DELIVERING ON OUR COMMITMENTS

Merck's actions to address antimicrobial resistance

MERCK

August 2024

Our commitment

Merck's efforts to prevent and treat infectious diseases

Antimicrobial resistance (AMR) poses a significant threat to global public health and development. In 2019, drug-resistant bacterial infections contributed to the deaths of an estimated 4.95 million people worldwide and were directly responsible for an estimated 1.27 million of these deaths. Each year, this growing crisis threatens millions of lives, undermines global food and healthcare systems, and negatively impacts economic development.

The time to act is now.

For more than a century, Merck has played a significant role in the discovery and development of novel medicines and vaccines to combat infectious diseases. For example, in the 1940s, Merck developed one of the first methods to mass-produce penicillin, one of the world's first antibiotics, and developed streptomycin, the first antibiotic effective against tuberculosis, in collaboration with Rutgers University. Despite the urgent need for new antibiotics to fight AMR, the number of companies conducting antimicrobial R&D has significantly declined and several large research-based pharmaceutical companies have exited the space due to market challenges. Without policy reforms to create an innovation ecosystem that enables a sustainable return, industry engagement and investment in the development and supply of novel antibiotics will likely continue to decrease.

In addition to our internal efforts, Merck is collaborating with key stakeholders to slow the threat of AMR and help ensure patients have access to effective antibiotics – now and in the future.

> *"AMR is not a future problem – it's here now, threatening human, animal, and environmental health as we know it. We must take swift, collaborative action to help reduce the risk of AMR before it's too late."*
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> **Jennifer Zachary, Executive Vice President and General Counsel at Merck and member of the Global Leaders Group on AMR**

One Health Global Leaders Group on Antimicrobial Resistance

Merck is proud to represent the biopharmaceutical industry in the One Health Global Leaders Group on Antimicrobial Resistance. Our Executive Vice President and General Counsel Jennifer Zachary is a part of this organization, which advocates to accelerate global action on AMR through a One Health approach.

AMR Industry Alliance

To drive and measure industry progress on AMR, in May 2017 we co-founded the AMR Industry Alliance, a coalition of research-based pharmaceutical companies, biotech companies, generic manufacturers, and diagnostic developers all working together to curb AMR by committing to address four key areas: research & science, appropriate use, access, and manufacturing. The AMR Industry Alliance has achieved several milestones, including developing standards to guide manufacturers in the global antibiotic supply chain on how to responsibly produce antibiotics and establishing a Stewardship Prize to recognize innovative approaches to supporting appropriate use of antibiotics in low- and middle-income countries (LMICs).

Merck Animal Health recognized as first industry partner of PREZODE

Merck Animal Health was the first industry partner of the Preventing Zoonotic Disease Emergence (PREZODE) Initiative. Launched at the One Planet Summit in January 2021 at the initiative of French government and now supported by nearly 170 partners, including 15 governments, the PREZODE Initiative is advancing global research efforts on animal, human, and environmental health to better understand, prevent, detect, and monitor zoonotic pandemic risks.

There is no single solution to the complex problem of AMR, but Merck is committed to investing our expertise and resources alongside governments and key stakeholders across sectors to address this global health crisis.

Key areas of engagement	Our commitments
 Driving innovation for One Health	Advancing incentives that reflect the societal value of new antimicrobials and vaccines and support sustainable investment in research and development
 Expanding access	Partnering to improve access to new antimicrobials, diagnostics, and vaccines globally while supporting appropriate use
 Advancing antimicrobial stewardship	Supporting governments and public health efforts to educate healthcare professionals and patients on appropriate use of antimicrobials, the value of vaccination, and expanded use of diagnostics
 Gathering data for AMR surveillance	Collecting and sharing surveillance data with public health bodies and healthcare professionals to improve the understanding of resistance trends and appropriate antimicrobial and vaccine use, which may be particularly important in LMICs where regional surveillance may not be available
 Protecting the environment	Developing science-driven, risk-based targets for discharge concentrations for antimicrobials and good practice methods to reduce the environmental impact of manufacturing discharges in partnership with independent technical experts

Driving innovation for One Health

Discovering and developing novel anti-infective medicines, vaccines and technologies

Merck's broad infectious disease product portfolio and pipeline span both human and animal health and include antibiotics, antivirals, antifungals, antiparasitics, vaccines, and novel approaches to address resistance.

Continued in-house focus on early discovery

Recognizing the urgent need for new antibiotics to address AMR, our scientists continue to pursue early-stage research in this space. Merck is invested and actively engaged in antibiotics research to discover novel approaches to overcome AMR. We recently published a full synthesis of darobactin A, a novel broad gram-negative targeting agent, and information on an early-stage narrow-spectrum asset targeting a Centers for Disease Control and Prevention (CDC) "Urgent Threat" in Nature Microbiology.

AMR Action Fund

In 2020, Merck and a group of more than 20 leading biopharmaceutical companies launched the AMR Action Fund, a groundbreaking $1B partnership that aims to bring two to four new antibiotics to patients by 2023. As a lead investor, Merck has committed $100 million over 10 years into the Fund to help enable ongoing clinical R&D in the absence of sufficient venture capital investment and bridge the gap between the innovative early antibiotic pipeline and patients. As of June 2024, the AMR Action Fund has invested in eight biotech companies that are developing antimicrobial therapeutics for priority pathogens, as determined by the World Health Organization (WHO) and CDC.

Pediatric clinical development

We continue to develop our antibiotic portfolio with additional studies and expanded indications for pediatric populations. Since 2016, Merck secured eight out of ten U.S. Food and Drug Administration (FDA) approvals for pediatric antibiotics.

Merck remains committed to generating data to help improve the health outcomes of pediatric patients.

- RECARBRIO™ (imipenem, cilastatin, and relebactam): As of 2024, RECARBRIO™ (imipenem, cilastatin, and relebactam) is being evaluated in a Phase 2/3 study in participants from birth to less than 18 years of age with a confirmed or suspected bacterial infection of one of the following primary infection types caused by certain gram-negative pathogens: hospital-acquired bacterial pneumonia (HABP) or ventilator-associated bacterial pneumonia (VABP); complicated intra-abdominal infection (cIAI); or complicated urinary tract infection (cUTI).
- ZERBAXA® (ceftolozane and tazobactam): In 2022, ZERBAXA® (ceftolozane and tazobactam) was approved to treat pediatric patients with certain cUTIs and cIAIs caused by certain gram-negative pathogens, after initial approvals to treat adults with certain cUTIs and cIAIs caused by certain gram-negative pathogens in 2014. As of 2024, ZERBAXA® (ceftolozane and tazobactam) is being evaluated in a Phase I PK and safety study of pediatric patients with HABP/VABP, following previous approval for the treatment of HABP/VABP in adults caused by certain gram-negative pathogens.
- DIFICID® (fidaxomicin): In 2020, DIFICID® (fidaxomicin) received FDA approval for the treatment of *Clostridioides difficile*-associated diarrhea (CDAD) in children aged six months and older.
- ZINPLAVA™ (bezlotoxumab): In 2023, ZINPLAVA™ (bezlotoxumab) was approved to prevent recurrence of *Clostridioides difficile* infection (CDI) in pediatric patients at high risk of CDI recurrence, after initial approval of this indication in adults in 2016.
- SIVEXTRO® (tedizolid phosphate): As of 2024, Merck recently completed two studies in pediatric patients less than 12 years of age – a Phase 1 PK and study in patients <2 years of age and a Phase 3 study evaluating the safety and efficacy of tedizolid phosphate in pediatric patients with acute bacterial skin and skin structure infections (ABSSSI). SIVEXTRO® (tedizolid phosphate) was previously approved for the treatment of patients 12 years of age and older with ABSSSI caused by certain Gram-positive microorganisms.

Calling for action to secure our antibiotic future

Despite the urgent need for new antibiotics to treat emerging resistance, the number of companies conducting antimicrobial R&D has significantly declined and several large research-based pharmaceutical companies have exited the space. Several leading biotech companies with late-stage or approved antibiotics have gone bankrupt or been sold, further impacting the already fragile R&D environment and limited pipeline. The lack of viable commercial ecosystem also threatens sustainable, secure supply and global access to existing antibiotics.

We recognize that this is an area of significant public health and medical need, and Merck continues to conduct research to discover and develop new antimicrobials. However, without substantial changes to the economic landscape, it will be difficult for the company to continue to justify significant investment into new antibiotic R&D programs. The AMR Action Fund can help to bridge the gap in investment in clinical development between the innovative early antibiotic pipeline and patients, but this is only a temporary solution. Without the implementation of new incentive models, the biotech companies supported by the AMR Action Fund are unlikely to survive, and the two to four novel antibiotics the Fund aims to bring to approval by 2030 may never reach patients. There is a short window of time to advance the pull incentives needed to support sustainable investment in this space – without action, the future of antibiotic innovation is at serious risk.

MERCK'S LEGACY
OF ANTIMICROBIAL DEVELOPMENT

1930s
Merck Research Laboratories played a central role in the development of sulfas, the first synthetic antimicrobial

1940s
Merck developed one of the first methods for mass production of penicillin, one of the world's first antibiotics, as well as streptomycin, the first antibiotic effective against tuberculosis, in collaboration with Rutgers University

1950s & 60s
Merck received approval for the first combined vaccine for measles, mumps, and rubella

1970s
Merck brought to market a vaccine to help prevent pneumococcal disease and an important cephalosporin antibiotic that covers a wide range of both gram-positive and gram-negative bacteria

1980s
Merck received FDA approval for two antibiotics, including the first carbapenem, which was effective against a broader spectrum of bacteria than any other previously marketed

1990s
Merck received FDA approval for a new oral third-generation cephalosporin antibiotic, as well as a varicella

2000s
Merck brought two antibiotics and two antifungals to market, including the first in a new class of drugs designed to counter invasive fungal infections; Merck also initiated the SMART surveillance study to monitor for trends in the development of resistance

2010s
Merck received FDA approval for four antimicrobial innovations, more than any other company, including the first new oral antibiotic in its class in almost 15 years; additionally, Merck also received approvals for a new treatment to reduce the recurrence of CDI in certain high-risk adults

2020s
Merck, along with a group of more than 20 leading biopharmaceutical companies, launched the AMR Action Fund to bring two to four new antibiotics to patients by the end of the decade; additionally, Merck received three expanded indications for recently approved antibiotics and brought forward vaccines for the prevention of invasive disease caused by several *Streptococcus pneumoniae* serotypes

TODAY
Merck continues to invest in R&D to bring new antimicrobials and vaccines to patients, collaborate with academic researchers, advocate for government action to create supportive markets for antimicrobial innovation, and work to improve appropriate antibiotic use globally

Expanding access

Enhancing affordable access to antibiotics for patients worldwide

Merck is collaborating with a range of partners to enable access to our products around the world.

When patients or animals develop life-threatening infections, it is critical that they have timely access to the most appropriate antibiotic. The Global Leaders Group on AMR reports that the greatest impact of AMR occurs in low-income settings, with Sub-Saharan Africa facing the highest burden of AMR globally. At the current level of action on AMR, there would be an average loss of 1.8 years of life expectancy globally due to AMR by 2035, but in some LMICs, for example in the Eastern Mediterranean region, life expectancy would fall by as many as 2.5 years in that period. In these contexts, expanding appropriate access to novel antibiotics could have a significant impact on disease.

As a multinational pharmaceutical company, we work to utilize our global reach to facilitate access through broad registration, commercialization, and a dedicated supply chain. Merck continues to explore mechanisms and partnerships to expand global access to our human and animal health products.

Recognizing the importance for patients and healthcare providers worldwide, Merck supports the access and availability of RECARBRIO™ (imipenem, cilastatin, and relebactam), ZERBAXA® (ceftolozane and tazobactam), and SIVEXTRO® (tedizolid phosphate) through our access pricing framework, making these products available at our lowest price to public and non-commercial providers of care in lower-income countries, recognizing the relative ability of governments to finance healthcare.

Merck is committed to achieving broad registration of our antibiotic and antifungal portfolio. For example, since U.S. FDA approval 10 years ago, ZERBAXA® (ceftolozane and tazobactam) has been registered in 85 countries, of which 11 are LMICs, and 10 million doses have been supplied worldwide. RECARBRIO™ (imipenem, cilastatin, and relebactam) has been registered in 50 countries and SIVEXTRO® (tedizolid phosphate) has been registered in 42 countries.

While the importance of expanding access in LMICs is well recognized, high-income countries can also face barriers in accessing new antibacterials. A 2021 study found that patient access to new antibacterials is limited in some high-income countries, often because a commercial launch is never executed after regulatory approvals. This study found that, of the 18 new antibacterials approved by the FDA between 2010-2019, Merck's DIFICID® (fidaxomicin) and ZERBAXA® (ceftolozane and tazobactam) were the only medicines available in all 14 high-income countries included in this study.

Merck collaborated with our partners in the AMR Industry Alliance to launch the Equitable and Responsible Access Roadmap, which examines barriers that are limiting access for patients, including antimicrobial regulatory issues, and offers a collaborative framework for governments and the private sector to address these challenges and strengthen healthcare systems.

WHO Essential Medicines List

Following applications from Merck, ZERBAXA® (ceftolozane and tazobactam) and SIVEXTRO® (tedizolid phosphate) were added to the 23rd WHO Essential Medicines List. According to the WHO, essential medicines are those that satisfy the priority healthcare needs of a population. They were selected based on disease prevalence and public health relevance, evidence of efficacy and safety, and comparative cost-effectiveness.

Tedizolid phosphate licensing agreement

In an ongoing effort to provide greater availability of tedizolid phosphate, Merck has entered into a licensing deal with Sun Pharmaceuticals to develop and gain approval for a generic form of tedizolid phosphate in India. This agreement will help to facilitate availability of this important antibiotic in India.

Global Alliance for Livestock Veterinary Medicine

Our company is a founding member and active participant in the Global Alliance for Livestock Veterinary Medicine (GALVmed), an initiative to improve access to medicines in Africa and Asia for small-scale livestock producers. GALVmed has developed new therapeutics alongside diagnostics and has been active in work to improve the regulatory process for existing products. GALVmed promotes sustainable availability, accessibility, and adoption of affordable and high-quality veterinary medicines. GALVmed's work to engage with small-scale livestock producer communities and understand their needs is important in creating stronger markets that ensure medicines are used correctly.

"We know AMR is one of the biggest global health threats and poses a significant challenge without a simple solution. Collaboration is essential to drive sustainable antibiotic innovation, promote responsible use of antibiotics and improve access to ensure patients worldwide can receive the antibiotics and vaccines they need."

Dr. Jenelle Krishnamoorthy, Vice President, Global Public Policy at Merck

Advancing antimicrobial stewardship

Supporting the responsible use of antimicrobials to improve outcomes, ensure a safe and sustainable food supply, and slow the development of resistance

The development of AMR is a natural evolutionary process, but it is accelerated by the inappropriate use of antimicrobial medicines in human, animal, and environmental sectors. We are committed to helping ensure antimicrobials are used responsibly.

We regularly review and update promotional materials to ensure alignment with stewardship principles, provide an antimicrobial stewardship (AMS) curriculum for relevant employees, and adopt innovative approaches to field sales representative compensation in some countries. In the U.K., for example, we worked to inform the rollout of a new "de-linked" subscription model for the reimbursement of innovative antibiotics. Through this new model, an antibiotic's reimbursement is based on its value to the health system rather than the volume prescribed. Companies that take part in this model will be required to focus solely on medical education and related stewardship activities with no incentives based on antimicrobial sales volume.

In both humans and animals, some vaccines may help prevent certain infections and can support responsible antibiotic use by potentially reducing the need for antibiotic use. Vaccine innovation is one way our company works to reduce many of the key drivers of AMR. Merck Animal Health invests significantly in promoting vaccination, manufacturing over **112 billion** vaccine doses annually. Merck Animal Health is working to develop vaccines for a wide variety of animal diseases, including those animal diseases where vaccines can reduce the need for antibiotic use.

Merck Animal Health is aligned with the Health for Animals Antibiotic Commitment, as well as the Codex Alimentarius Commission's Compendium of Codex standards on Foodborne Antimicrobial Resistance. The Codex standards outline clear principles for the responsible and prudent use of antimicrobials across the food-producing sector in support of public health. They are developed through science-based and consensus-driven consultations organized by the Food and Agriculture Organization, the WHO, and the World Organization for Animal Health.

Merck supports the responsible use of antimicrobials through key initiatives and collaborations focusing on education, implementation, research, and/or advocacy, including the following programs:

Community and hospital-based initiatives

We have worked with over 1,100 hospitals in 28 countries as an AMS resource and partner to develop and implement patient-centric, product-agnostic AMS programs around the world. We've also provided significant grant funding for over 70 investigator-initiated AMS research projects unrelated to Merck products. For example, in Peru, Merck supported early implementation of AMS programs at three hospitals in EsSalud that resulted in an increase in resources and processes available for AMS programs, as well as a reduction in the consumption of broad-spectrum antimicrobials in two of the hospitals. The research and results of the project, which were published in the Chilean Journal of Infectology, were recognized with the Kaelin Research Award in 2020.[1]

Animal Health

Merck Animal Health is advancing a range of new technologies that could help to reduce use of antibiotics in animal health. For example, our SenseHub™ Dairy and SenseHub™ Feedlot products actively monitor cows' behavior 24/7 and alert the farmer to deviations from normal behavior. This can help the farmer and veterinarian determine potential illness or disease earlier than visual observation alone. Maintaining a healthy herd can, in turn, reduce the use of antibiotics.

Generating data to support appropriate prescribing

Throughout the clinical development process, we gather relevant data on how our products should be used in clinical practice in order to support appropriate use. Merck continues to generate real-world evidence and support investigator-initiated studies to inform the use of ZERBAXA® (ceftolozane and tazobactam) and RECARBRIO™ (imipenem, cilastatin, and relebactam) and other antimicrobial agents. Results are shared with the scientific community through appropriate forums, including peer-reviewed publications.

1. Hernández-Gómez C, et al., Programas de optimización del uso de antimicrobianos en Perú: Un acuerdo sobre lo fundamental, *Revista chilena de infectología*, 2019, 36.

Gathering data for AMR surveillance

Identifying trends in pathogen incidence and AMR

One key way Merck supports AMS and responsible use of antimicrobials is through our investments in AMR surveillance. Surveillance studies can help identify trends in pathogen incidence and AMR and provide early indicators of resistant strains. We recognize the important role surveillance plays in combating AMR, and we have taken steps to make our AMR surveillance data accessible to researchers and public health authorities around the globe.

SMART

One of the world's largest and longest-running AMR surveillance studies, SMART has enabled researchers to monitor the susceptibility of gram-negative bacteria to antibiotics and identify trends in the development of resistance. Since its initiation in 2002, SMART has collected approximately 500,000 isolates from over 200 sites in more than 60 countries around the world – with more than 20 participating sites in LMICs. In 2020, Merck launched a new global SMART surveillance website with expanded functionality as part of an effort to make SMART data more accessible. The website includes heat maps of resistance patterns and improved functionality for SMART investigators, including data that is highly relevant for prescribers to inform appropriate use of antibiotics. Additionally, we are working to ensure that researchers around the globe have greater access to these important data. Merck has put in place a mechanism for researchers to request access to anonymized source data on AMR surveillance collected through SMART.

AMR Register

Merck is a member of the AMR Register, which was created by Vivli, a non-profit organization. Launched in 2022, this first-ever online platform allows biopharmaceutical companies to share susceptibility data on infection-causing pathogens. The AMR Register allows pharmaceutical companies to securely share their data with researchers, national governments, and multilateral organizations such as the United Nations, CDC, and the WHO. Researchers can use the AMR Register to translate masses of AMR surveillance data into meaningful action that saves lives and preserves antibiotics for future generations.

Animal Health AMR surveillance

Merck Animal Health advocates for robust and science-based AMR surveillance systems, including NARMS (National Antimicrobial Resistance Monitoring System) in the United States. This public health surveillance system tracks changes in the antimicrobial susceptibility of enteric (intestinal) bacteria found in ill people, retail meats, and food animals.

Other key surveillance studies

Merck has been involved in a number of AMR surveillance programs, including STAR (Surveillance of Tedizolid Activity and Resistance) for gram-positive bacteria, like methicillin-resistant Staphylococcus aureus (MRSA) and PACTS (Program to Access C/T Susceptibility) for gram-negative organisms, providing a source of evidence on C/T in vitro activity against strains that may be underrepresented in clinical trials; as well as local surveillance programs, including CANWARD in Canada and BSAC in the U.K. Merck also supported U.S. and international surveillance programs to monitor ribotype prevalence and antibiotic resistance for *Clostridioides difficile*.

Protecting the environment

Understanding and managing the production of antibiotics

Merck remains committed to understanding and managing the environmental impacts of our products, including the potential impact from the production of antibiotics. Guided by our commitments in the Industry Roadmap for Progress on AMR, Merck is working with our partners in the AMR Industry Alliance to inform science-based manufacturing standards to help ensure scrutiny of industry manufacturing supply chains. In 2022, the AMR Industry Alliance published its Antibiotic Manufacturing Standard. The Standard, facilitated by BSI Standards Limited, provides clear guidance to manufacturers in the global antibiotic supply chain to ensure that their antibiotics are made responsibly, helping to minimize the risk of AMR in the environment. In June 2023, an independent third-party certification program was launched for manufacturers to demonstrate that their antibiotics are manufactured responsibly and according to the requirements of the Manufacturing Standard, leading to a new model of transparency.

As reflected in the 2023 AMR Industry Alliance progress report on manufacturing and the environment, Merck and other Alliance members are advocating for the broad adoption of the Common Antibiotic Manufacturing Framework, which outlines science-driven, risk-based targets for discharge concentrations.

Active residues of antibiotics and resistant bacteria can find their way into the environment in several ways. This requires action from many different stakeholders.

Investments in water infrastructure technology
Over the past several years, our wastewater treatment plants have been upgraded to ensure the environment is protected. In doing so, we are working to eliminate factory discharges of residual pharmaceutical products that may impact human and animal health as well as the environment.

Forward-Looking Statement of Merck & Co., Inc., Rahway, N.J., USA

This document of Merck & Co., Inc., Rahway, N.J., USA (the "company") includes "forward-looking statements" within the meaning of the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995. These statements are based upon the current beliefs and expectations of the company's management and are subject to significant risks and uncertainties. There can be no guarantees with respect to pipeline candidates that the candidates will receive the necessary regulatory approvals or that they will prove to be commercially successful. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements.

Risks and uncertainties include but are not limited to, general industry conditions and competition; general economic factors, including interest rate and currency exchange rate fluctuations; the impact of pharmaceutical industry regulation and health care legislation in the United States and internationally; global trends toward health care cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; the company's ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of the company's patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions.

The company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise. Additional factors that could cause results to differ materially from those described in the forward-looking statements can be found in the company's Annual Report on Form 10-K for the year ended December 31, 2023 and the company's other filings with the Securities and Exchange Commission (SEC) available at the SEC's Internet site (www.sec.gov).