaths per year in Europe, 23,000 deaths per year in the United States², and more than 500,000 deaths each year globally.

If not addressed, AMR will erode the health, societal and economic gains the world has made through antimicrobials towards a more sustainable and equitable future. The UK AMR Review³ quantified the potential global picture in 2050 if no actions are put in place. Even using conservative assumptions with respect to the current AMR growth, both studies revealed that without global action, an additional 10 million people would die every year from drug-resistant infections by 2050 – more than current deaths from cancer. Predictive macroeconomic models suggest that if AMR is not addressed it would cause a global economic damage similar to the 2008-2009 financial crisis⁴ with eight trillion USD in global productivity losses per year by 2050, and a cumulative 100 trillion USD loss over the next 35 years⁵.

The rise of antimicrobial resistant bacteria is a global public health emergency and is driving an urgent need to use currently available solutions like vaccines to slow down the rise of AMR while discovering and developing new antimicrobial molecules and AMR-relevant vaccines.

¹ <http://documents.worldbank.org/curated/en/323311493396993758/pdf/114679-REVISED-v2-Drug-Resistant-Infections-Final-Report.pdf>

² <https://www.cdc.gov/drugresistance/index.html>

³ <https://amr-review.org/>

⁴ <http://documents.worldbank.org/curated/en/323311493396993758/pdf/114679-REVISED-v2-Drug-Resistant-Infections-Final-Report.pdf>

⁵ <http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002184>

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SANOFI'S POLICY POSITION

Sanofi's position on combating AMR resistance is articulated around the following priorities:

1. Enabling Appropriate Patient Access to Antimicrobials, Diagnostics and Vaccines

- Reducing uncontrolled or inappropriate access to antimicrobials is essential for effectively combating AMR.
- All patients who need them should have access to appropriate high-quality antimicrobials and other anti-infectives, including new classes and generations of anti-microbial products. This includes products that treat bacterial infections, as well as vaccines which can prevent both viral and bacterial diseases.
- All stakeholders, including national governments,, industry, international bodies,... should work together to develop new business models, which will improve access to current and new antimicrobials, diagnostics and AMR-relevant vaccines globally, while supporting appropriate use and good stewardship.

2. Preserving Medical Value of Current Antimicrobials

- Sanofi supports the antimicrobial stewardship principles set out by the World Health Organization (WHO) Global Action Plan on antimicrobial resistance and the G20 Health Ministers' Declarations from Berlin in 2017 and Argentina in October 2018, which also recognize the need for strong infection prevention measures and the need for vaccines to be prioritized across health systems to prevent the emergence and contain the spread of AMR.^{6,7,8}
- The development of drug resistance can be reduced through better and more appropriate use of existing antimicrobials. Antimicrobials should only be used by those patients who need them and when used, efforts should be made to deliver the right antimicrobial for the medical condition being treated.
- Promotional activities should align with the mission of advancing stewardship and preserving the utility of antimicrobials.
- Counterfeit medical products present a significant challenge to public health. Falsified antimicrobials, containing low or no dose of active principle, or containing multiple contaminants, pose a specific threat by facilitating the development of AMR.
- The appropriate and responsible use of antimicrobials in livestock should be promoted, as part of a 'one health' approach.

⁶ <https://www.who.int/antimicrobial-resistance/global-action-plan/en/>

⁷ https://www.google.com/search?q=G20+Health+Ministers%E2%80%99+Declarations+from+Berlin+in+2017&rlz=1C1GCEB_enFR785FR785&og=G20+Health+Ministers%E2%80%99+Declarations+from+Berlin+in+2017&aqs=chrome..69i57.1431j0j7&sourceid=chrome&ie=UTF-8

⁸ <http://www.g20.utoronto.ca/2018/2018-10-04-health.html>

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- The development and use of new, effective and rapid point-of-care diagnostic tests for the identification and characterization of resistant bacteria can make a significant contribution to ensuring that the right antimicrobial is used for the medical condition being treated. Additional incentives should be considered to facilitate the development and use of such tests to support clinical decision-making.
- Harmonization across national standards for clinical breakpoints (e.g., the European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints⁹ and Clinical Laboratory Standards Institute (CLSI) clinical breakpoints) would reduce the complexity of determining resistance.
- Appropriate use of antimicrobials and vaccines can be improved through the better education of those responsible for prescribing and dispensing.
- The development of educational initiatives that aim to improve public understanding of the problems of drug resistance and support positive behavior change regarding antimicrobial use should be encouraged.
- Building better surveillance capabilities and greater sharing of surveillance data will improve the identification and understanding of resistance trends, which will help to drive appropriate AMR strategies, including stewardship and appropriate access.

3. Increase The Uptake of Vaccines

- Vaccines are part of the solution to help mitigate the threat of AMR. They can prevent viral infections which are often inappropriately treated with antibiotics¹⁰ and can lead to secondary bacterial superinfections. Vaccines can also target drug-resistant bacterial infections.
- Increasing the use of currently available vaccines is an immediate action that should be taken to maintain the medical value of current antimicrobials while new anti-infectives are being developed.
- National governments should recognize the value of vaccines as an immediate complementary tool to slow down the rise and spread of AMR by including them in their national AMR action plan and encouraging the use of currently available vaccines.

4. Reducing Environmental Impact

- Improving efforts to reduce the impact on the environment resulting from the production of antimicrobials is crucial to combat AMR.
- Manufacturers and suppliers have the responsibility to review and assess their processes to ensure they are implementing best-practice to control emissions of antibiotics into the environment, in line with agreed technical standards.

⁹ **Breakpoints** are an integral part of modern microbiology laboratory practice and are used to **define** susceptibility and resistance to antibacterials. Depending on the testing method, they are expressed as either a concentration (in mg/liter or µg/ml) or a zone diameter (in mm).

¹⁰ Fleming-Dutra, K.E. et al. Prevalence of inappropriate antibiotic prescriptions among US ambulatory care visits, 2010–2011. *J. Am. Med. Assoc.* 315, 1864–1873 (2016).

- Every manufacturer should put in place an action plan for reducing the environmental impact of antimicrobial manufacturing and should strive to have fully-implemented mitigation programs in place where needed.
- Companies have a responsibility to control the manufacturing sites of their antimicrobials suppliers to assess their environmental, safety and hygiene compliance and practices. Companies should require their suppliers to meet Pharmaceutical Industry Shared Management (PSCI) Principles.
- A transparent and practical mechanism demonstrating that industry supply chains meet the required standards would encourage individual companies to improve their existing manufacturing processes.
- “Take-back” programs can help consumer education initiatives to promote safe and appropriate disposal of unused/unwanted medicines.
- Cross-industry initiatives are effective means of creating and promoting shared principles, standards and best practices for responsible and sustainable supply chain management.

5. Incentivizing and Supporting Research and Development

- Public-private partnerships and research collaborations contribute to the advancement of knowledge and the development of new antimicrobial treatment and prevention options and should be encouraged.
- Governments and other funding agencies should provide globally coordinated funding dedicated to supporting competitive research and development of novel antimicrobial compounds, , and of new vaccines for pathogens that pose a threat to human health. The mechanisms for accessing such funding should be efficient and ensure accountability through non-burdensome reporting requirements. Such funding should include provision for the training of scientists
- Strong intellectual property frameworks and other exclusivity incentives are vital to bringing new drugs to market, and can encourage data sharing in pre-competitive environments.
- The exchange of data through a shared repository is an effective means of addressing scientific challenges and gaps in the industry pipeline.
- Harmonized target product profiles and the definition of acceptable safety profiles for novel antimicrobials are essential in the fight against AMR.
- Specific areas of AMR-related research need to be prioritized, including how to sustain access to and innovation in the natural products domain and how to test new immune-modulating agents for their potential impact on infectious diseases.
- Sanofi also supports the AMR research priorities set forth in the Pew Charitable Trusts scientific roadmap¹¹.

¹¹ <http://www.pewtrusts.org/en/research-and-analysis/reports/2016/05/a-scientific-roadmap-for-antibiotic-discovery>

- Centralized efforts and dedicated funding to revive clinical development of legacy/stopped compounds could provide a fast, although temporary, relief to the current AMR situation.
- Sustainable clinical trial networks and patient registries can speed up both the recruitment of investigator sites and patients; in reducing costs by facilitating implementation of new and adapted clinical trial designs.
- Vaccines and novel alternatives to antimicrobials should be eligible for the same incentives as antimicrobials when they are also targeted to combat AMR.
- Priority pathogen lists, for example as produced by the WHO, should provide clear direction on which pathogens to prioritize for the development of new vaccines to combat AMR.

6. Incentivizing and Streamlining the Regulatory Environment

- Regulators and industry should work together to establish new accelerated and streamlined regulatory pathways for new antimicrobials and vaccines contributing to AMR reduction, that take into account the specific challenges associated with the development of both conventional and innovative antimicrobials and AMR-relevant vaccines.
- Greater harmonization of regulatory requirements and processes at the global level can make a significant contribution to both streamlining the development and introduction of new antimicrobials, and reducing the costs associated with bringing these new drugs to market.

7. Incentivizing Commercial Investment

- Pricing of antimicrobials in the current business model is a disincentive to further investment due to frequent negative net product value (NPV) assessments or inadequate return on investment
- A new economic model for antimicrobials is needed. It might include one or more of the following elements; market entry rewards (a reward, either lump-sum or phased payments, granted upon achieving market approval), non-transferrable exclusivity, transferrable exclusivity, insurance licensing. Specific incentives are also needed to promote the uptake of vaccines that could contribute to AMR reduction.
- The medico-economic model used for drugs for rare diseases, which provides a balance between pricing and guarantees of sustained availability and education programs to ensure optimal usage, could be applicable to certain antimicrobials.
- Commercial incentives should be centralized or managed globally to reduce complexity and cost.
- Incentives should be tailored to reward innovation by focusing on specific attributes of the target product. Precise target product profiles, along with a target for the number of products fulfilling these profiles, should be determined in advance and made transparent.

- Vaccines and novel alternatives to antimicrobials, when targeted against AMR, as well as new, effective and rapid point-of-care diagnostic tests for the identification and characterization of resistant bacteria, should be eligible for the same market incentives as antimicrobials.
- Overall, worldwide AMR policies should be flexible to allow systems to respond to new and emerging pathogens.