Antimicrobial Resistance Statement

Summary

Antimicrobial resistance (AMR) is one of the defining scientific, health and economic challenges of our time. Without urgent and meaningful action to address specific diseases and system-level issues, patients, families and communities around the world will face a tremendous threat in the years ahead from untreatable infections. While AMR is fundamentally driven by the ability of pathogens to evolve, its impact is greatly amplified by factors that span economic, healthcare and agricultural domains.

Given the breadth of the AMR issue, specific initiatives aimed at solving individual components of the problem won't be enough. Rather, addressing AMR will require a comprehensive effort from multiple partners—governments, civil society and industry—working together with shared accountability for measurable outcomes. These partners must improve how we prevent infections in the first place, effectively deploy and deliver current tools across all countries, and spur the development of new innovations.

At Johnson & Johnson, we are taking action to be a part of the solution to AMR. We have focused efforts across our business to address many facets of the AMR challenge, and we are championing a new sustainable ecosystem model to work with partners and further change the trajectory of health for humanity.

Click here for the Executive Summary: Antimicrobial Resistance Statement.

Context

Whether you are a nurse in South Africa, a cancer survivor on chemotherapy in Europe, a newborn in China, or a patient about to undergo surgery in the United States, the possibility of acquiring an infection that is resistant to many, if not all, available therapies is unacceptably high. While the circumstances are the result of unique health systems and market failures, the shared threat of AMR is one of the most pressing global healthcare issues of our time. Despite many laudable efforts, more needs to be done to maintain and increase the awareness of this important issue and move beyond calls for action toward activities that drive meaningful change. Failure to act will have a staggering impact on both global public health and the global economy.

From a health perspective, AMR is responsible for an estimated 700,000 annual deaths worldwide, including more than 50,000 in the United States and Europe. By 2050, those numbers could increase to 10 million globally—a greater global impact than we currently face from diseases like cancer and diabetes.[i] As a nation's health and wealth are intertwined, AMR is expected to have a catastrophic economic impact as well, drawing parallels to the 2008 global financial crisis. Cumulatively, AMR could cost the global economy more than $100 trillion between 2014 and 2050.[ii] This makes AMR one of the most significant global health security issues facing nations over the next several decades. These threats have been detailed in several reports, including the O'Neill AMR Review, the Access to Medicine Foundation's AMR Benchmark, the World Health Organization (WHO)'s AMR Global Report on Surveillance, the World Bank report on Drug-Resistant Infections, the AMR Industry Alliance's 2018 Progress Report, and others.

Resistant pathogens can cause outbreaks locally or be carried within and across national borders. While the impact and threat of AMR are global, the main causes and consequences of AMR play out differently in developing and emerging markets compared to developed countries. That said, three responsive strategies are critical in every context:

1) ***Preventing individuals from acquiring resistant infections:*** Broad awareness and education strategies are needed to advance infection prevention. In addition, vaccines play a crucial role in preventing a range of AMR-relevant infectious diseases around the world. Other tailored strategies are needed depending on the local context. In places like the United States and Europe, healthcare-acquired infections (HAIs) are a major driver of AMR-related infections and can be prevented with appropriate tools.

2) ***Treating existing AMR-related infections:*** Giving patients with AMR-related infections the best chance at recovery requires preserving and extending the effectiveness of current therapies. To do so, therapeutics must be appropriately used in humans and animals. Surveillance to track prevalence of resistant pathogens and the effectiveness of existing therapies, and establishing and adhering to environmental protections are crucial additional components of effective strategies. Success requires that robust health systems be in place to diagnose, track and treat AMR-related infections.

3) ***Discovering and developing new tools to reverse the trend of growing drug resistance:*** Infectious pathogens will continue to evolve and develop resistance to new and existing therapies. The unique nature of the AMR market (where product use should be carefully stewarded after approval so treatments reach the right patients at the appropriate dosages, preventing the development of further resistance) drives the need for tailored incentives to reward innovation and spur further R&D investment. Furthermore, new diagnostics are essential to ensure antimicrobial use is limited to those with appropriate infections.

Johnson & Johnson's Contributions to Addressing AMR

As the world's largest and most broadly based healthcare company, Johnson & Johnson is committed to changing the trajectory of health for humanity. It is impossible to achieve this goal without addressing the global threat of AMR. We have a diverse set of investments and commitments to address a wide range of AMR efforts.

Policy & Advocacy: In addition to the product-specific approaches outlined below, we have leveraged our size and scale to promote shared accountability in addressing AMR. We are a proud signatory to the AMR Roadmap and the Davos Declaration on Combating AMR and remain committed to their one-health principles. We have been active members of the AMR Industry Alliance, including contributing to multiple position papers and presentations, and serving on the board. We have also testified before the U.S. Congress on the topic, and have provided input and support to other international and domestic actions to address AMR, including the U.S. National Action Plan for Combating Antimicrobial Resistant Bacteria, ongoing World Economic Forum AMR working groups, the EU Action Plan on AMR and the Global Health Security Agenda AMR Action Package.

Drug-Resistant Tuberculosis (DR-TB): Globally, more people die of tuberculosis (TB) than any other infectious disease, and drug-resistant tuberculosis (DR-TB) currently accounts for approximately one-third of all AMR-related deaths. In 2017, DR-TB infected 558,000 people around the world—with cases in nearly every country globally—and claimed 230,000 lives. Currently only one in three people with DR-TB is diagnosed and one in four treated. Every untreated individual can infect up to 15 additional people over the course of a year, posing a global health security threat.

Until recently, the standard of care for multidrug-resistant TB (MDR-TB) treatment required a complex regimen of approximately 14,000 pills taken over two years, with daily injections for six months, which had significant side effects and only moderate success. Simpler, safer, and more effective treatments are essential to decrease the overall burden of DR-TB—and Johnson & Johnson has invested in these R&D efforts for more than two decades.

In 2012, through our Janssen Pharmaceutical Companies, we received accelerated approval from the U.S. FDA for SIRTURO® (bedaquiline), our medicine for the treatment of MDR-TB as part of a combination therapy.[iii] It was the first TB drug with a novel mechanism of action to be approved in more than 40 years. Today, bedaquiline is approved in 59 countries, and we have delivered more than 90,000 courses of treatment to patients in need in 118 countries, including all 30 countries with the highest burdens of MDR-TB.

Bedaquiline is one of the last lines of defense against MDR-TB. To address this, we have taken numerous steps to promote broad, equitable access to bedaquiline while ensuring appropriate use and stewardship in line with WHO guidelines to prevent the development of resistance.

Access: We committed to donate 105,000 courses through a four-year donation program operated in partnership with the U.S. Agency for International Development and JSC Pharmstandard (shipments will be processed through the end of 2019). More than 130 countries are eligible to access bedaquiline at a not-for-profit price through the Stop TB Partnership's Global Drug Facility. This price enables us to support manufacturing distribution and surveillance programs to safeguard the antibiotic's effectiveness. Manufacturing agreements have also been put in place to ensure a steady supply.

Stewardship: We have been working with a variety of local, national and global stakeholders. This includes making healthcare provider training available and undertaking appropriate pharmacovigilance and surveillance activities to monitor resistance to bedaquiline and companion treatments within the same regimen, such as through the Drug Resistance Emergence Assessment in MDR-TB (DREAM). DREAM is a global drug resistance surveillance study implemented by Johnson & Johnson to assess the emergence of resistance to bedaquiline. By mid-2018, thousands of bacteria recovered from TB patients from 10 countries were tested and preliminary results indicate that the prevalence of resistance to bedaquiline has remained very low.

We are proud that our approach to ensuring the appropriate use of bedaquiline was noted as the most comprehensive for any single AMR product in the recently published Antimicrobial Resistance Benchmark. The Benchmark also recognized our strong performances in R&D, Manufacturing & Production, and Appropriate Access & Stewardship, largely centered around our TB-related activities.

Johnson & Johnson is committed to the fight against TB for the long haul. In 2018, ahead of the first-ever United Nations (UN) High-Level Meeting on TB, we announced a comprehensive 10-year initiative in support of the UN Sustainable Development Goal target of ending the TB pandemic by 2030. Johnson & Johnson will work with partners to improve detection of undiagnosed cases of TB, broaden access to bedaquiline for MDR-TB, and accelerate R&D to discover next-generation TB treatments.

Other Anti-Infective Vaccines & Therapies: Beyond DR-TB, we have many ongoing research projects to develop new drugs or vaccines for AMR-relevant diseases, in both developed and developing countries. According to the AMR Benchmark published by the Access to Medicine Foundation, Johnson & Johnson has one of the largest antimicrobial (including anti-viral) R&D pipelines within the research-based pharmaceutical industry, with 48 projects targeting 15 priority pathogens, including novel therapies and vaccines.[iv] These include projects targeting *E. coli*, influenza, Respiratory Syncytial Virus (RSV), hepatitis B, and HIV. For RSV and influenza, we are complementing our work on new therapeutics

with additional efforts to develop an evidence base that supports appropriate and broader adoption of more sensitive and rapid diagnostic testing to improve care and management of patients with acute respiratory infections.

HAI Prevention: One of the major drivers of AMR-related infections in developed markets like the United States and Europe is HAIs. Many HAIs are preventable with appropriate strategies in place. Across the Johnson & Johnson Medical Devices Companies, we seek to reduce the risk of these infections through a variety of antimicrobial and sterilization tools and technologies. These include:

- DePuy Synthes' Expert Tibial Nail (ETN) PROtect, which releases an antibiotic locally into the implant's surrounding tissues;[v]
- Certain DePuy Synthes' bone cements (e.g., SMARTSET® GHV & GMV), which contain the antimicrobial gentamicin;
- Ethicon Biopatch®, a protective disk with Chlorhexidine Gluconate, shown to reduce catheter-related blood stream infection (CRBSI), local infections and skin colonization of microorganisms commonly related to CRBSI; and
- Ethicon Plus sutures coated with the antimicrobial triclosan, shown to reduce surgical site infection (SSI).

As a healthcare leader dedicated to helping customers deliver the best care for patients, we maintain a vigilant focus on leveraging our products, expertise and capabilities to protect patient lives. The world needs new antimicrobials, and we must ensure that we protect existing antimicrobials against resistance. This will require new investments in basic science, development of new medicines and tools, and new frameworks for appropriate use and antimicrobial surveillance.

Environmental Considerations: Across the Johnson & Johnson Family of Companies, we take a proactive, comprehensive approach to minimize the environmental antibiotic exposure from our research and manufacturing. We have a defined environmental risk-management strategy to reduce the risk of antibiotic discharge during manufacturing. Elements of this strategy are publicly available.[vi] This includes establishing and applying science-based discharge limits and auditing both our own sites and third-party manufacturers. To help drive standardized approaches to evaluating the environmental, health and safety performance of suppliers across the pharmaceutical industry, including antibiotic suppliers, we are active members of both the AMR Roadmap Manufacturing Work Group and the Pharmaceutical Supply Chain Initiative. We have reported transparently on our progress in this area through both the Access to Medicine Foundation's Antimicrobial Resistance Benchmark and the AMR Industry Alliance Progress Report.

Policy Position

The complexity of AMR and its potential for catastrophic impact on people and caregivers worldwide requires that stakeholders across multiple sectors (e.g., government, industry, civil society) work together toward a shared agenda. While the goal is ambitious, successful global efforts around HIV, polio eradication and other health issues show it is achievable.

We must address multiple AMR systemic failures, including: lack of early research; the high costs and risks of developing new medications and diagnostics; and the barriers to finding, diagnosing and treating patients across all geographies and economic backgrounds. Solving just one issue in isolation is not enough; incentivizing companies to develop new innovative medicines will not make an impact if health systems are not able to deliver them to patients and steward their effectiveness. And, even the best health systems will not be able to help patients if companies do not continue creating innovative tools.

At Johnson & Johnson, we have publicly pledged our support and are aligned with the calls to action outlined in the Davos Declaration on AMR and the AMR Roadmap. We believe that, as an industry, our responsibility is to bring our skills and experiences in discovery, R&D, market access and promoting appropriate use to the table.

We see the following areas as critical for encouraging company engagement, and support corresponding investments and initiatives championed by governments and other stakeholders to build more robust health systems.

R&D Incentives: The global pipeline for new products targeting resistant infections is not sufficient, given the size and scale of the challenge posed by AMR. In some cases, this may be due to scientific barriers that can be broken down with additional investments in basic research, though the range of resistant pathogens is very large and constantly changing, which requires a diverse body of research. In most areas though, incentive models do not align with the unique AMR marketplace, where product use must be carefully stewarded and targeted to the right patients to prevent the development of further resistance. As there is no one-size-fits-all approach to this challenge, we support a basket of incentive programs designed to spur additional at-risk investment in AMR development. With few exceptions, the lack of such investment to date has directly contributed to the AMR crisis we see today.

We applaud the various “push” mechanisms, such as Biomedical Advanced Research and Development Authority’s CARB-X, set up to encourage innovation in this area. We see opportunity for further use of “pull” and market-based incentives such as:

- **Priority Review Vouchers:** Building on our experience with SIRTURO, we are a strong proponent of the U.S. Priority Review Voucher (PRV) system, which grants companies that

successfully develop a drug for certain underserved diseases or populations a voucher for expedited review of another therapeutic candidate. While the market value of a PRV is highly variable and does not in itself provide recompense for a full-scale drug development program, we believe this system should be maintained in the United States and explored elsewhere as an incentive for AMR research.

- **Transferable Exclusivity Vouchers:** Similar to PRVs, transferable exclusivity vouchers could be a powerful motivator for companies to invest in AMR research or other areas of unmet medical need. These incentives would allow companies that develop specific neglected medicines to extend the exclusivity period of a separate product in a defined therapeutic category for a defined time. Like PRVs, they have the advantage of not requiring any appropriated funding from governments. We support further exploration of this model.

- **Market Entry Rewards:** New products targeting resistant infections should be used judiciously, which poses a challenge to market entry in the current landscape where innovator companies have only a limited period in which products have marketing exclusivity. Providing a reward for companies that reach a defined milestone (e.g., bringing a product to market), can overcome this barrier. Implementing this effective solution necessitates that governments or other sources secure adequate funding for these rewards.

- **Special Procurement / Health Technology Assessment (HTA):** We support pre-proposals for special procurement mechanisms or HTAs that address the complexity and unique nature of the AMR marketplace. These assessments should appropriately value innovations in this marketplace compared to older standard of care products that have decreasing efficacy over time as resistance grows. New economic models are needed that account for the societal value and address the challenges of demonstrating the value of innovative antibiotics approved based on data from non-inferiority trials. Doing so will help improve the predictability of demand and overall investment in research.

Regardless of the additional incentive models that may be pursued, it is important to maintain existing regulatory exclusivities and intellectual property protections for companies that bring innovations to the market. As we have experienced with SIRTURO, these protections are a key element of any comprehensive strategy to stimulate innovation and access to new treatments.

Specific incentive tools to address the gap of fit-for-purpose diagnostic tools and technologies are also needed. Finally, we support initiatives like the Coalition for Epidemic Preparedness (CEPI) and others that seek to incentivize the development and access to new vaccines that can limit the spread of resistant infections.

Regulatory Approvals: The approval of therapies targeting resistant infections poses unique challenges in clinical design and evaluation. We commend guideline changes and legislative efforts to streamline regulatory pathways (e.g., ADAPT in the United States and the FDA / EMA / PMDA Tripartite Agreement). Building on this progress, we believe further gains can be made by continuing to harmonize regulatory data requirements across countries. Where appropriate, mutual recognition of approvals can expedite access worldwide.

Appropriate Use & Access: Ensuring new and existing anti-infective tools and products are used appropriately is paramount to addressing the AMR issue globally. This requires concerted action on several fronts:

- **Health Infrastructure & Delivery:** A critical factor to addressing the threat of AMR is the existence of a robust health system that can effectively find and treat AMR-related infections, and work to prevent their spread.

  We have been proud to work with the government of South Africa and others in their accelerated case finding, training and treatment programs. We aim to ensure they have the appropriate technology to promote sufficient access of SIRTURO and we encourage donors and governments to make the necessary investments to deal with this critical challenge. This includes training healthcare workers and providing them with appropriate infrastructure, ensuring patients have access to essential care and services, tracking and reporting resistant infections, and more.

  Globally, we are proud to champion the Universal Health Coverage (UHC) movement and believe that actions to address AMR will be most sustainable when taken as part of country-level efforts to achieve UHC.

- **Diagnostics:** As noted by the U.S. Centers for Disease Control (CDC), overprescribing of antibiotics is a significant problem that contributes to drug resistance: more than 40% of outpatient antibiotic prescriptions are for acute respiratory infections, and it is estimated that half of these are not necessary.[vii] We support the CDC's recommendations for prescribers and patients to promote appropriate use of antibiotics. Additionally, we believe there is an important need for diagnostics that can help ensure the right treatments are used for the right patients. Beyond the R&D incentives mentioned previously, reimbursement reforms are also needed to encourage doctors and providers to use these diagnostic tools.

- **Medical Devices:** We support the creation and adoption of guidelines that favor use of technologies designed to reduce the risk of HAIs in hospitals, and policies that encourage health workers and hospitals to adopt systematic checklists regarding the use of these technologies.

- **Animal Use:** While we do not have an Animal Health business, we do recognize the importance of good antibiotic stewardship in animal populations and support global and local efforts that limit the inappropriate use of antibiotics in these settings. We support ending the use of prophylactic dosing of antibiotics for infection prevention and growth promotion, as well as limiting use in animals of antibiotics that are critical for human use.

Environmental Considerations: We support the environmental management and transparency principles captured in the Antimicrobial Resistance Roadmap document. We encourage other manufacturers of antibiotics to endorse, embrace and enact these principles as well, and report on their progress in meeting these principles.

Ecosystem Approach: While we see implementing the policy solutions mentioned above as critical to ensuring additional industry engagement in AMR, they will not be sufficient in isolation. As we learned from our experience with SIRTURO, working collaboratively with all stakeholders in a country is what ultimately creates rapid improvements and drives patient outcomes. Solving for AMR will require a new way of thinking, where stakeholders work transparently in mission-oriented consortia designed to enforce better collaboration and create mutual accountability for results. The incentives of all stakeholders—industry, government and civil society—must be aligned toward reducing the further development of resistant infections and the delivery of better health outcomes for patients and caregivers.

We therefore believe we need a new, sustainable, pathogen-specific ecosystem model to deliver against AMR. Success will require committed leadership across sectors, ambitious yet measurable priorities and targets, detailed execution plans, regular performance management, and public accountability.

Conclusion

Anti-infective drugs and technologies have been some of the most effective health innovations in the history of modern medicine, responsible for dramatic gains in life expectancy globally. They are the backbone of modern medicine. And yet, without meaningful, collective action we risk squandering these gains and returning to an era where infection outpaces innovation and patients are left without treatment options. Working together, we can address this threat and change the trajectory of health for humanity.

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[i] https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf
[ii] https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf
[iii] Approval is through Subpart H--Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses.
[iv] Priority pathogens identified by the Access to Medicine Foundation based on lists from the World Health Organization and/or the U.S. Centers for Disease Control.

[v] As of this publication, this device is not cleared or approved for use in the United States.
[vi] Pharmaceuticals and Personal Care Products in the Environment Policy (https://www.jnj.com/about-jnj/company-statements/impact-of-pharmaceuticals-and-personal-care-products-in-the-enviroment);
Annual Health for Humanity Report (http://healthforhumanityreport.jnj.com/downloads);
Responsibility Standards for Suppliers (https://www.jnj.com/about-jnj/company-statements/responsibility-standards-for-suppliers);
Control of Pharmaceutical Manufacturing Discharges Maturity Ladder Approach (http://onlinelibrary.wiley.com/doi/10.1002/etc.3163/pdf;
http://onlinelibrary.wiley.com/doi/10.1002/etc.3260/full);
PSCI Research Library (https://pscinitiative.org/resource?resource=289);
Temple University / WET Center database of PNECs (http://www.nsfwetcenter.org/wp-content/uploads/2016/10/WET-Center-Phamaceutical-PNEC-list-3.pdf).
[vii] https://www.cdc.gov/media/releases/2016/p0503-unnecessary-prescriptions.html