



MSD

INVENTING FOR LIFE

**GLOBAL
ANTIMICROBIAL
RESISTANCE
ACTION PLAN**

ANTIMICROBIAL RESISTANCE GLOBAL ACTION PLAN

MSD'S LONGSTANDING COMMITMENT TO PREVENTING AND TREATING INFECTIOUS DISEASES

Combating antimicrobial resistance, a global public health threat

Vaccines and antibiotics have revolutionized infectious disease prevention and treatment, saving millions of lives worldwide. Rising levels of resistance to antimicrobials is a serious threat to public health, food safety and global security.

Antimicrobial resistance (AMR) reduces the effectiveness of treatments for infectious diseases and jeopardizes health care gains to society that rely on the ability to effectively treat bacterial infections, such as:



organ
transplantation



cancer
chemotherapy



major
surgery

WHAT IS AMR?

Antimicrobials are medicines to treat and prevent infectious diseases caused by pathogens such as bacteria, viruses, fungi and parasites. Antibiotics, which are used to treat bacterial infections, are one of the most important types of antimicrobials.

AMR occurs when a pathogen evolves to survive antimicrobial treatment. While such evolution is inevitable, AMR is developing more quickly due to the inappropriate use of antimicrobials. Action is needed to slow down the development and spread of AMR so that the antimicrobials we have continue to work for as long as possible.

WHY IS IT A PROBLEM?

AMR is responsible for an estimated 25,000 deaths per year in the E.U. The loss to E.U. health care and productivity as a result of AMR is estimated at €1.5 billion annually.¹

New antibiotics are urgently needed to address growing resistance; however, there are relatively few in development. Over the past two decades, there has been a significant decline in the number of companies conducting antibiotic and antifungal R&D. Today, only six of the top 50 pharmaceutical companies have antibiotics in clinical development.

¹ European Medicines Agency, European Centre for Disease Prevention and Control. Joint technical report: the bacterial challenge—time to react. 2009. Available at: <https://ecdc.europa.eu/en/news-events/bacterial-challenge-time-react-0>

MSD IS TAKING ACTION TO COMBAT AMR

For more than 80 years, MSD, known as Merck in the United States and Canada, has played a significant role in the discovery and development of novel medicines and vaccines to treat and prevent infectious diseases in both humans and animals. Today, MSD is one of only a few large pharmaceutical companies that has sustained a focus in research and development (R&D) aimed at producing new vaccines and medicines to prevent and treat bacterial infections.

MSD Research Laboratories played a central role in the development of the first antimicrobials.

MSD continues to invest in early- and late-stage antibiotic R&D and markets a number of antimicrobial products and vaccines for the treatment or prevention of infectious disease in markets around the globe.



1930s

1940s

TODAY

MSD developed one of the first methods for mass production of penicillin.

In January 2016, the company and over 100 biopharmaceutical, generic medicines and diagnostic companies, as well as key trade associations, launched a joint declaration at the World Economic Forum setting out bold commitments and calling for governments and industry to take action against AMR.

At the U.N. High Level Meeting on AMR in September 2016, MSD and 12 other leading companies released the *Industry Roadmap for Progress on Combating AMR*. This document laid out additional commitments to reduce the environmental impact from the production of antibiotics, help ensure antibiotics are only used by those who need them, improve access to antibiotics globally, and explore new opportunities for collaborations between industry and the public sector. We are a founding board member of the AMR Industry Alliance, comprised of signatories of these documents, to drive and measure industry progress against these commitments.

AS A GLOBAL HEALTH CARE LEADER, MSD IS:



LEADING IN INFECTION PREVENTION

through the development and production of vaccines to prevent infections and reduce the need for antibiotics.



DRIVING INNOVATION

to discover and develop new treatments and antibiotic alternatives to address AMR.



ADVOCATING FOR POLICY SOLUTIONS

to support sustainable investment in the development of new tools to combat AMR.



ADVANCING ANTIMICROBIAL STEWARDSHIP

to improve patient outcomes and slow the development of AMR.



SUPPORTING GLOBAL AMR SURVEILLANCE

through our Study for Monitoring Antimicrobial Resistance Trends (SMART), which provides data to the scientific community on AMR trends.



PROTECTING AND MAINTAINING ANIMAL HEALTH

by promoting vaccination and the responsible use of antibiotics.

“ MSD 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

ANTIMICROBIAL RESISTANCE GLOBAL ACTION PLAN

MSD'S LEADERSHIP IN INFECTION PREVENTION

Developing and delivering a broad portfolio of vaccines to prevent infection and reduce the need for antibiotic therapy in humans and animals

Vaccination has been internationally recognized as a key intervention to combat antimicrobial resistance (AMR). By increasing vaccine population coverage, immunizations have the potential to significantly reduce the need for antibiotic use by preventing infectious diseases in both humans and animals.

MSD has been working to discover and develop vaccines for more than a century. Our unique vaccines have helped to prevent a number of serious diseases, having a significant impact on human life and population health. Today, we remain dedicated to the complex business of researching and producing vaccines.

“ Vaccines are a powerful force of global health. MSD is on a mission to ensure that more people can access our vaccines, regardless of where they live or their financial circumstances. ”

- Mike Nally, President, MSD Vaccines

With a portfolio of vaccines designed to address the needs of children, adolescents and adults, MSD is committed to protecting against preventable diseases and infections throughout the life course. Today, common pathogens that may cause respiratory infection, diarrhea and sepsis are increasingly showing resistance to first-line antibiotics. MSD is working to prevent such infections and thereby decrease AMR.



MSD is currently evaluating V114, an investigational 15-valent pneumococcal vaccine designed to protect against *Streptococcus pneumoniae* infection and expand coverage of two additional serotypes beyond those currently available. 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 pneumonia caused by *S. pneumoniae*.¹



MSD Animal Health is one of the world's largest producers of vaccines for animals. The company has invented and developed a broad array of vaccines, as well as anti-infective and anti-parasitic therapies, to advance animal health and reduce the need for antibiotic use. Vaccination and other strategies are in development to reduce foodborne infections caused by *Salmonella* and *Campylobacter*.



In 2009, MSD and the Wellcome Trust established Hilleman Laboratories, named after MSD scientist and vaccines pioneer, Dr. Maurice Hilleman. This joint venture was designed with the mission to develop affordable vaccines for global health. Hilleman Laboratories has multiple programs evaluating early stage vaccine candidates to address gaps that exist in low resource settings where disease burden is often highest.

¹ Laxminarayan R, Matsoso P, Pant S, Brower C, Røttingen J, Klugman K, Davies S, Access to effective antimicrobials: A worldwide challenge, *Antimicrobials: access and sustainable effectiveness*, *Lancet*, 2016, 387: 168–75.

Collaboration is necessary to tackle the global rise of AMR. MSD is working with governments, industry partners, international health and development organizations, and donor groups to raise awareness about the wider benefits of vaccines to combat AMR and is responding to the call for investment in developing new vaccines.

We are also working with government and nongovernmental organizations to build sustainable and effective vaccination programs that reliably reach people. Strong vaccine ecosystems ensure the broadest access to existing vaccines needed to combat AMR and facilitate rapid uptake when new vaccines come to market.

MSD IS COMMITTED TO DEVELOPING INNOVATIVE VACCINES THAT KEEP BOTH HUMANS AND ANIMALS HEALTHY AND REDUCE THE NEED FOR ANTIBIOTIC USE.

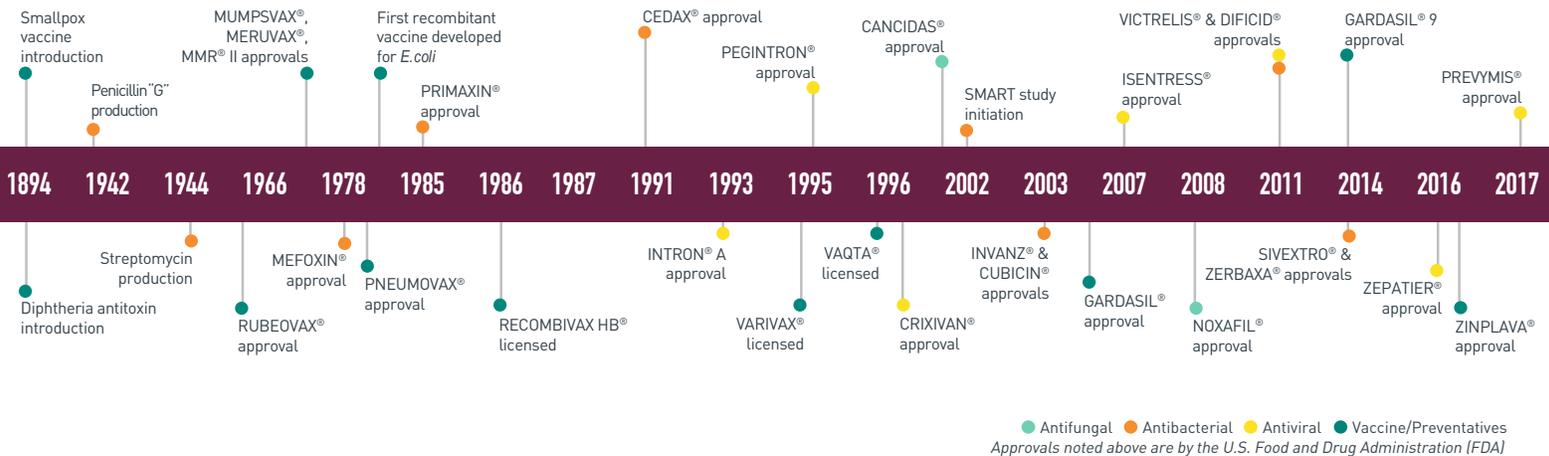
ANTIMICROBIAL RESISTANCE GLOBAL ACTION PLAN

MSD'S COMMITMENT TO INNOVATION

Investing in infectious disease research and development (R&D) to address unmet medical needs

For more than 80 years, MSD has played a significant role in the discovery and development of novel medicines and vaccines to treat and prevent infectious diseases. In the 1930s, MSD Research Laboratories played a central role in the development of antimicrobials, and in 1942, we developed one of the first methods for mass production of penicillin. These products have saved millions of lives worldwide.

Today, MSD continues to focus on antimicrobial and vaccine R&D and has programs spanning discovery through late-stage clinical development.



MSD remains one of only a few large pharmaceutical companies pursuing R&D to develop new medicines and vaccines to prevent and treat bacterial infections. Our broad portfolio spans both human and animal health and includes antibiotics, vaccines and novel approaches to reduce the need for antibiotics.

Our recent highlights:



MSD has introduced two novel antibiotics, ZERBAXA® (ceftolozane/tazobactam) and SIVEXTRO® (tedizolid), since 2014. These products contribute to the Infectious Disease Society of America's 10x'20 initiative goal of having 10 new systemic antibiotics by the year 2020.



MSD's ZINPLAVA® (bezlotoxumab) was approved by the European Medicines Agency in January 2017 to prevent the recurrence of *Clostridium difficile* infection (CDI) in adults at high risk of recurrence of CDI. Based on data from the European Centre for Disease Prevention and Control, researchers estimate that there are over 150,000 cases of hospital-acquired CDI in Europe each year.¹



To facilitate scientific exchange, MSD scientists published approximately 150 peer-reviewed articles on antimicrobial-related studies (antibacterial and antifungal) in scientific journals in 2016.

¹ <http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002150>

“ Infectious diseases remain one of the great public health threats in the world today. At MSD, we have never wavered in our commitment to invest in developing anti-infective therapies that prevent and treat serious infectious diseases. ”

- Dr. Nicholas Kartsonis, Vice President, Infectious Disease Clinical Research, MSD Research Laboratories

MSD'S ANTIBIOTIC RESEARCH PIPELINE

With a focus on addressing unmet medical needs, MSD has dedicated significant resources to both early- and late-stage R&D for antibiotics, with particular focus on developing novel compound classes against Gram-negative bacteria and other organisms prioritized by health authorities. We are currently evaluating MK-7655a, a combination of relebactam, a novel investigational β -lactamase inhibitor, and imipenem/cilastatin (an approved carbapenem antibiotic), in Phase 3 trials. MK-7655a is being studied for the treatment of serious infections including complicated intra-abdominal infections, complicated urinary tract infections and hospital-acquired pneumonia. Additionally, ZERBAXA® (ceftolozane/tazobactam) and SIVEXTRO® (tedizolid) are being studied in Phase 3 trials for the treatment of hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia.

Recognizing the serious threat posed by infectious diseases, as of December 2017 MSD has:

5 **Compounds in late-stage development** for the potential treatment or prevention of infectious diseases

20 **Ongoing Phase 2/Phase 3 clinical trials** evaluating compounds addressing infectious diseases

14 **Active collaborations** with institutions from around the globe focused on the development of novel anti-infective therapies

6 **Products** for the treatment or prevention of infectious diseases approved in the last 36 months

OUR COMMITMENT TO COLLABORATION

In addition to our own antimicrobial research efforts, MSD also collaborates with scientists worldwide. Through our MSD Innovation Network (MINt), we actively work with scientists in the antimicrobial field to investigate novel therapeutic targets, evaluate new pathways for drug targeting, and develop novel tools and technologies to facilitate research. MSD also has a number of ongoing collaborations with scientists at leading universities. MSD is collaborating with Moderna Therapeutics to discover and develop mRNA-based vaccines and therapeutics to treat infectious diseases.

UNITING AGAINST MULTI-DRUG RESISTANT TUBERCULOSIS: TB DRUG ACCELERATOR PROGRAM



Nearly 200,000 people die each year from multi-drug resistant tuberculosis (TB) and new treatments are desperately needed. Through the TB Drug Accelerator Program, MSD is sharing compound libraries and relevant data with scientists around the world. To date, almost 3 million small molecules have been screened for activity. In collaboration with others, we are further evaluating several candidates identified through initial screening.

INVESTING IN NOVEL ANTIBIOTICS: PROKARYOTICS



MSD has partnered with Prokaryotics, a small biotechnology company comprised of internationally renowned academics and collaborators, to develop, manufacture and commercialize a collection of early pre-clinical programs and compounds with potential application as novel antibiotics targeting Gram-positive and Gram-negative bacterial cell envelope enzymes.

MSD IS COMMITTED TO DISCOVERING AND DEVELOPING CRITICAL NEW ANTIMICROBIAL THERAPIES THROUGH ITS OWN R&D EFFORTS AND COLLABORATIONS WITH KEY STAKEHOLDERS.

ANTIMICROBIAL RESISTANCE GLOBAL ACTION PLAN

MSD'S ADVOCACY TO SUPPORT SUSTAINABLE INVESTMENT IN ANTIMICROBIAL INNOVATION

Supporting a range of incentives that promote antimicrobial research and development (R&D) and encourage antimicrobial stewardship

New antibiotics are urgently needed to address the growing threat of resistance; however, there are relatively few in development. Over the past two decades, there has been a significant decline in the number of companies conducting antibiotic and antifungal R&D. Today, MSD is one of only a few large pharmaceutical companies that has sustained a focus on R&D aimed at producing vaccines and medicines to prevent and treat bacterial infections.

Antibiotic discovery and development present specific scientific, regulatory and economic challenges:



Scientific challenges

Bacteria are resilient and constantly evolving. It is increasingly difficult to develop medicines that balance the ability to kill bacteria (effectiveness) with the risk of serious side effects in humans (safety and tolerability).



Regulatory challenges

While there have been some recent improvements in regulatory guidance and harmonization to facilitate development of novel antimicrobials, clinical trial enrollment and design still present important challenges.



Economic challenges

Novel antibiotics are generally undervalued by reimbursement systems relative to the benefits they bring society. Uptake of novel antibiotics is slow, since they are usually used sparingly to preserve effectiveness when resistant infections are relatively rare and there may be limited availability of appropriate diagnostics and surveillance data. Reimbursement systems, including hospital bundled-payment mechanisms, can discourage use of novel antibiotics, even when they are the most appropriate treatment for a patient.

ADDRESSING THE CHALLENGES OF ANTIBIOTIC DEVELOPMENT

Addressing scientific and economic challenges

We believe market-based mechanisms represent the most efficient way to sustainably incentivize investment in antibiotic R&D. The pharmaceutical industry and private investors have demonstrated their willingness to take on the necessary risk and uncertainty that come with the development of an approved medicine that addresses unmet needs.

The unique challenges and dynamics of the antibiotics market require unique measures to establish an economic environment that will incentivize ongoing antibiotic R&D. Adoption of a suite of incentives by governments would create market conditions that enable a predictable and sustainable return on investment for successful innovation to combat AMR.

This suite of incentives is needed to address challenges across the product life cycle and meaningfully impact investment decisions.

Push Incentives

Reduce the risk of early investment in antibiotic R&D

These incentives stimulate pre-clinical and clinical R&D. Some examples include **grants** and **refundable tax credits**.

Delinked Mechanism

Rewards innovation earlier in a product's life cycle when use is low

Partially-delinked incentives would provide a certain level of economic return regardless of sales volume early in the product life cycle, addressing a key economic challenge for novel antibiotics. Some examples include **market entry rewards** and **transferable exclusivity**.

Reimbursement and HTA Reform

Enable appropriate access to novel antibiotics and stabilize the economics of antibiotic R&D

Reimbursement reform for hospital-administered antibiotics is needed to address bundled-payment mechanisms that may discourage the appropriate use of novel antibiotics. Health Technology Assessment (HTA) reform is also needed to better capture the societal value of novel antibiotics.

Addressing regulatory challenges

Regulatory reform is needed to facilitate clinical development of novel antibiotics. MSD supports legislation and regulation to enable regulatory authorities to streamline, accelerate and reduce the cost of clinical trials required for review and approval of antibiotics, and for new indications for existing antibiotics to address serious infections. We welcome the progress on regulatory harmonization of antibiotic clinical trial guidance by the European Medicines Agency, the U.S. Food & Drug Administration (FDA) and the Japan Pharmaceuticals and Medical Devices Agency.



MSD is involved in several public-private partnerships to improve clinical trial design, recruitment and streamline regulatory processes, including the Duke Clinical Trials Transformation Initiative and the Foundation for the National Institutes of Health Biomarkers Consortium Hospital-Acquired Bacterial Pneumonia/Ventilator-Associated Bacterial Pneumonia (HABP/VABP) working group.

We have engaged with the FDA to address issues related to the development delays that impact the approval process of bacterial susceptibility testing devices. MSD is currently working with multiple device manufacturers to implement the FDA's recently issued guidance on coordinated development of antimicrobial drugs and devices in order to enable availability of manual susceptibility testing of our Phase 3 compound MK-7655a at the time of launch.

Research to support evidence-based policy

MSD actively participates in international and country-level initiatives to explore how value-based reimbursement and other models can incentivize sustainable investment in antimicrobial development:



The company is a member of DRIVE-AB, a public-private consortium funded by the Innovative Medicines Initiative (IMI) to develop new economic models to incentivize antibiotic R&D and responsible antibiotic use. IMI is a joint undertaking between the European Union (E.U.) and the European Pharmaceutical Industry Association.



MSD has also supported research and expert meetings on addressing AMR, including through new valuation mechanisms and commercial models. The company provided an unrestricted grant to the Duke Margolis Center for Health Policy to develop proposals for antimicrobial R&D incentives that could work within the U.S. health system. Their report, recommending a market entry reward with phased introduction of novel value-based contracts with antibiotic developers, was published in September 2017.



Our company, in collaboration with GSK and Roche, supported the Office of Health Economics (OHE) to develop new elements which could be incorporated into HTA value frameworks for novel antibiotics. These new elements aim to better capture the societal value of novel antibiotics in HTA reviews. As part of this work, OHE organized a Value Forum in London in February 2017, which brought together regulators, reimbursement agencies, clinicians and the pharmaceutical industry. The recommendations from the Value Forum have contributed to the debates around new approaches to assess the value of novel antibiotics at the national and E.U. level.

The mechanisms to both incentivize R&D and promote appropriate use of antimicrobials need to be well integrated into country/regional health systems where these products are used. These efforts can and should be collaborative and coordinated across key countries. In Europe, the U.S. and Japan, MSD and relevant industry associations are 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. Further details on the key principles and proposals for incentives that MSD supports can be found in the International Federation of Pharmaceutical Manufacturers & Associations' policy position on antimicrobial R&D.

A SUITE OF INCENTIVES IS NEEDED TO ADDRESS THE CHALLENGES ACROSS THE ANTIBIOTIC PRODUCT LIFE CYCLE. MSD SUPPORTS POLICIES THAT PROMOTE SUSTAINABLE INVESTMENT IN INNOVATION TO COMBAT AMR AND DRIVE APPROPRIATE USE OF ANTIMICROBIALS.

ANTIMICROBIAL RESISTANCE GLOBAL ACTION PLAN

MSD'S COMMITMENT TO ANTIMICROBIAL STEWARDSHIP

Supporting the appropriate use of antimicrobials to improve patient outcomes, population health and value of care

The development of antimicrobial resistance (AMR) is an inevitable consequence of the use of antimicrobial medicines, but widespread unnecessary and excessive use accelerates the process and exacerbates the problem. Antimicrobial stewardship (AMS) refers to a systematic approach to optimize the prescribing and use of antimicrobials, including the appropriate drug, dose, duration, route of administration and setting of care for a given diagnosis, with de-escalation of therapy when appropriate.

MSD supports AMS efforts in order to:



Improve patient outcomes and population health



Slow the emergence of resistance



Reduce toxicity and improve quality of care



Reduce health care and societal costs

MSD believes that industry, governments, health care providers and other stakeholders must work together to support the appropriate use of antimicrobials. As we work to develop new antimicrobials to treat resistant pathogens, we also need to implement evidence-based policies and programs to slow the development of resistance to current medicines.

“ We are proud to reaffirm our longstanding commitment to develop new therapeutics to fight infectious diseases, and to continue to collaborate with others to support AMS to help slow the rate of emerging resistance. ”

- Dr. Julie Gerberding, Executive Vice President and Chief Patient Officer

SUPPORTING APPROPRIATE USE OF ANTIMICROBIALS AROUND THE WORLD

MSD is collaborating with hospitals around the world to develop and implement patient-centered AMS programs. Since 2008, we have worked with over **1,100 hospitals** in **28 countries**. Through these programs, more than **10,000 health care providers** have been trained and over **500 clinical treatment pathways** have been implemented based on local hospital microbiological data. MSD serves as an AMS resource, knowledge and/or logistics partner, depending on the needs of the hospital. This collaborative model allows for customization at the local level based on epidemiology, formulary and patterns of use, resource availability, clinical setting and institutional infrastructure.



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 in different regions around the world to build up a global network to conduct AMS training and education.



In 2009, MSD launched its first AMS hospital program in India. Currently, the company is expanding its user-friendly eAMS mobile platform, which assists physicians in making evidence-based antimicrobial therapy decisions.



MSD has partnered with key scientific societies in Spain to develop an AMS certification – AMS Programa de Optimización de Antimicrobianos (PROA) Excellence – for healthcare professionals through the Universidad Internacional Menéndez Pelayo and for AMS Centers of Excellence via an external Quality Certification Agency. This project is fully aligned with Spain's National AMR Action Plan.

ADVANCING KEY AMS INITIATIVES AND COLLABORATIONS

MSD provides significant grant funding and supports a wide range of AMS initiatives and collaborations. The company has provided financial support for over 30 investigator-initiated AMS research projects across the globe. Study topics include doctor-patient communications to improve adherence, the impact of rapid diagnostic tests on the use of antibiotics and patient safety metrics. Some additional examples of the initiatives MSD supports include:

Educational and Advocacy Initiatives



The CIDRAP Antimicrobial Stewardship Project, a multifunctional web-based platform, providing access to comprehensive, high-quality information and educational resources on AMS practice, research and policy. It features a dynamic, content-rich website designed to actively engage a diverse, international audience.



The Center for Disease Dynamics, Economics & Policy's Global Antibiotic Resistance Partnership to support expansion of its work developing actionable policy proposals on AMR in low-income and middle-income countries.



The Society for Healthcare Epidemiology of America's AMS Research Workshop's annual conference dedicated to teaching AMS research methodology and sharing best practices regarding demonstrating and disseminating the impact of AMS.



The George Washington University Antibiotic Resistance Action Center's work with the Urgent Care Association of America 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.

Hospital-Based Initiatives



ILÚM Health Solutions, a MSD subsidiary, offering health systems a specialized, technology-enabled service designed to address the unique challenges of infectious diseases. In November 2017, ILÚM acquired Teqqa, which provides precision analytics for infectious disease management. This strengthens ILÚM's ability to help hospitals accelerate patient access to appropriate interventions, efficiently track prescribing and patient outcomes, and communicate within the hospital workflow.



The U.S. Centers for Disease Control and Prevention (CDC)/CDC Foundation and Duke University's two-year collaborative project to develop standardized patient safety outcomes measures that are meaningful and practical for hospital AMS programs.



The National Quality Forum's AMS Playbook providing practical guidance for acute care facilities to implement the CDC's core elements of hospital AMS programs.

Diagnostic-Focused Initiatives



A round of Discovery Awards, which gave small seed-grants to teams applying for the Longitude Prize, a program to support the development of new diagnostics for AMR.



Work with antimicrobial susceptibility testing device manufacturers to expedite the inclusion of MSD antibiotics on their susceptibility panels. These devices detect possible antibiotic resistance and enable clinicians to make appropriate prescribing decisions. MSD provides direct financial support to device manufacturers, as well as all required powders and bacterial isolates with known resistance patterns to inform the development of susceptibility tests. These are also made available to the CDC and relevant hospital labs.

AMS IS A CRITICAL COMPONENT IN ADDRESSING THE GROWING THREAT OF AMR. MSD IS COMMITTED TO FUNDING EDUCATION, IMPLEMENTING EFFECTIVE PROGRAMS, ADVOCATING FOR POLICY CHANGES, AND IDENTIFYING AND SUPPORTING UNMET RESEARCH NEEDS.

ANTIMICROBIAL RESISTANCE GLOBAL ACTION PLAN

MSD'S ONGOING COMMITMENT TO GLOBAL ANTIMICROBIAL RESISTANCE SURVEILLANCE

Supporting the appropriate use of antimicrobials to improve patient outcomes and population health

Surveillance studies can help identify trends in pathogen incidence and antimicrobial resistance (AMR) and provide early indicators of the emergence of resistant strains.

AMR surveillance:



Allows for the assessment of incidence rates of resistance to various antibiotics globally, regionally, by country and at the hospital-level.



Provides important information to understand and control the spread of resistance mechanisms within the local environment.



Informs treatment decisions on an institutional and regional level, and provides early indicators of future unmet medical needs that guide research efforts to develop new therapeutics.

THE STUDY FOR MONITORING ANTIMICROBIAL RESISTANCE TRENDS (SMART)

Recognizing the importance of AMR surveillance, MSD initiated SMART, one of the world's largest AMR surveillance studies, in 2002. Findings from SMART are available through more than **60 published journal articles** and over **100 medical congress presentations**. We make these data publicly available to the scientific community through the SMART database online.

AS OF 2017, SMART CONSISTS OF



Through SMART, researchers can:



Monitor the susceptibility of Gram-negative bacteria to antimicrobials in complicated intra-abdominal infections, complicated urinary tract infections and respiratory tract infections worldwide.



Identify changes in resistance patterns of community- or hospital-acquired organisms, including those that produce extended-spectrum β -lactamases (ESBLs). ESBLs are enzymes capable of breaking down antibiotics, such as penicillins, broad-spectrum cephalosporins and monobactams, characterized by a β -lactam ring structure.



Molecularly characterize resistant bacterial isolates in order to better understand the mechanism of resistance and inform future antibiotic discovery.

THE SIGNIFICANCE OF SMART

The SMART study is a valuable resource in determining pathogen prevalence and antibiotic susceptibility. These data can be used to support antimicrobial stewardship programs and establish regulatory susceptibility breakpoints.

Further, SMART:



Allows for both global and local analysis, and the ability to identify differences in community- versus hospital-acquired infections.



Provides timely, comprehensive data promoting informed, evidence-based choices. SMART is an important adjunct to local institutional data and may help inform treatment for potentially resistant infections.



Offers insight into the local and regional distribution of Gram-negative bacteria, allowing tracking of prominent pathogens over time. Gram-negative bacteria are increasingly resistant to available antibiotics.

SHINING A SPOTLIGHT ON OUR SURVEILLANCE PROGRAMS BEYOND SMART

MSD is involved in a number of AMR surveillance programs beyond SMART, including PACTS (Program to Assess Ceftolozane/Tazobactam Susceptibility) for Gram-negative bacteria, such as *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*; STAR (Surveillance of Tedizolid Activity and Resistance) for Gram-positive bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA); as well as local surveillance programs, including CANWARD in Canada and BSAC in the U.K. MSD also supports U.S. and international surveillance programs to monitor ribotype prevalence and antibiotic resistance for *Clostridium difficile*.



LEVERAGING GLOBAL SURVEILLANCE DATA TO DEVELOP RAPID DIAGNOSTICS

Recognizing the urgent need for diagnostics to predict pathogen susceptibility, MSD is collaborating with OpGen to develop new rapid diagnostics and information technology products. MSD will provide OpGen with access to its archive of over 200,000 bacterial pathogens gathered over the last 15 years through SMART.

Access to MSD's SMART surveillance network data has the potential to greatly accelerate OpGen's development efforts in validating its rapid diagnostic tools, which may be used to guide patient management choices. Increased access to rapid diagnostics may improve patient outcomes and slow the pace of AMR.



MSD RECOGNIZES THE IMPORTANT ROLE SURVEILLANCE PLAYS IN COMBATING AMR AND IS CONTINUING TO MAKE ITS DATA MORE ACCESSIBLE.

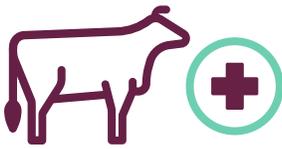
ANTIMICROBIAL RESISTANCE GLOBAL ACTION PLAN

MSD'S COMMITMENT TO PROTECTING AND MAINTAINING ANIMAL HEALTH

Supporting vaccination and the responsible use of antibiotics in animals

A safe, secure, affordable and sustainable food supply requires healthy animals. MSD Animal Health believes in vaccination as an important tool for prevention and in the responsible use of antibiotics to improve and maintain the well-being of animals.

When used responsibly, veterinary antibiotics:



Treat and prevent disease in animals



Protect human health by reducing the spread of zoonotic disease

MSD Animal Health is dedicated to preserving and improving the health, well-being and performance of animals through science. We are one of the world's largest manufacturers of vaccines for animals, producing over **90 billion doses each year**.

Recognizing the global public health threat caused by antimicrobial resistance (AMR), MSD has adopted a OneHealth approach: we collaborate with partners and stakeholders to ensure antibiotics are effective now and in the future for all species to attain optimal health for people, animals and our environment. In October 2017, MSD Animal Health worked with HealthforAnimals to develop global animal health commitments related to the responsible use of antibiotics, investment into the development of new products, and promotion of vaccination and other forms of disease prevention.

PRIORITIZING VACCINE USE

Vaccines are considered a first line of defense against bacterial and viral diseases. By preventing specific diseases, vaccines help to minimize the need for treatment, including antibiotics, for sick animals.

MSD Animal Health is commercializing or developing vaccines for all 15 prioritized animal diseases where vaccines can reduce antibiotic use in animals, as recognized by the World Organization for Animal Health (OIE). We have multiple initiatives to help farmers protect animal health and ensure a safe food supply.

A SUCCESS STORY: INTRODUCING VACCINATION TO AQUACULTURE IN NORWAY

In the 1980s, the aquaculture industry was growing and thriving in Norway and other Northern European countries. Unfortunately, thousands of farmed fish were affected by bacterial diseases, including vibriosis and furunculosis. At the time, the only available treatment option for these diseases was antibiotics; however, it was clear that alternative therapies were needed because veterinarians and farmers did not want to use antibiotics long-term to treat these diseases.

MSD Animal Health invented both cold water vibriosis and furunculosis vaccines in 1987 and 1990, respectively. Upon the introduction of these vaccines, the use of antibiotics in fish feed dropped dramatically. Today, the company remains the major vaccine supplier to the Norwegian salmon industry, the world's largest salmon producer.



STRENGTHENING MSD ANIMAL HEALTH'S VACCINE PORTFOLIO

MSD Animal Health was granted first-of-its-kind approval by the U.S. Department of Agriculture for its innovative technology platform. This flexible and adaptable platform enables the rapid development of vaccines which can be crafted to fit the needs of an entire population of animals or tailored to the needs of a specific farm. Tailored vaccines provide a unique solution for disease prevention.

This technology was instrumental in producing the first conditionally licensed vaccines for porcine epidemic diarrhea virus (PEDv) and H5 avian influenza. PEDv is a deadly virus that has killed more than 8 million piglets since suddenly emerging in the U.S. in 2013. Avian influenza is a fast-moving, highly contagious disease that devastated poultry producers across the U.S. and Europe in 2015 - 2016. MSD Animal Health's flexible production platform gives farmers another tool to stay ahead of evolving disease challenges.



EDUCATING FARMERS ON THE VALUE OF VACCINES: TIME TO VACCINATE

MSD Animal Health launched *Time to Vaccinate*, a program designed to help farmers in Europe better recognize the benefits of vaccinating their cattle as a preventative tool. *Time to Vaccinate* supports farmers who have already adopted vaccination, as well as farmers who want to know more about how vaccination can improve productivity and animal health.

The program features farmers sharing their stories about how they manage disease with the use of vaccinations for diseases such as bovine respiratory disease, but also with the use of proper housing, nutrition, ventilation and other methods. The goal is to improve animal health and well-being, and the livelihoods of farmers through increased vaccination.



ANTIMICROBIAL STEWARDSHIP EFFORTS IN ANIMAL HEALTH

Responsible use of antimicrobials in animal health remains a priority for MSD. We are committed to helping veterinarians and farmers manage disease, optimize animal performance and preserve the effectiveness of antimicrobials. We are advancing antimicrobial stewardship through education, implementation, research and advocacy initiatives.

Protecting the Herd: Whisper® Veterinary Stethoscope System



MSD Animal Health offers the Whisper® Veterinary Stethoscope System as part of its portfolio of vaccines and pharmaceutical products for the cattle industry. This non-invasive technology can quickly measure the severity of bovine respiratory disease so an appropriate treatment can be selected for the infected animal only, instead of prophylactic antibiotic treatment for the herd.

Controlling Respiratory Diseases in Swine: ResPig® Management System App and Website



MSD Animal Health launched the innovative ResPig® app and dedicated website to support veterinarians and farmers in their efforts to control respiratory diseases in swine. This platform identifies areas of improvement, cost and potential outcomes of porcine respiratory disease complex. It also provides control and prevention strategies specific to farmers' needs.

Maintaining Healthy Flocks: The Convenience Program®



Respiratory disease is a global threat to the health of poultry flocks. MSD Animal Health has partnered with veterinarians and poultry producers to ensure an early start on disease prevention to maintain healthy flocks. The Convenience Program® is a training-based program designed to help poultry producers optimize vaccination processes and improve chick health.

MSD IS COMMITTED TO PROTECTING ANIMAL HEALTH AND ENSURING A SAFE FOOD SUPPLY.

ANTIMICROBIAL RESISTANCE GLOBAL ACTION PLAN

MSD'S COMMITMENT TO ENSURING PROMOTIONAL ACTIVITIES SUPPORT ANTIMICROBIAL STEWARDSHIP

Building internal capacity to ensure our promotional activities encourage the appropriate use of antimicrobials

At the U.N. High-Level Meeting on Antimicrobial Resistance (AMR) in September 2016, MSD and 12 other leading companies signed onto the *Industry Roadmap for Progress on Combating Antimicrobial Resistance*. In this document, we committed to “by the end of 2017, examine our promotional activities to ensure they align with the goal of advancing antimicrobial stewardship (AMS) and eliminate those that do not, to protect the utility of antibiotics by encouraging their correct use.”

Based on guidelines from the relevant organizations, including the World Health Organization and U.S. Centers for Disease Control and Prevention, MSD developed a framework of AMS principles to guide the review of our promotional materials: the “**Star of Stewardship**.” This framework describes different aspects of appropriate use, including diagnosis, drug, duration, de-escalation of therapy, dose and door (setting of care).

The Star of Stewardship

To ensure our promotional practices support AMS, MSD antibiotic and antifungal promotional materials must align with the following principles:

DRUG

Is this the right drug for the right patient and pathogen? Do our promotional materials provide information regarding risk factor identification such as condition, patient or indicated microorganisms (i.e., how to determine which patients are most likely to benefit from our drugs)? When permitted, do we provide access to real-world outcomes data to facilitate selection of the right drug for the right patient?

DOSE

Where relevant, do our materials reflect any necessary dosing modifications for special populations? Are our materials consistent with the pharmacokinetics and pharmacodynamics data in the label?

DURATION

Does the suggested duration of treatment align with the approved label?

DIAGNOSIS

Do our materials focus only on approved indications?

DE-ESCALATION OF THERAPY

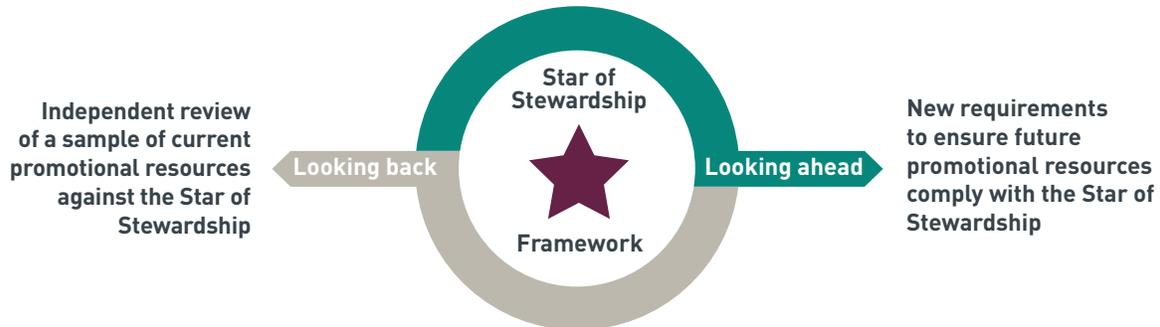
Is there an opportunity to de-escalate therapy? Is this opportunity shown appropriately?

DOOR (SETTING OF CARE)

Do our materials reflect consideration of severity of illness? If applicable, do our materials provide information to support decision making for multiple care settings (e.g., outpatient infusion centers)?

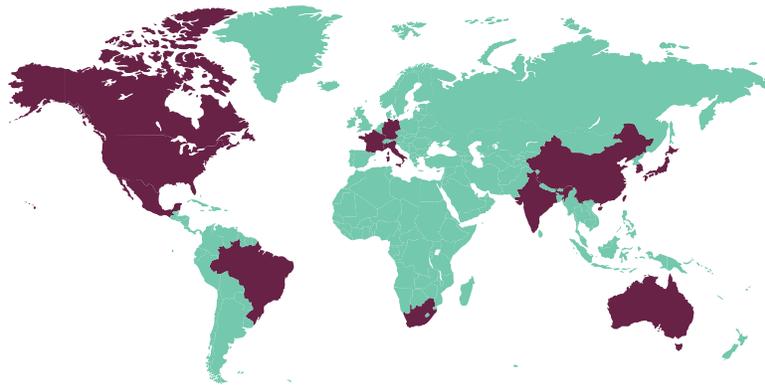
ENSURING PROMOTIONAL MATERIALS SUPPORT AMS

In September 2017, MSD developed and added a section to the mandatory e-learning training for all of MSD's certified medical reviewers responsible for approval of commercial materials on the Star of Stewardship.



As part of our commitment, the company also commissioned a retrospective independent review of a sample of promotional resources for a range of approved antibiotic and antifungal products from diverse global markets, including developing countries, to assess alignment with stewardship principles. A total of 19 promotional pieces for a variety of MSD's antibacterial and antifungal products from 14 countries were reviewed.

The review found that the majority of resources are consistent with the Star of Stewardship principles. The company will train marketing teams and promotional reviewers who have responsibility for antibiotics and antifungals on Star of Stewardship principles.



BUILDING A CULTURE OF AMS WITHIN MSD

To underscore its commitment to combating the growing threat of AMR, MSD has established an internal, cross-functional AMS Council comprised of senior leaders to advance AMS through education, project implementation, research and advocacy.



MSD developed and launched an AMS competency to increase awareness of AMR and the importance of AMS, including the Star of Stewardship. This training will be required for all relevant MSD employees, including promotion managers and brand teams that work on antibacterials and antifungals.



The company is collaborating with the Global Chief Medical Officer Network to take steps to improve awareness of AMR and AMS amongst approximately 9 million employees from nearly 55 participating companies across the world.

MSD IS COMMITTED TO ADVANCING AMS THROUGH ITS PROMOTIONAL ACTIVITIES.



MSD

INVENTING FOR LIFE

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 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 2016 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).