# Pfizer Policy Position on Antimicrobial Resistance

The world faces a large and growing problem due to infections caused by bacterial pathogens that are resistant to antibiotics. Minor infections can become serious and even fatal when these pathogens are involved. Other medical interventions that depend on antibiotics, such as surgery and transplants, are becoming more risky and may become impossible in the future due to the dwindling supply of new antibiotics. Many factors contribute to pathogen resistance. Pfizer endorses a four–part strategy to help address this issue: stewardship, surveillance, vaccination, and R&D incentives. Antimicrobial stewardship practices can help to reduce the spread of antimicrobial resistance (AMR) by applying greater oversight of antibiotic usage and more judicious prescribing practices. Regional and global surveillance of antibiotic resistance patterns are an important tool to assess both the nature of the problem and the effectiveness of our efforts to combat them. Vaccines serve as a significant tool to prevent disease infection and decrease antibiotics use. We must also focus on reversing the shrinking pipeline of new antibiotics and support the development of additional vaccines. Pfizer believes that a mix of economic incentives, coupled with regulatory reforms specifically focused on antibiotics and vaccines for drug resistant strains and emerging infectious diseases, can successfully incentivize new R&D.

## Background

Antibiotic resistance is a global problem. Unlike almost every other class of drug, antibiotics drive their own obsolescence by selecting antibiotic-resistant bacteria. Infections by antibiotic-resistant bacteria extract a significant public health and economic burden on healthcare systems.

An industry Declaration on Antimicrobial Resistance (AMR) was announced at the World Economic Forum in Davos, Switzerland on January 20th 2016. Pfizer along with 85 companies and 9 associations, from 18 different countries signed the declaration. The Declaration sounds a strong call-to-action for governments and industry to collaborate on antibiotic stewardship policies; access to AMR educational materials, and new R&D incentives, such as IP mechanisms, and to support research and development of new products to treat and prevent infections. In addition, the G7 countries released a Declaration on addressing antibiotic resistance at the G7 Health Ministers meeting in Berlin in October 2015.[1] Countries in the WHO South-East Asia Region signed a declaration on antimicrobial resistance in Jaipur in 2011 to prioritize action against antibiotic resistance.[2] During the Sixty-eighth World Health Assembly in May 2015, the WHO released the Global Action Plan on Antibiotic Resistance.[3] The Pan American Health Organization (PAHO) is also leading a regional response and will provide technical support to member countries in addressing the strategic objectives derived from the WHO global action plan on AMR.[4]

A report on antibiotic research, commissioned by the Swedish Government and issued by the London School of Economics and Political Science (LSEPS),[5] makes a broad recommendation for governments to create new incentives to promote the research and development of antibiotics in light of the growing concern over resistance to existing first line antibiotics. The LSEPS report differentiates current R&D incentives into two primary types – push and pull.

- Push incentives focus on removing barriers to the developer, largely by decreasing the costs for investments in R&D. These incentives tend to impact the earlier stages of the development process, and include R&D tax credits and grants.
- Pull incentives involve the promise of financial reward only after a technology has been developed, and include monetary prizes, market entry rewards, and intellectual property extensions.

Lego-Regulatory incentives[6] include advanced marketing commitments, accelerated assessment and approvals, the Generating Antibiotic Incentives Now (GAIN) act, the Limited Patient Antibiotic Drug Act (LPAD), and 21st Century Cures.

A recent report entitled, *Securing New Drugs for Future Generations: The Pipeline of Antibiotics* published in May 2015 made similar recommendations including the focus on innovation prizes. That report also focused on the need to de-couple antibiotic market entry from usual market-driven incentives, based upon use of the product in order to protect against over-prescribing.[7]

## Key Facts and Figures

- In the United States, AMR bacteria cause at least 2 million infections each year. CDC estimates that 23,000 people die each year as a direct result of these infections.[8] Many more people die from other conditions that are complicated by an antibiotic-resistant infection.
- Anti-microbial resistant infections cause over 50,000 deaths annually in Europe and the US; hundreds of thousands more die in other regions.[9]

- The National Action Plan for Combating Antibiotic-resistant Bacteria states that stewardship practices could prevent 619,000 infections and 37,000 deaths from antibiotic-resistant bacteria in the US over the next five years.[10]
- The economic burden created by antibiotic resistance in the United States is estimated at $55bn ($20bn in health service costs and $35bn in lost productivity) per year.[11]
- In the EU, Iceland and Norway, the burden of additional hospital care due to AMR infections was estimated to be approximately €1.6bn in 2012.[12]
- In India, 57% of the infections caused by *Klebsiella pneumoniae*, a dangerous superbug, were found to be resistant to one type of last-resort drug in 2014, up from 29% in 2008.[13]
- Based on studies by KPMG and RAND Europe, a continued increase in resistance would reduce world GDP by 2-3.5% by 2050.[14]
- In the EU, the economic burden associated with antibiotic resistant infections is estimated to be about €1.5 billion per year.[15]
- A US study found the mean cost per patient for hospitals treating methicillin-resistant *Staphylococcus aureus* (MRSA infections) is up to 40% greater than the cost for treating methicillin-sensitive *Staphylococcus aureus* (MSSA).[16]

## Pfizer's Position: Antimicrobial Stewardship

Proper management of antibiotic use requires an evidence-based approach, prescriptively applied to discrete health care settings, as well as the individual patient's situation. Thus, it is necessary for infectious disease specialists, microbiologists, clinical pharmacists and other key caregivers to work together as a team. Pfizer believes that multiple strategies aimed at improving the appropriate use of anti-infectives should be employed at health care institutions and endorses strategies that ensure patient access to the medicines that treat serious infections. Pfizer and other pharmaceutical companies have developed and endorsed antibiotic stewardship strategies through the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA). More details can be found on the IFPMA website at: http://www.ifpma.org/innovation/anti-microbial-resistance.html. Recently, Pfizer partnered with the British Society for Antimicrobial Chemotherapy and the University of Dundee to launch the Massive Open Online Course (MOOC) on antimicrobial stewardship. The course helps health care professionals understand and address the global threat of antimicrobial resistance, focusing on how to responsibly use high-quality antibiotics safely in everyday practice. As of December 2015, over 5,000 healthcare professionals had completed the course, with over 15,000 registrants.

## Pfizer's Position: AMR Surveillance

Regional and global surveillance of antibiotic resistance patterns provides physicians with important information to choose the most effective antibiotics and to plan and assess stewardship and strategies. Pfizer sponsors three AMR surveillance programs; T.E.S.T., ZAAPS and LEADER. The goal of all three programs is to provide resistance information regarding Pfizer products and other antibiotics so that physicians can make the most appropriate choices for their patients. It also allows us to assess stewardship and access.[17]

## Pfizer's Position: Vaccines and AMR

In addition to appropriate use of antibiotics, vaccines are essential tools in our fight against infectious disease. Vaccines protect the vaccinated individual by direct immunization and can protect others through indirect immunization (assuming the overall vaccination rate is high enough). The evidence is mounting that vaccines can provide an effective tool for reducing disease caused by drug-resistant strains.[18] It has been reported that the pneumococcal conjugate vaccine not only reduces the incidence of invasive antibiotic-resistant pneumococcal infections in young children receiving the vaccine, but it also reduces transmission of these strains to their younger siblings and to adults.[19] The Centers for Disease Control and Prevention now advocates this concept that developing new vaccines can decrease rates of antibiotic-resistant infections.[20] A report titled, Role of Vaccination in Reducing Antimicrobial Resistance, was published by Vaccines Europe in 2013.[21] It cites evidence supporting the preventive use of antibacterial vaccines to protect individuals and communities against infectious disease, including those caused by resistant bacterial strains. Pfizer believes that vaccines are essential tools in our fight against antibiotic resistant infections. Vaccines and antibiotics should be used together to produce synergistic gains in public health, particularly since vaccines can extend the clinical utility of antibiotics. By reducing infections and limiting their transmission, vaccines allow providers to prescribe antibiotics less frequently and therefore, to be used more sparingly and under closer supervision. We thus agree with the call for national immunization plans that ensure access to vaccinations for citizens of all ages, as outlined by Vaccines Europe (2013).

## Pfizer's Position: New Infectious Disease R&D Incentives and the GAIN Act

There have been recent proposals in the US and EU that examine push-pull models as a means to circumvent what is perceived to be failure of the market to provide enough incentives for AMR R&D, requiring government intervention. The Report to the President on Combating Antibiotic Resistance, based on recommendations of the U.S. President's

Council of Advisors on Science and Technology (PCAST), was submitted in September 2014.[22] The report makes eight recommendations including modernization of clinical trials, antimicrobial stewardship and infection surveillance, more funding for basic research, international cooperation, and restrictions on use of antibiotics in agriculture. Also singled out in the report was the essential need to incentivize new R&D.

In 2012, the Generating Antibiotic Incentives Now (GAIN) Act was enacted into US law. The GAIN Act provides pharmaceutical companies incentives to develop new antibiotics to combat the growing problem of antibiotic resistance. One of the GAIN Act's key provisions is that it provides five years of additional exclusivity to qualified new antibiotics (QIDP) at the time of their entry into the market. This five year exclusivity is in addition to the applicable Hatch-Waxman five-year new chemical entity (NCE) exclusivity, three-year new clinical studies exclusivity, seven-year orphan drug exclusivity, or six-month pediatric exclusivity.[23] The GAIN Act also adds additional six months of exclusivity for approved antibiotics that have been paired with a companion diagnostic test.

Pfizer believes that a mix of different, complementary incentives is needed to encourage increased AMR-focused antibiotic and vaccine development, which could include measures such as transferable regulatory data/marketing exclusivity, transferable IP mechanisms, transferable priority review vouchers (tPRV), market entry rewards, and R&D tax credits , within the framework of the regulatory and IP systems applicable to the particular jurisdiction..[24]

- Novel Intellectual Property Mechanisms: A transferable regulatory data/marketing exclusivity or IP extension for the development of an antibiotic drug that in turn could be applied to a different drug in that company's portfolio could create meaningful incentives for antibiotic and vaccine development. Such incentives could be designed to be both equitable for governments and society, while providing a reasonable return for private enterprises and new antibiotics for society. In the EU the equivalent of GAIN incentives (additional 5 years' regulatory exclusivity or IP protection for the product itself) may be useful as well as one year of exclusivity transferable to another product.
- Transferable Priority Review Vouchers (tPRV): In the US the tPRV provides the option to transfer a priority review to a higher value asset; these have been used successfully in the United States. Since transferable priority review vouchers can be exchanged or "sold" between companies, this feature creates a strong incentive for smaller companies. PRVs should be supported by the US legislature and its use expanded as a potential positive impact on antibiotics R&D.
- R&D Tax Credits: Tax credits have appeal to both large and small companies. However, it is primarily an incentive for larger companies that have the capability and resources necessary to take drug candidates through from discovery to regulatory approval.
- Regulatory Flexibility: Acceptance of innovative clinical trial protocols and a willingness to run trials with evidence that recognizes the unique characteristics of antibiotics and how they work (e.g. greater use of pool microbiological data across body sites, augmenting that with non-clinical susceptibility and pharmacokinetic (PK) data) are needed. It would also help development if the regulatory changes envisioned by the GAIN Act in the US would be applied to the European regulatory system. This could include the automatic acceptability of new antibiotic drug and vaccines into EU accelerated regulatory schemes (PRIME and Adaptive Pathways).
- Diagnostics: Regulatory and economic incentives should also include the development of diagnostic assays, which can differentiate antibiotic-resistant from antibiotic-sensitive strains of bacteria, and will be a key enabler for the development of targeted, new generation antibiotics.

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[2] http://www.searo.who.int/entity/world_health_day/media/2011/whd-11_amr_jaipur_declaration_.pdf?ua=1
[3] WHA Global Action Plan on antimicrobial resistance. http://apps.who.int/gb/ebwha/pdf_files/WHA68/A68_ACONF1Rev1-en.pdf
[4] PAHO Foundation; Proposal to develop a plan and structure to mobilize and facilitate multi-sector support of AMR control in Latin America and the Caribbean. October 2015
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[12] ibid
[13] Center for Disease Dynamics, Economics & Policy. 2015.State of the World's Antibiotics, 2015. CDDEP: Washington, D.C. http://www.health-e.org.za/wp-content/uploads/2015/09/The-State-of-the-World's-Antibiotics-.pdf
[14] ibid
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[21] Vaccines Europe at: http://www.vaccineseurope.eu/wp-content/uploads/2013/09/AMR-and-Vaccines-June-2013.pdf
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