DELIVERING ON OUR COMMITMENTS

MERCK'S ACTIONS TO ADDRESS ANTIMICROBIAL RESISTANCE

MERCK
INVENTING FOR LIFE

December 2020

OUR LEGACY

Merck's Longstanding Commitment to Preventing and Treating Infectious Diseases

Since Alexander Fleming's discovery of penicillin and subsequent work to scale up its production in 1928, antimicrobials have saved millions of lives worldwide. But now, as Fleming warned almost a century ago, bacteria are growing more resistant to antibiotics, complicating patient and animal care, and threatening public health and economic stability across the globe. In 2020, the World Health Organization (WHO) named antimicrobial resistance (AMR) as one of the most urgent health challenges we will face in the next decade.

For over a century, Merck has played a leading role in combating AMR, not only discovering and developing a range of novel medicines and vaccines that treat and prevent infectious diseases in humans and animals, but also supporting responsible use of these products. Today, Merck is one of the last remaining large pharmaceutical companies that focuses on the research and development (R&D) of new treatments for a broad range of infections. This sustained commitment to preventing and treating infectious diseases is central to fulfilling our mission to save and improve lives.

Driving Progress in the Pharmaceutical Industry

Merck has been working to address AMR for years, but collective action and a shared commitment are vital to make progress against this global health threat. We are committed to a "One Health" approach, working with key stakeholders to ensure antibiotics remain an important tool in improving and maintaining human and animal health. We believe in the responsible use of antibiotics. Merck is proud to be leading industry's progress on AMR.

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 the end of the decade. As a lead investor, Merck has committed $100 million over 10 years into the Fund to help bridge the gap between the innovative early antibiotic pipeline and patients.

Declaring Our Commitments

In 2016, Merck joined over 100 companies, organizations and trade associations to launch **a joint declaration** that set out bold commitments to address AMR. Additionally, Merck and 12 other leading companies came together to develop a detailed **Industry Roadmap for Progress on Combating AMR** which explored new opportunities for collaboration between industry and the public sector. In 2017, Merck Animal Health led the global animal health industry effort to develop the **HealthforAnimals Antibiotic Commitment**, which was signed onto by 200 companies and over 700,000 veterinarians.

AMR Industry Alliance

To drive and measure industry progress on AMR, we co-founded the **AMR Industry Alliance**, a coalition of large pharmaceutical companies, biotech companies, generic manufacturers and diagnostics developers all working together to curb AMR by committing to address four key areas: research & science, appropriate use, access and manufacturing.

> *"Merck remains deeply committed to working with governments, health care providers and others to drive antibiotic innovation, promote appropriate use and enhance access for patients."*
>
> **Kenneth C. Frazier, Chairman and Chief Executive Officer**

DRIVING INNOVATION FOR ONE HEALTH

Continuing to discover and develop novel anti-infective medicines, vaccines and technologies

Our antimicrobial, COVID-19 and vaccine R&D programs span discovery to late-stage clinical development and address the key unmet needs established by public health authorities.

Recent FDA Regulatory Filings

With initial US approval in 2019 and expanded approval in 2020, the FDA approved RECARBRIO® (imipenem, cilastatin, and relebactam) to treat adults with complicated urinary tract infections (cUTI), complicated intra-abdominal infections (cIAI), and hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) caused by certain susceptible Gram-negative microorganisms. Also in 2019, the FDA approved expanded indications for ZERBAXA® (ceftolozane and tazobactam) to treat adults with HABP/VABP caused by certain susceptible Gram-negative microorganisms; ZERBAXA® (ceftolozane and tazobactam) had received initial approvals to treat adults with certain cUTIs and cIAIs in 2014. In 2020, DIFICID® (fidaxomicin) received FDA approval for the treatment of *Clostridioides difficile*-associated diarrhea (CDAD) in children aged six months and older.

Investing in the Development of Vaccines

Merck is currently evaluating V114, an investigational 15-valent pneumococcal conjugate vaccine (PCV) designed to help prevent disease caused by *Streptococcus pneumoniae* infection, which includes two additional serotypes not in currently available PCVs. Universal coverage with a pneumococcal vaccine could avert up to 11.4 million days of antibiotic use per year in children younger than five years of age – a 47% reduction in the amount of antibiotics used for treating pneumonia caused by *S. pneumoniae*.[1] Additionally, Merck Animal Health is working to develop vaccines for a wide variety of animal diseases, including those animal diseases prioritized by the World Organization for Animal Health (OIE) where vaccines can reduce antibiotic use.

Collaborative Research Spanning Discovery to Late-stage Development

In addition to our own research efforts, Merck works with partners to advance antimicrobial R&D. For example, through our partnership with **Prokaryotics**, we are working to develop, manufacture and commercialize pre-clinical programs and compounds to potentially target Gram-positive and Gram-negative bacteria. We have ongoing collaborations with Armata Pharmaceuticals to develop proprietary synthetic phage candidates (viruses that target and eliminate specific bacteria). We are committed to sharing data through the **TB Drug Accelerator Program** and the **Shared Platform for Antibiotic Research and Knowledge** (SPARK). Merck currently has 15+ ongoing clinical trials addressing bacterial infections.

Continued Focus on Early Discovery

In 2017, we established the **Merck Exploratory Science Center** in Cambridge, Mass, which focuses on the earliest stages of discovery research to better understand the underlying biology of human disease. The center's research explores the most promising areas of emerging disease biology and will be used to inform Merck's ongoing drug discovery with a special focus on infectious disease.

Calling for Action to Secure our Antibiotic Future

Despite the growing threat of AMR and widespread recognition of the need for new antibiotics, over the past two decades the number of companies conducting antibiotic and antifungal R&D has drastically declined. We recognize that this is an area of significant need and our company has an important role to play. 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. We continue to advocate for policies that would enable a predictable and sustainable return on investment for antimicrobial R&D. We collaborate industry-wide, working closely with policymakers, infectious disease societies and other key stakeholders to develop and advance evidence-based proposals to address the challenges of antibiotic R&D. As part of the AMR Action Fund, we are working to bridge the gap between the innovative early antibiotic pipeline and patients, but this is only a temporary solution. If incentives structures are not put in place, the future of antibiotic innovation is at serious risk.

COVID-19 and AMR

Due to the COVID-19 pandemic the world is now keenly aware of our vulnerability to infectious diseases, including bacterial infections. Additionally, the influx of patients into hospitals from COVID-19 has placed enormous pressure on healthcare systems worldwide. Some treatment centers have seen increases in the number of antibiotics prescribed as a precaution against secondary bacterial infections.[2] While some studies have shown that rates of secondary infections are low overall in COVID-19 patients, other data has demonstrated that up to 50% of COVID-19 patients who died also had a secondary bacterial infection.[3] While the evidence on the interrelationship between COVID-19 and AMR is still being collected, observations to date only serve to further underscore the importance of good antimicrobial stewardship (AMS) practices and the need for effective antibiotics. We can learn the lessons from COVID-19 and ensure - particularly as countries look to implement recovery measures post pandemic - that we take action now to address the threat of a crisis of AMR.

1. Laxminarayan R, et al., Access to effective antimicrobials: A worldwide challenge, Antimicrobials: access and sustainable effectiveness, *Lancet*, 2016, 387: 168–75. 2. Vaughn V, et al., Empiric Antibacterial Therapy and Community-onset Bacterial Co-infection in Patients Hospitalized with COVID-19: A Multi-Hospital Cohort Study, *Clinical Infectious Diseases*, 2020. 3. Lai C, et al., Co-infections among patients with COVID-19: The need for combination therapy with non-anti-SARS-CoV-2 agents?, *Journal of Microbiology, Immunology and Infection*, 2020, 53: 505–512.

MERCK'S LEGACY
OF ANTIMICROBIAL INNOVATION

1930s — Merck Research Laboratories played a central role in the development of the first antimicrobials

1940s — Merck developed one of the first methods for mass production of penicillin

1950s & 60s — Merck received approval for the first measles, mumps and rubella vaccines

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 approval for two antibiotics that treat a variety of bacterial infections in the respiratory tract, urinary tract and more

1990s — Merck received approval for an antibiotic, as well as a varicella vaccine

2000s — Merck brought two antibiotics and two antifungals to market, as well as initiated the SMART surveillance study

2010s — Merck received 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 approval for a new innovative treatment to reduce the recurrence of CDI in certain high risk adults

TODAY — Merck continues to invest in early and late stage antibiotic R&D and makes available a number of antimicrobial products and vaccines for the treatment or prevention of infectious diseases in markets around the globe

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 the inappropriate use of antimicrobial medicines has accelerated this process. We are committed to helping ensure antimicrobials are used responsibly. We are collaborating with a broad group of stakeholders, including governments, regulators, veterinarians, producers, and healthcare providers, to implement evidence-based AMS policies and programs for both humans and animals.

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 45 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]

Educational and Advocacy Initiatives:

Merck has made significant financial contributions to support AMS, including grant funding to support a wide range of AMS initiatives and collaborations. From 2017 to 2020, Merck provided an independent grant to develop and implement an educational campaign to improve AMR and AMS health literacy and maintain or improve patient satisfaction in the urgent care clinic setting. Additionally, Merck provided an independent grant for a multifunctional, online AMS resource providing comprehensive, high-quality information.

Merck Animal Health continued its collaboration with the Association of American Veterinary Medical Colleges (AAVMC) to sponsor an international grant program designed to help mitigate the global public health problem of AMR. Originally launched in 2019 and administered through the AAVMC's Council on International Veterinary Medical Education (CIVME), the Merck Animal Health CIVME Antimicrobial Stewardship Grant program seeks to improve instructional programs related to AMR in educational institutions around the world.

Animal Health Initiatives:

Merck Animal Health is making significant investments to support vaccination and responsible use of antibiotics in animals. We are one of the world's largest manufacturers of vaccines for animals, producing over 102 billion doses each year. We are commercializing or developing vaccines for prioritized animal diseases where vaccines can reduce antibiotic use in animals, as recognized by the OIE. Through our **Time to Vaccinate** program, we are working with farmers around the world to raise awareness of the benefits of vaccination and other tools to shift farmers' focus from making animals healthy to keeping them healthy.

Our Merck Animal Health Intelligence operating unit further advances our commitment to addressing unmet needs in animal health. Our cutting-edge technologies and services allow access to real-time, actionable data and insights to enable precise animal health management and health outcomes. Our leading technologies have advanced the way we identify animals, monitor their activity, anticipate their health needs and determine which animals require treatment.

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.

AMR SURVEILLANCE

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.

Study for Monitoring Antimicrobial Resistance Trends (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, 50,000 of which were collected in 2018 alone. 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.

Animal Health AMR Surveillance

Merck Animal Health continues to participate in AMR research activities, including antimicrobial susceptibility testing, data dissemination and publication. We also advocate 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 (CDC), retail meats (FDA), and food animals (USDA).

ENSURING PROMOTIONAL PRACTICES SUPPORT AMS

Our internal practices are fully aligned with our global AMS efforts. Based on guidelines from organizations like the WHO and the U.S. Centers for Disease Control and Prevention, Merck's "Star of Stewardship" framework guides our efforts to support optimal patient-centered AMS: that is, the right drug is given at an appropriate dose for an adequate duration in the ideal setting of care based on an accurate diagnosis, and therapy is narrowed when possible. Using this framework, we regularly examine, review and update our promotional materials. We have developed an AMS curriculum that is available for all relevant Merck employees, including promotion managers and brand teams who work on antibiotics and antifungals. Our company is exploring new approaches in certain countries to field sales representative compensation that support AMS, including pilots where field sales representatives are not incentivized based on sales volume 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. For example, evidence generated in support of the expanded FDA approvals of ZERBAXA® (ceftolozane and tazobactam) and RECARBRIO® (imipenem, cilastatin, and relebactam) for the treatment of adults with HABP or VABP caused by certain susceptible Gram-negative microorganisms provides important information for prescribers about the appropriate and responsible use of these products in challenging patient populations and clinical settings. Merck also continues to generate real world evidence and support investigator-initiated studies to inform the use of these and other antimicrobial agents. Results are shared with the scientific community through appropriate forums, including peer-reviewed publications.

EXPANDING ACCESS

Enhancing Affordable Access to Antibiotics for Patients Worldwide

Low- and middle- income countries (LMICs) with higher burdens of infectious diseases and weak health systems often struggle to provide even basic access to generic antibiotics. In these contexts, there are major challenges to expanding responsible access to novel antibiotics. However, when coupled with strong AMS programs, enhanced access to antibiotics can have a significant impact on disease.

Merck is aiming to achieve broad registration of our antibiotic and antifungal portfolio. For example, since FDA approval, ZERBAXA® (ceftolozane and tazobactam) has been registered in nearly 74 countries, 25 of which are LMICs. Some other antimicrobial products, including PRIMAXIN® (imipenem/cilastatin), are registered in 96 countries.

Beyond registrations, we are collaborating with hospitals around the world, particularly in LMICs, to strengthen AMS programs and promote responsible use of available antibiotics.

Merck works with international organizations, governments and stakeholders to identify and address issues of access, sustainability and bottlenecks for existing antimicrobial and diagnostic options. In recent years we've provided independent grants to several organizations aiming to address access and responsible use issues in LMICs:

The Center for Disease Dynamics, Economics & Policy's Global Antibiotic Resistance Partnership supports the expansion and development of National Action Plans and policy proposals on AMR in several LMICs.

Florida International University and the Pan American Health Organization developed and disseminated regional guidelines for implementing AMS programs in Latin America and the Caribbean, optimizing both inpatient and ambulatory antimicrobial prescription practices.

> *"We cannot be short-sighted, and we cannot be complacent, especially about antibiotic resistance. We must put measures in place to ensure that we have the antibiotics we need — today and in the future. The time to act is now."*
>
> **Dr. Julie Gerberding,**
> **Executive Vice President & Chief Patient Officer**

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 to ensure good practices for antibiotic discharge in both our own and third-party supplier operations. Through the AMR Industry Alliance, we are working to broaden adoption of the Common Antibiotic Manufacturing Framework and 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, and 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 harm human and animal health as well as the environment.

Merck's Science-driven Approach

In a **peer-reviewed, scientific article** published in *Integrated Environmental Assessment and Management*, Joan Tell, Ph.D., Merck's Director, Occupational and Environmental Health Sciences, described the work of AMR Industry Alliance companies to develop the Common Antibiotic Manufacturing Framework, a set of minimum environmental expectations for antibiotic manufacturers, and discharge targets to manage antibiotic discharge based on previously unpublished, company-generated, environmental toxicity data.[1]

1. Tell J, et al., Science-based Targets for Antibiotics in Receiving Waters from Pharmaceutical Manufacturing Operations, *Integrated Environmental Assessment and Management*, 2019, 15.

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

This document of Merck & Co., Inc., Kenilworth, 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 products that the products 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 the global outbreak of novel coronavirus disease (COVID-19); 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 2019 Annual Report on Form 10-K and the company's other filings with the Securities and Exchange Commission (SEC) available at the SEC's Internet site (www.sec.gov).

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