International Federation
of Pharmaceutical
Manufacturers & Associations

RETHINKING THE WAY WE FIGHT BACTERIA

IFPMA

Table of contents

Introduction

Antibiotics made modern medicine possible. Before the introduction of antibiotics, such as penicillin in the 1940s, infectious diseases as simple as common skin infections claimed countless victims. In the early 1900s, 90% of children with bacterial meningitis died. Complex medical interventions like organ transplants, hip replacements and even chemotherapy are all made possible or better by the use of antibiotics. But a hallmark of antibiotics is that they lose their effectiveness over time as bacteria naturally evolve and mutate and so become resistant to the medicine's power.

The problem of antimicrobial resistance (AMR) is growing[1], and seventy years after their introduction the rise of bacterial resistance to popular and historically effective antibiotics has become a grave threat to global public health. We now face the possibility of a future without effective antibiotics for several types of bacteria that cause life-threatening infections in humans.

The problem of AMR extends across the globe. In 2013, the CDC released a report[2] stating that in the United States, at least 2 million people become infected with bacteria that are resistant to antibiotics and at least 23,000 people die each year as a direct result of these infections. In the EU, multidrug-resistant bacteria cause about 400,000 infections a year and at least 25,000 deaths annually, and generate healthcare costs and productivity losses of €1.5 billion[3]. But while there are high levels of resistance in developed countries, the most alarming levels of resistance are in developing countries. For example a study found that in 2013 more than 58,000 babies died from antibiotic-resistant infections in India[4]. At the global level, a report published by the United Kingdom AMR Review Team estimated that a continued rise in resistance by 2050 would lead to 10 million people dying every year and a reduction of 2% to 3.5% in Gross Domestic Product (GDP).

In 2014, a resolution was adopted at the World Health Organization's World Health Assembly calling for the development of a Global Action Plan to fight against Antimicrobial Resistance. The development of a Global Action Plan has considerably increased the visibility of AMR at international level. At a national level, AMR is also gaining prominence on the policy agenda, with the implementation of national action plans. At the regional level, the development of public private partnerships such as IMI in Europe has helped incentivize innovation. Finally, AMR is high on the agenda of the G7 leaders who have publicly referred to this issue as one of the most important global threats.

We believe that a globally coordinated, multi-faceted policy approach is urgently needed to address each of the challenges contributing to resistance. IFPMA and its member companies are committed to continue in the fight against antimicrobial resistance.

1 Streptococcus pneumoniae (S. pneumoniae), another common pathogen, causes bacterial meningitis and bacterial pneumonia, among other conditions. In 1987, only 2 of every 10,000 S. pneumoniae infections—0.02 percent—were resistant to penicillin, the antibiotic of choice. By 2004, this figure had risen to 1 in 5—20 percent—a 1,000-fold increase (CDC 2005). http://www.extendingthecure.org/executive-summary

2 Antibiotic Resistance Threats in the United States, 2013.

3 Bacterial Challenge: Time to React, ECDC/EMEA Joint Technical Report. Stockholm, 2009.

4 Ramanan Laxminarayan et al, Antibiotic resistance—the need for global solutions, The Lancet Infectious Diseases Commission, Volume 13, No. 12, p1057–1098, December 2013.

WHY WILL WE ALWAYS NEED NEW ANTIBIOTICS?

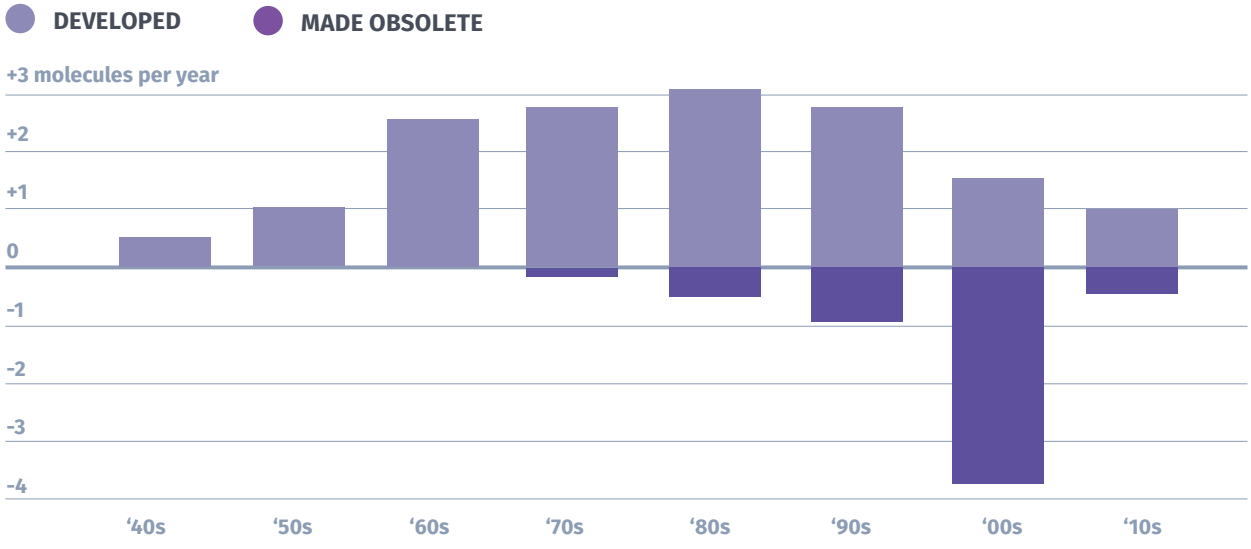
Antimicrobial resistance is a naturally occurring phenomenon. Bacteria have always possessed the ability to protect themselves from naturally occurring antibiotics by acquiring resistance through the exchange of genetic material with other bacteria.

This survival mechanism, which bacteria have developed over billions of years, eventually enables them to develop resistance to most antibiotics. As a result, even our most recently approved and most effective drugs will gradually decline in efficacy, making research and development of new antibiotics a constant need. Two further factors have accelerated the development of this resistance: widespread use of antibiotics, and time-consuming diagnostic tools leading to the inappropriate use of antibiotics. Over the last twenty years the resistance problem has increased as antibiotic-resistant bacteria have become more prevalent and multidrug-resistant strains have emerged in many species that cause disease in humans. Stopping AMR might be biologically impossible, but the healthcare community can refine, develop and adopt practices to slow resistance and ensure that the global stock of antibiotics remains viable for a longer period.

AN URGENT NEED

There is a dearth of new antibacterial medicines as the growth in antimicrobial resistance has been accompanied by a sharp decline in the development of new antibacterial medicines. Over the past three decades only two new classes of antibacterial medicines have been discovered, compared to 11 in the previous 50 years. It is now widely accepted that the increase in resistance and the decline in the number of new drugs coming to market together pose a major threat to health in all countries. The number of antibiotics becoming obsolete due to resistance significantly exceeds the number of new therapies being approved[5]. Concerted action is needed to boost antibiotic development, to face a growing public health threat.

AVERAGE NEW ANTIBIOTIC MOLECULES PER YEAR



Source: Michael S. Kinch, Denton Hoyer, et. al.,Yale Center for Molecular Discovery.

5 Michael S. Kinch, Denton Hoyer, et. al.,Yale Center for Molecular Discovery.

IN 2014, 2 NOVEL ANTIBIOTICS AGAINST TUBERCULOSIS WERE APPROVED AFTER A DISCOVERY VOID OF OVER 3 DECADES.

Otsuka's Delamanid is a new medication with a novel mechanism of action indicated to treat adults with pulmonary multidrug-resistant tuberculosis (MDR-TB), a form of tuberculosis resistant to at least isoniazid and rifampicin, the main first-line medicines. In 2014, delamanid was approved in Japan and South Korea and granted conditional marketing authorization in the European Union in combination with other existing anti-TB medications. In November 2014 the WHO issued interim policy guidance on the use of delamanid which paves the way for country adoption and future access in other high-burden countries.

Janssen's Bedaquiline is a new medicine for pulmonary multi-drug resistant tuberculosis (MDR-TB) with a novel mechanism of action in over forty years. SIRTURO®, which is administered by directly observed therapy, is indicated as part of combination therapy in adults with pulmonary MDR-TB. To date, SIRTURO® has received accelerated approval in the United States and has been registered in the Russian Federation by JSC Pharmstandard; the company Janssen signed a license agreement with in 2013 for Russia and the Commonwealth of Independent States. Additional approvals were granted in 2014 by high burden countries such as South Korea, South Africa, the Philippines and Peru. Regulatory filings have also been submitted in China, India, Thailand, Vietnam and Colombia.

The growth of resistance combined with the high attrition rate of antibiotic drugs in development makes it crucial that enhanced investments be made in research and development to ensure that a sufficient pool of antibiotics is available at any time to treat common and rare infections. The recent discovery of new antibiotics should not disrupt sustained efforts in discovering new antibiotics. The fight against antimicrobial resistance is a long term one as new antibiotics will always be needed.

What is resistance?

The Center for Disease Control and Prevention (CDC) defines resistance as “the ability of bacteria or other microbes to resist the effects of an antibiotic. Antibiotic resistance occurs when bacteria change in some way that reduces or eliminates the effectiveness of drugs. The bacteria survive and continue to multiply causing more harm”[6]. Some bacteria are naturally resistant to certain types of antibiotics. However, bacteria may also become resistant in two ways:

1 By a genetic mutation

2 By acquiring resistance from another bacterium

6 For more information visit http://www.cdc.gov/getsmart/antibiotic-use/antibiotic-resistance-faqs.html

1

A genetic mutation

MUTATION : THE 3 WAYS RESISTANCE BUILDS

A **Efflux pump:** Bacteria pump out the antibiotics before they can start attacking bacteria.

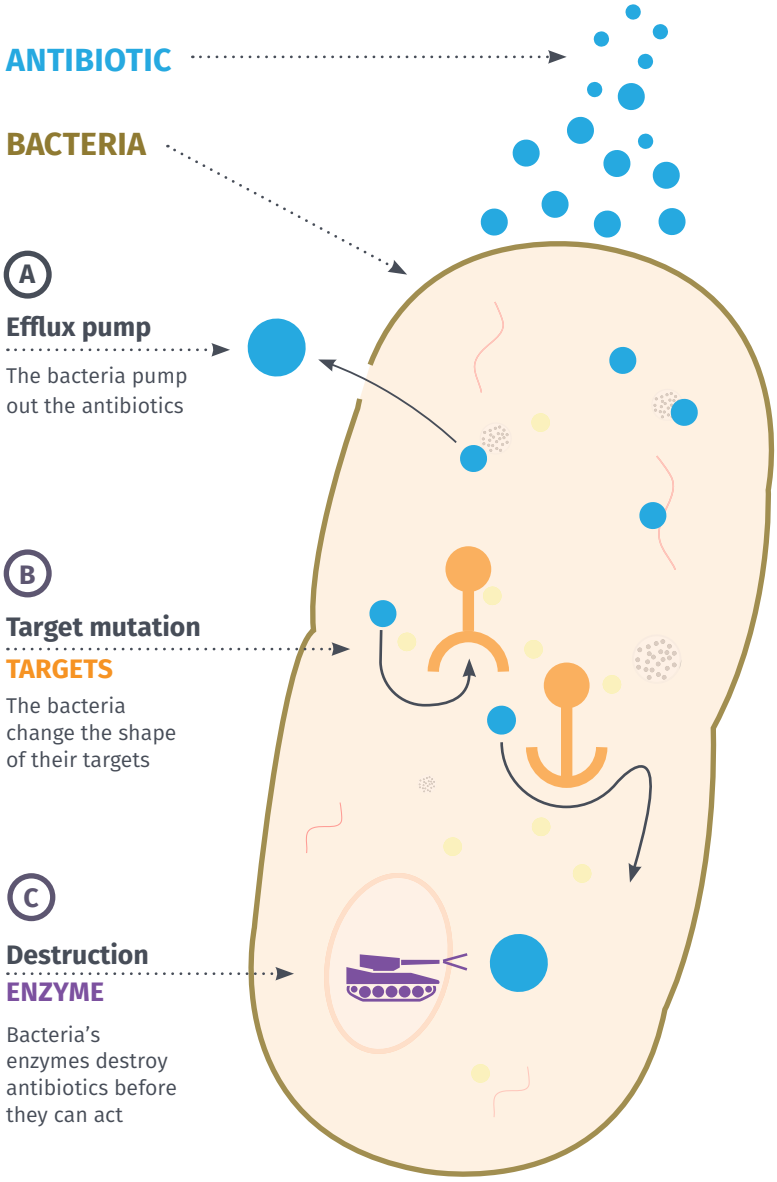
B **Target mutation:** Bacteria change the shape of its targets so that the antibiotic cannot attack it.

C **Destruction:** Bacteria develop the ability to neutralize the antibiotic before it can do harm for example by changing the shape of the antibiotic.

WHY DO WE SAY THERE ARE GOOD AND BAD BACTERIA?

Good bacteria act as protectors of our body as they compete with pathogenic bacteria for space and nutrients. Sometimes, we put the population of beneficial bacteria at risk. For example, when we take antibiotics to treat an infection of harmful bacteria, we also kill helpful bacteria.

3 MAIN MECHANISMS OF MUTATION CREATING RESISTANCE



Source: Adapted from Reflexions, The university of Liege website that makes science accessible. http://reflexions.ulg.ac.be/cms/c_12956/en/antibiotics-against-bacteria?part=3

2

By acquiring resistance from another bacterium

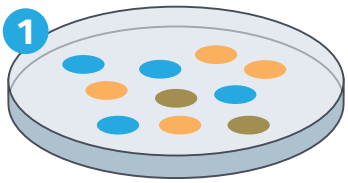
WHY DOES TAKING ANTIBIOTICS FAVOR THE BUILDING OF RESISTANCE?

Antibiotic use promotes development of antibiotic-resistant bacteria. Every time a person takes antibiotics, sensitive bacteria are killed, but sometimes one of the bacteria survives because it has the ability to neutralize or escape the effect of the antibiotic; that one resistant bacterium can then multiply and replace all the bacteria that were killed off. Repeated and improper uses of antibiotics are primary causes of the increase in drug-resistant bacteria.

WHAT IS SELECTION PRESSURE?

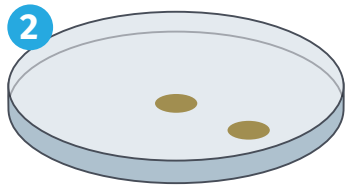
According to the Food and Drug Administration (FDA), selection pressure is the increased prevalence and dissemination of resistance. It is an outcome of natural selection and should be viewed as an expected phenomenon of the Darwinian biological principle "survival of the fittest"[7].

SELECTION PRESSURE: WHY DOES THE USE OF ANTIBIOTICS FAVOR THE EMERGENCE OF RESISTANCE?

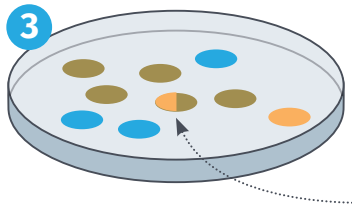


Good & bad bacteria compete for space and nutrients

- "Bad" bacteria causing the disease susceptible to ABs
- Good bacteria
- Resistant bacteria



Antibiotics will kill both good and bad bacteria. The resistant bacteria can more easily reproduce.



More resistant bacteria are growing in proportion with the use of antibiotic.

Some bacteria can transfer the resistance to others

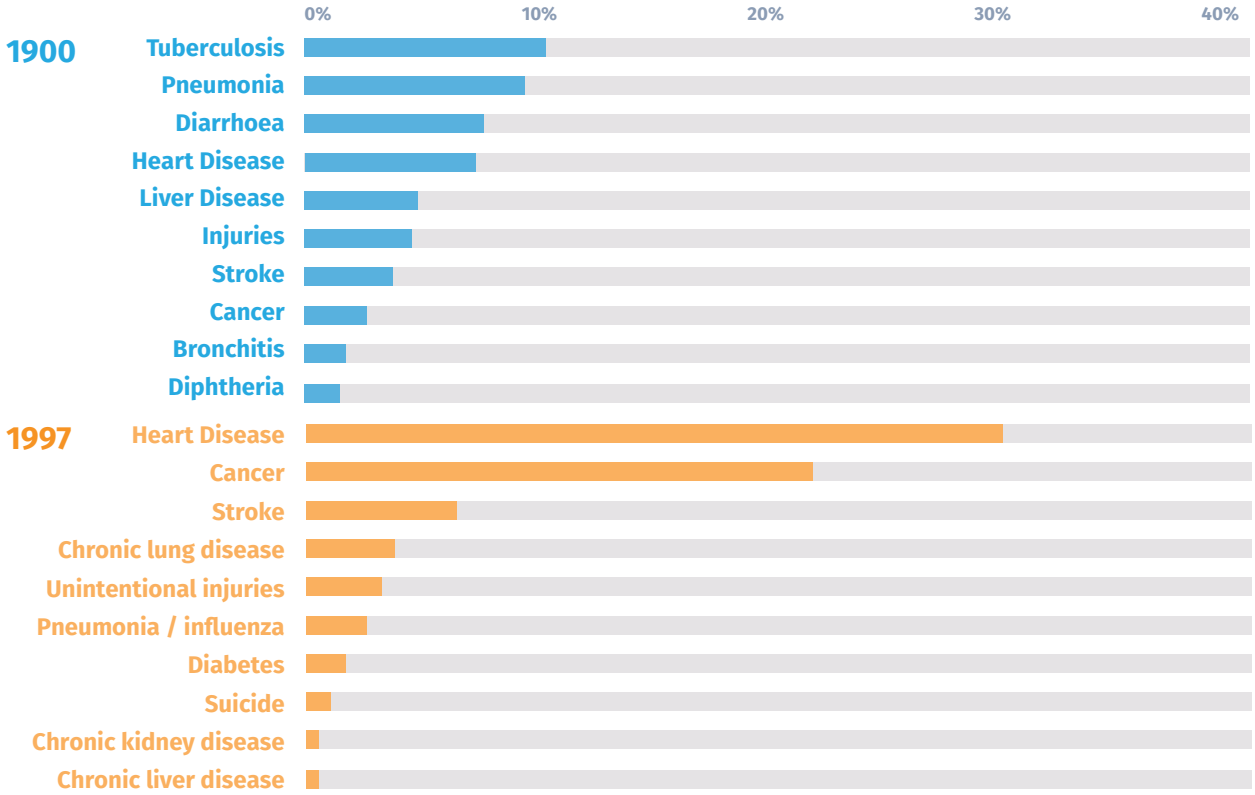
7 For more information: http://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/ucm134455.htm

WHAT WOULD A POST-ANTIBIOTIC ERA LOOK LIKE?

The introduction of antibiotics and immunization has been a key contributor to the reduction of deaths from infectious diseases and helped to make modern medicine possible by allowing the use of chemotherapies for cancer, organ transplantation, etc. Chronic diseases are now the leading causes of death.

IMPACT OF THE INTRODUCTION OF ANTIBIOTICS ON PUBLIC HEALTH[8]:

The 10 leading causes of death as percentage of all deaths – United States, 1900 and 1997



If antibiotics stopped working, the most common health conditions would become impossible to treat and infections resistant to antibiotics would affect people from all ages. Simple infections could become a deadly threat not only for the most fragile, but also any healthy person.

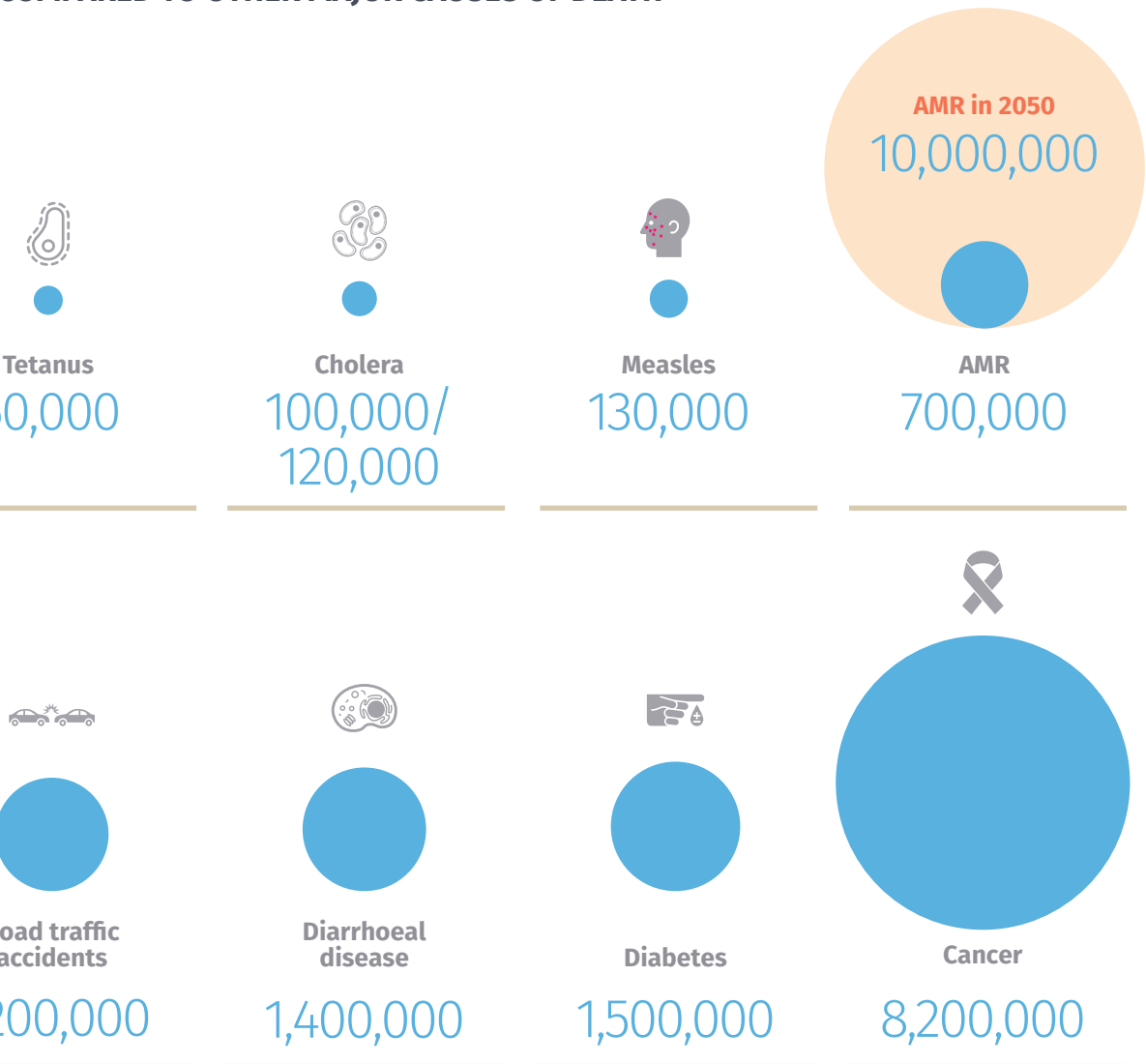
8 Mitchell L. Cohen, Changing patterns of infectious disease, Nature 406, 762-767(17 August 2000) doi:10.1038/35021206

WHAT WILL HAPPEN IF WE DO NOT ADDRESS AMR?

EPIDEMIOLOGICAL AND ECONOMIC DATA[9]

Initial studies looking at what could potentially be the cost of inaction in both epidemiological and economic terms estimated that a continued rise in resistance by 2050 would lead to 10 million people dying every year and a reduction of 2% to 3.5% in Gross Domestic Product (GDP). It would cost the world up to 100 trillion USD.

DEATHS ATTRIBUTABLE TO ANTIMICROBIAL RESISTANCE EVERY YEAR COMPARED TO OTHER MAJOR CAUSES OF DEATH



Source: Adapted from the Review on Antimicrobial Resistance 2014.

9 UK Independent Review Team Report, December 2014.

EXAMPLES OF HEALTH CONDITIONS AND INTERVENTIONS WHICH WOULD NOT BE POSSIBLE WITHOUT EFFECTIVE ANTIBIOTICS

BABIES & CHILDREN

- Neo-natal care
- Diarrhoeal disease

ADULTS

- Appendix operations
- Women delivering by caesarean section
- Treatment of sexually transmissible diseases
- Organ transplantation
- Urinary tract infections

OLDER PEOPLE

- Cancer treatments
- Hip replacement

"Drug-resistant infections already kill hundreds of thousands a year globally, and by **2050** that figure could be more than **10 million**. The economic cost will also be significant, with the world economy being hit by up to **$100 trillion by 2050** if we do not take action."

Jim O'Neill, Chairman of the Review on AMR

What can we do to prevent misuse and minimize the growth of resistance?

Education

Prevention

Optimized use

EDUCATION

Antibiotics are a critical element in managing bacterial infections in people of all ages. However, inappropriate use and overuse have the potential to make them ineffective over time and taking antibiotics for the wrong illness can be dangerous.

Preventing resistance requires healthcare professionals, industry, policy makers and the public to work together in a joint approach to promote appropriate antibiotic use.

Educating healthcare professionals and patients is key to minimizing resistance. Antibiotics must be used correctly for the right conditions and only when necessary. Supporting healthcare professionals to make appropriate prescribing decisions and ensuring patients understand their medicines and how to take them is essential.

Educational programs supporting healthcare providers on getting patients the right medicine at the right time, which includes prescribing only when necessary, can support this approach.

Public understanding of what antbiotics do and don't treat is critical. When prescribed antibiotics, ensuring patients know how to take the medicine prescribed and understand the importance of finishing the full course of medication is also an essential element to support this understanding. Understanding that most coughs and colds are caused by viruses, which are not cured by antibiotics, is also a key element in education programmes.

Infections can be caused by two main kinds of germs, viruses and bacteria. Antibiotics only cure infections caused by bacteria. They have no effect against infections caused by viruses, like the flu or colds.

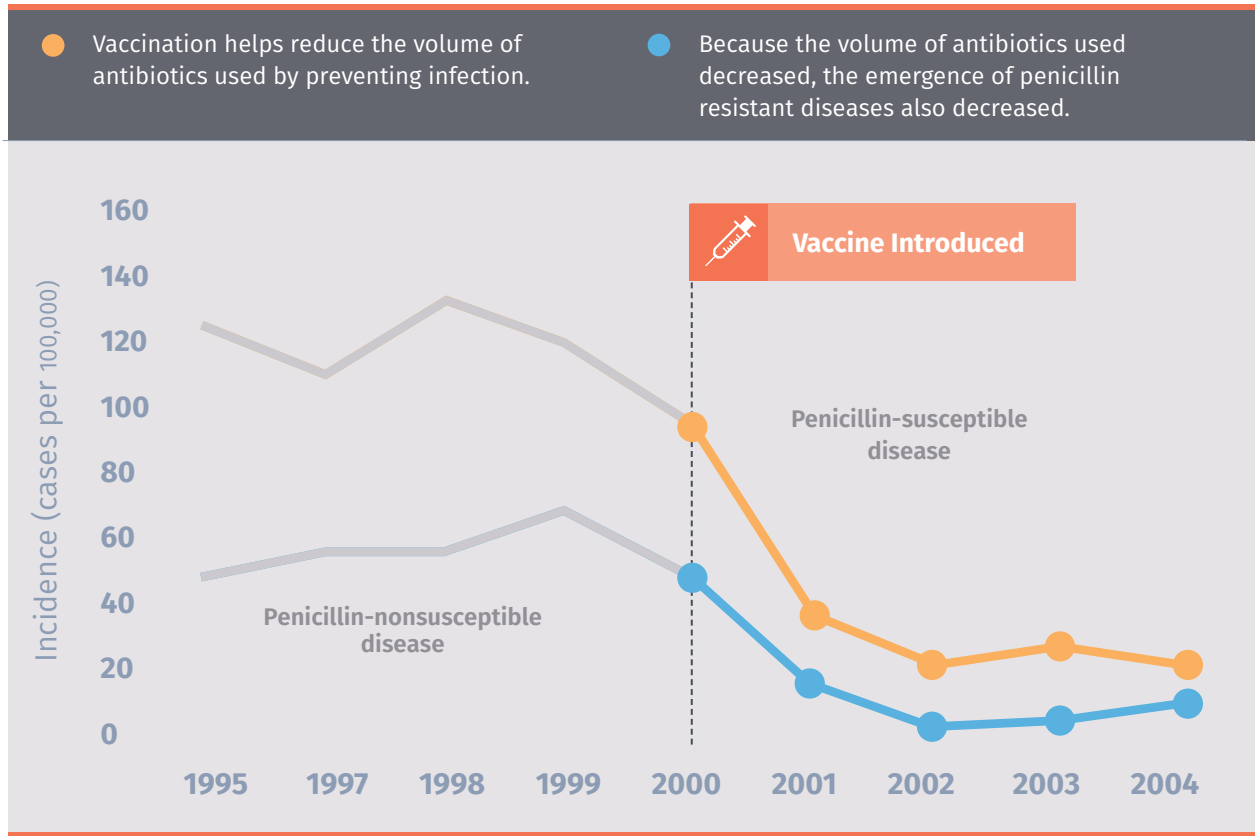
PREVENTION

In contrast to the challenge of resistance to antibiotics, vaccines remain a consistent weapon in the fight against infectious diseases. While they are not efficacious in people already infected, vaccines can help directly in the fight to limit resistance to antibiotics because they 1) reduce the need for antibiotic use; 2) have the potential to reduce the misuse of antibiotics (e.g. where the vaccine targets a viral infection); and 3) combat bacteria that are resistant to available antibiotic treatments so as to stop the spread of the disease. In each case, vaccines lower the spread of pathogenic bacteria which in turn allows for better management of antibiotics. Vaccines will continue to be a key weapon in our arsenal to reduce the spread of antibiotic resistance.

Examples of the three-fold role of vaccination.

1. Immunization can help reduce the use of antibiotics (for example for tuberculosis or pneumonia); it therefore indirectly reduces the opportunities for resistant bacteria to develop.

IMPACT OF THE INTRODUCTION OF PNEUMOCCOCAL VACCINE ON INFECTION CONTROL AND ON RESISTANCE



Source: Adapted from Kyaw M. H., et al. 2006. Effect of introduction of the pneumococcal conjugate vaccine on drug-resistant Streptococcus pneumoniae. N. Engl. J. Med. 354:1455–1463.

2. Immunization helps reduce the misuse of antibiotics. In the case of viral vaccines, protection from a virus will reduce the number of viral infections which in some cases are mistakenly diagnosed as a bacterial infection and thus treated with antibiotics. For example there is a common misuse of antibiotics against influenza.

3. Immunization may help prevent the development of resistant bacteria (*c. difficile, E, Coli, s. Aureus* etc.)

A NON-EXHAUSTIVE LIST OF EXISTING VACCINES TARGETING POTENTIALLY ANTIMICROBIAL RESISTANT BACTERIA[10]

DISEASES	PATHOGEN	VACCINE TYPE(S)
Cholera	*V. cholerae*	Inactivated, recombinant toxin subunit
Diphtheria	*C. diphtheria*	Toxoid
Invasive pneumococcal disease	*S. pneumoniae*	Polysaccharide
Meningitis	*N. meningitidis*	Polysaccharide, conjugate
Meningitis, pneumonia, epiglottis	*H. influenzae type B*	Conjugate
Tetanus	*C. tetani*	Toxoid
Meningitis, bacteremia/sepsis, (pneumonia), otitis media	*S. pneumoniae*	Conjugate
Typhoid fever	*S. typhi*	Polysaccharide, Live attenuated
Whooping cough	*B. pertussis*	Inactivated, sub-unit, toxoid

Source: Vaccines Europe, Role of vaccination in reducing antimicrobial resistance, June 2013.

More vaccines targeting bacteria are currently under development as described in the pipeline inventory featured at the end of this publication.

10 Vaccines Europe, Role of vaccination in reducing antimicrobial resistance, June 2013 http://www.vaccineseurope.eu/wp-content/uploads/2013/09/AMR-and-Vaccines-June-2013.pdf

OPTIMIZED USE

The use of rapid test diagnostics

The ability to identify targeted pathogens with rapid diagnostic tests (RDTs) could greatly improve appropriate treatment involving the use of antibiotics. Currently, the most accurate and widespread identification of bacteria takes 36–48 hours to provide results. As delays in initiation of effective therapy can lead to increased sickness or even death of the patient, physicians frequently must treat patients empirically while still waiting for test results, or may not even undertake those tests at all. This may lead to inappropriate prescription of antibiotics or even the misdiagnosis of viral infections as bacterial. The absence of effective RDTs has also led physicians to rely on broad spectrum antibiotics as opposed to more targeted treatments. We must be realistic about what can be achieved through improved diagnostics: even the latest tools can take 24 hours or more to produce a result, and they often require a level of resources that in developing country settings limit their use. Nevertheless, improved diagnostic tools are an important part of the response to the AMR challenge.

Combatting the use of sub-standard and falsified medicines

Available data suggest that antibiotics are one of the most falsified and/or substandard pharmaceutical products in developing countries[11]. Substandard antibiotics often have a lower dosage of the active ingredient which directly contributes to build resistance[12], as what does not kill bacteria makes them stronger. A study published in the International Journal of Tuberculosis and Lung Disease[13] assessed the quality of two treatment packs of two first-line anti-tuberculosis drugs in 19 cities in 17 low- and middle-income countries. The study showed that 9.1% of the drugs sampled failed basic quality control tests. The failure rate was 16.6% in Africa, 10.1% in India, and 3.9% in other middle-income countries. Approximately half of these failing products contained some active ingredients making them likely to contribute to drug resistance. In addition, falsified medicines may contain the wrong ingredients, the wrong dose, no active ingredients at all or dangerous substances. Ensuring the good quality of antibiotics and securing the supply chain are necessary measures to prevent the development and spreading of multi-resistant bacteria.

Stewardship

Antibiotic stewardship must be an integral part of any solution to overcome antibiotic resistance. Cases where antibiotics are overused or misused exist worlwide. To address this, clear guidelines and pathways for medical intervention, including timelines, are required to stabilize the growth of resistance antibiotic. Stewardship programs can facilitate the use of appropriate treatment protocols and trigger appropriate reporting processes that will combat the development of bacterial resistance. For any of these programs the challenge will be not to become a gatekeeper to antibiotic usage.

Adequate antibiotic stewardship must be a systematic effort from multiple partners. Governments and policymakers can implement systems that reward healthcare providers for implementing high quality stewardship programs. Hospital systems, individual hospitals and medical societies and physicians, as well as IT teams that support efficient information-sharing and analysis can all contribute towards ensuring that all aspects of appropriate use of antibiotics are captured

11 WHO. Counterfeit Drugs: Guidelines for the Development of Measures to Combat Counterfeit Drugs. Geneva: WHO, 1999; 1–60.

12 Michael A. Kohanski, Mark A. DePristo, James J. Collins. Sublethal Antibiotic Treatment Leads to Multidrug Resistance via Radical-Induced Mutagenesis. Molecular Cell, Volume 37, Issue 3, 311-320, 12 February 2010 DOI: 10.1016/j.molcel.2010.01.003.

13 Bate R, Jensen P, Hess K, Mooney L, Milligan J (2013) Substandard and falsified anti-tuberculosis drugs: a preliminary field analysis. Int J Tuberc Lung Dis 17: 308–311 Available: http://www.aei.org/files/2013/02/05/-substandard-and-falsified-antituberculosis-drugs-a-preliminary-field-analysis_142125219328.pdf

in high quality stewardship programs. Pharmaceutical manufacturers can also partner with health care delivery systems to share information and expertise that will contribute towards the development of robust and responsible stewardship programs. IFPMA's member companies adhere to the conditions of IFPMA Code of Pharmaceutical Marketing Practices[14], supplemented by member association and company Codes, which set standards for the ethical promotion of medicines. IFPMA calls on other stakeholders to adopt codes of practice with regard to the marketing and prescribing of medicines. In addition, the pharmaceutical industry and national industry associations have participated in the development of national action plans and workshops on how to reduce antibiotic use. It is only through ongoing, sustainable partnerships that we can tackle this challenge.

EXAMPLE: ANTIBIOTIC STEWARDSHIP PROGRAMMES IN INDIA

India suffers from significant rates of resistance to antibiotics and unfortunately, the use of antibiotics is not monitored systematically. Antibiotics can be bought over-the-counter in India and to date, the government has not established clear guidelines for the use of antibiotics. With 20,000 hospitals and over a million people in India, a systemic approach is crucial to any anti-microbial stewardship effort. In 2012, a partnership was initiated across multiple medical societies in India, to establish "A Roadmap to Tackle the Challenge of Antimicrobial Resistance". This first step toward systemic change outlined the roles and responsibilities of many groups well positioned to improve the use and monitoring of antibiotics, including the Indian government, semi-governmental agencies, physician associations, hospital administrators, medical educators and medical journals. With such a comprehensive assessment now public, the work of reaching each and every one of the 20,000 hospitals and of changing the mindset that has promoted such free use of antibiotics has begun. Region by region, hospital by hospital, the partnerships between government, the health care providers and also the pharmaceutical industry are starting to make a difference. The impact of these efforts, will overtime significantly help reduce antimicrobial resistance rates across India.

14 http://www.ifpma.org/uploads/media/Consensus_Framework-vF.pdf

Why is it difficult to develop new antibiotics?

A UNIQUE CHALLENGE

There is a unique market dynamic for antibiotics where new therapies should be used at a minimum level to ensure their preservation and delay as much as possible the development of resistance. This dynamic goes against the traditional economic market logic, which is based on a price/volume model. To ensure continued investment in antibacterial R&D, a new economic model must be developed.

Antibiotics generally provide a low return on investment. This is explained by different factors:

- The limited use of new therapies because they are kept in reserve as medicines of last resort.
- The relatively short period for which antibiotics are taken compared with drugs for chronic diseases.
- Antibiotics development costs can be very high where highly selective patient populations are required (patients with resistance to existing treatments) to carry out clinical trials.
- While effective new antibiotics provide a range of benefits to society, there is still a low value placed on them. This calls for a broader consideration of value than traditional reimbursement approaches[15].

There are 3 main types of challenges for manufacturers in the development of new antibiotics:

DISCOVERY

The discovery of new antibiotics is not a simple task. Scientific challenges are immense in new antibiotics research given the existence of multiple resistance mechanisms. As a result, progress depends on sustained efforts by industry over a period of many years, combined with the existence of, as well as scientific progress by, diverse groups of trained scientists within academia and industry.

DEVELOPMENT

Clinical trials on new antibiotics are difficult to carry out. Because placebo-controlled trials for serious bacterial infections are unethical, scientists need to use a more challenging (non-inferiority) design for trials of new antibiotics. Regulators need to find a balance between statistical conservatism and physician and patient needs[16].

EXAMPLE: CLINICAL TRIALS FOR NEW TUBERCULOSIS (TB) MEDICINES

Clinical trials are often lengthy since standard TB treatment requires several months of daily observed therapy of the study drug combined with a cocktail of existing drugs and for drug-resistant forms of TB, treatment could be up to 24 months. This means in order to effectively produce clinical trial results for regulatory approval, one must complete the full 24 month observation period plus a follow up. When added all together, this means taking studies through phase III requires more than 5 years. Additionally, the several drugs required to compose the regimen must also be procured and paid for by the study sponsor. This long treatment regimen poses a huge cost to ensure patient compliance and proper pharmacovigilance.

15 Kevin Outterson, John H. Powers, Gregory W. Daniel and Mark B. Mc Clellan, Repairing The Broken Market For Antibiotic Innovation, Health Affairs, 34, no.2 (2015):277-285

16 Letter from IDSA to FDA Division of Dockets Management. The Infectious Diseases Society of America's Commentary on Food and Drug Administration Draft Guidance HFA-305. 17 November 2010.

ECONOMIC

- The low value placed on antibiotics; effective new antibiotics provide a range of benefits to society, calling for a broader consideration of value than traditional reimbursement approaches.
- The limited use of new therapies because they are kept in reserve as medicines of last resort.
- The relatively short period for which antibiotics are taken compared with drugs for chronic diseases.

EXAMPLES: THE LOW VALUE PLACED ON INNOVATIVE ANTIBIOTICS

- For patients with severe Multiple Drug Resistance (MDR) infections, treatment with an innovative antibiotic effective against MDR pathogens can mean the difference between life and death. Budget and payment structures do not always differentiate first line antibiotics with innovative antibiotics effective against MDR pathogens. This negatively impacts health systems' ability to reimburse innovative antibiotics.
- Severe MDR strains of formerly treatable pathogens can emerge rapidly, potentially causing outbreaks of multi-resistant infections that imperil significant populations as well as causing major economic disruption. A diversity of effective antibiotics can provide the necessary protection against such a scenario, but traditional added value analysis places no value on this type of antibiotic diversity.

As a consequence to these barriers, many companies have scaled down their capabilities for developing new antibiotics[17]. Research has shown that the current reimbursement environment sends incorrect signals to antibiotics developers, because the return on new antibiotics that address the significant harms of AMR is far less than the societal value that these drugs deliver[18].

To re-incentivize investment in antibiotic R&D, a new economic model is needed that includes both push and pull mechanisms.

INCENTIVISING NEW R&D FOR ANTIBIOTICS

Push mechanisms move research forward; they help "de-risk" companies' initial investments by pooling funds and expertise.

- **Public Private Partnerships** (PPPs) help de-risk initial investment by sharing cost and pooling expertise. This cooperative tool is a crucial link in the process of bringing new discoveries to patients, particularly where there is little commercial investment. While PPPs are helping offset some of the R&D costs, they are not a structural solution as they focus on development and supply and do not address the need for sufficient ROIs.
- **Tax credits** increase the return on investment of successful medicines by subsidizing the cost of R&D through the reduction of tax liability. While tax credits can help de-risk R&D investments, they usually do not have the ability to incentivize investment in R&D on its own if there is a clear market failure. Also, this push mechanism mostly appeals to bigger companies.

Pull mechanisms encourage funding by helping increase the potential ROI and improving the predictability of the demand.

17 Kinch MS et al. Drug Discovery Today, July 2014.

18 Sertkaya, Eyraud, Birkenbach, Franz, Ackerley, Overton, and Outterson, "Analytical Framework for Examining the Value of Antibacterial Products" US Department of Health and Human Services, April, 2014

- **Prizes** are funds that create rewards for successful development of new products, which are paid in a lump sum once a product obtains necessary marketing approval. While prizes can create a immediate incentive, they do not support continued development.

- **Extended Data Exclusivity** provides a limited duration of time during which only the owner or generator of preclinical and clinical trial data can use it for purposes of marketing authorization. This creates additional incentive for pharmaceutical companies to make the large R&D investments required. However, Extended Data Exclusivity has not been proven to create sufficient incentives to invest and does not integrate the preservation criteria.

- **Priority Review Vouchers** reward a manufacturer that developed a new medicine for neglected diseases with a voucher that could be redeemed for priority review of a future medicine, probably a potential blockbuster drug.

- **Advance Market Commitments (AMCs)** help to replicate market forces, making funding available only if companies succeed in producing the desired product, while ensuring low prices to increase developing country access.

While all the above mechanisms help improve ROI, they do not fully solve the economic market failure and should not be considered as standalone solutions. To that effect, new models should be developed in addition to push and pull incentives.

Incentivize Efforts

Help "de-risk" companies initial investments by pooling funds and expertise

Base Research

Traditional Research

Product Development

Clinical Research

Delivery & Access

Regulatory Approval

Production Capacity

PUSH MECHANISMS

+ Product Development Partnerships
+ Tax Credits
+ Grants

PULL MECHANISMS

+ Prizes
+ Extended Data Exclusivity
+ Priority Review Voucher
+ Advance Market Commitments

Incentivize Results

Encourage funding by helping increase the return on investment (ROI) and increase the predictability of demand.

Source: Adapted from International AIDS Vaccine Initiative

New models should fulfill a set of criteria including:

- Support pricing and access that reflects the life-saving value of antibiotics and encourages the development of new antibiotics before resistance reaches crisis.
- Provide alternative sources of funding where budget-constrained local access decisions would limit patient access to these medicines.
- Incentivize and reward appropriate use of all antibiotics, providing an alternative source of revenue to create a market for new antibiotics that are held in reserve.

EXAMPLES:

Premium pricing could contribute to create better ROIs; however there will be access challenges to overcome given constraints in hospital budgets. Price alone will not deliver a sustainable model or help reduce the uncertainty of future demand antibiotics face due to unpredictable resistance patterns. Additional challenges of this model include ensuring stewardship and appropriate use is promoted and implementation at a global level.

Delinking revenue from usage aligns with both economic and public health goals; de-linking the volume of sales from the reward paid for a new antibiotic reduces uncertainty for companies and helps address the drive to increase usage. This model is based on the idea of rewarding innovation via fixed payments that are not a function of drug usage volume. Value would be created by companies by reducing commercial uncertainty and for payers by reducing budgetary uncertainty. Challenges of this model include lack of agreement by stakeholders on how it would be implemented and what would be the criteria for innovative antibiotics.

A model inspired by the Advance Market Commitments under which governments would contribute to a pooled fund which would issue fixed payments to innovators could be an option. In addition, for de-linkage to work, various models need to be explored to provide an acceptable ROI. Identifying the right amount of payments is critical: too low and companies will continue to disinvest from antibiotic R&D; too high and payers may exit the system. A joint approach to financial modeling will be needed, between company and payers together with a level of trust and realistic expectations from all parties.

7 RECOMMENDATIONS FOR A NEW ECONOMIC MODEL TO INCENTIVIZE INNOVATION, MEET PRESERVATION GOALS AND ENSURE ACCESS TO ANTIBIOTICS

1. Provide **attractive and predictable prospects** of Return on Investment (ROI) to encourage further investments.
2. **Reward risk**-taking for both small and large companies.
3. **Envisage Antibiotics R&D as a system** by incentivizing both the bringing of a new medicine to registration and continued development.
4. Reward innovation by **taking into account the societal value** of having new antibiotics available in advance of resistance rates needing them.
5. **Meet preservation goals** by preventing usage volume incentives.
6. Be applicable at a **global level**.
7. Facilitate **access to all patients** with infections resistant to other antibiotics.

Conclusion

Antibiotics have been critical to medicine and public health for over seventy years. They have helped wipe out conditions that killed people in the past and are essential in managing bacterial infections today as well as making modern surgery possible. However, antibiotic resistance is one of the most pressing health threats facing the world today.

We have reached a critical point in the development of these critical medicines. Today new innovations are necessary to combat bacterial resistance but the discovery of new antibiotics is not a simple task and is highly risky and expensive. To re-incentivize investment in antibiotic research and development we must examine how new treatments are developed and funded. The societal value of having new antibiotics available needs to be acknowledged in how this innovation is rewarded.

Supporting research and development of antibiotics to deliver effective medicines as promptly as possible and ensuring fair reward for this development will help to ensure sustainable antibiotic treatments are available to address the health challenges of the future.

IFPMA and its member companies are committed to working closely with our stakeholders to address these challenges in a coordinated way.

IFPMA

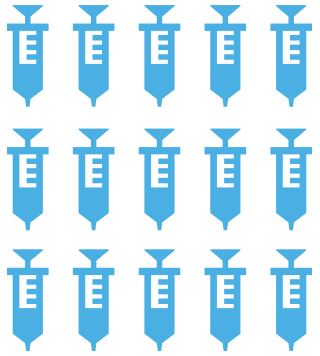
IFPMA MEMBERS' ANTIBACTERIAL COMPOUNDS PIPELINE INVENTORY 2015

KEY NUMBERS

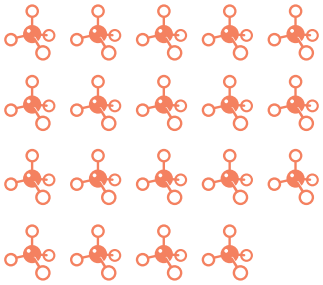
Total number of antibacterial compounds in development: **34**

Number of IFPMA member companies involved: **11**

PROPORTION OF MOLECULES AND VACCINES

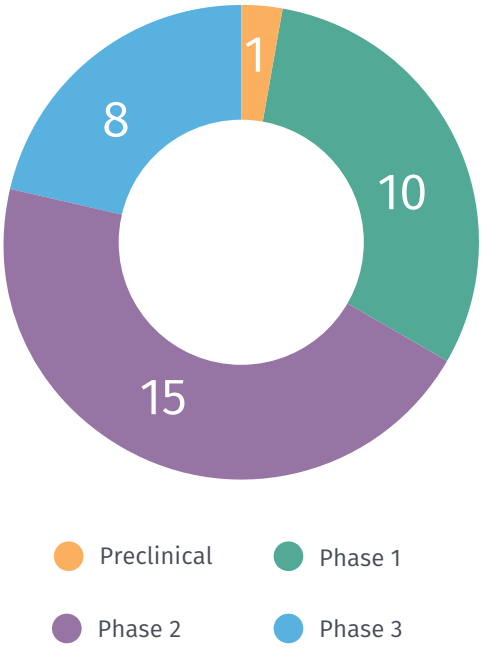


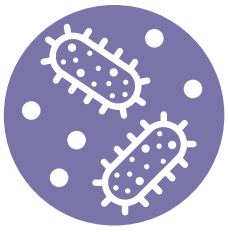
15 vaccines



19 molecules

STAGES OF DEVELOPMENT OF ANTIBACTERIAL COMPOUNDS





15 compounds target Gram-negative bacteria. Gram-negative bacteria are generally more resistant to antibiotics than Gram-positive bacteria.

Company	Compound Name or identifier	Compound Category	Spectrum: Gram-positive, Gram-negative, or both	Current development phase
AZ/Actavis	CAZ-104 Ceftazidime/ Avibactam	Small molecule	Gram-negative	Phase 3
	CXL-104 Avibactam/ Ceftaroline	Small molecule	Gram-negative	Phase 2
AZ	CAZ-104 Ceftazidime/ Avibactam	Small molecule	Gram-negative	Phase 3
	CXL-104 Avibactam/ Ceftaroline	Small molecule	Gram-negative	Phase 2
	AZD5847	Small molecule	M. tuberculosis	Phase 2
	AZD0914	Small molecule	Gram-negative	Phase 1
	MEDI4893	Large Molecule	Gram-positive	Phase 1
	ATM-AVI (Avibactam/ Astreonam)	Small molecule	Gram-negative	Phase 1
	MEDI3902	Large molecule	Gram-negative	Phase 1
Bayer	Ciprofloxacin DPI (dry powder for inhalation)	Small molecule	Gram-negative	Phase 3
	Amikacin Inhale	Small molecule	Gram-negative	Phase 3
	Tedizolid	Small molecule	Gram-positive	Phase 3
GSK	Streptococcus pneumoniae	Vaccine	Gram- positive	Phase 2
	GSK2140944	Small molecule	Gram-positive	Phase 2
GSK/Aeras	Tuberculosis	Vaccine	M. tuberculosis	Phase 2
Janssen	ExPEC	Vaccine	E. Coli	Phase 1
Merck & Co / MSD	Imipenem/MK-7655	Small molecule	Gram-negative	Phase 2
	MK-3415/MK-6072	Large molecule	C. difficile	Phase 3
	V114 – Pneumococcal Conjugate	Vaccine	Gram-positive	Phase 2
Novartis	Acellular pertussis booster	Vaccine	Gram-negative	Phase 1
	Acellular pertussis combos	Vaccine	Gram negative	Preclinical
	MenABCWY	Vaccine	Gram-negative	Phase 2
	Staphylococcus aureus	Vaccine	Gram-Positive	Phase 1
	Typhoid	Vaccine	Gram-negative	Phase 2
	Group B streptococcus (GBS) conjugate	Vaccine	Gram positive	Phase 2
Pfizer	PF-06425090	Vaccine	C. difficile	Phase 1
	PF-06290510	Vaccine	Staphylococcus aureus	Phase 2
Roche	RG7929	Large Molecule	Gram negative	Phase 2
	RG6080	Small Molecule	diazabicyclooctane beta-lactamase inhibitor (BLI)	Phase 1
Sanofi	ACAM-Cdiff	Vaccine	C.difficile	Phase 3
	Streptococcus pneumoniae	Vaccine	S. pneumoniae	Phase 1
	Tuberculosis recombinant subunit	Vaccine	M. tuberculosis	Phase 2
Otsuka	Delamanid	Small molecule	M. tuberculosis	Phase 3
	Delamanid (paediatric)	Small molecule	M. tuberculosis	Phase 2

ABOUT IFPMA

IFPMA represents the research-based pharmaceutical companies and associations across the globe. The research-based pharmaceutical industry's 2 million employees research, develop and provide medicines and vaccines that improve the life of patients worldwide. Based in Geneva, IFPMA has official relations with the United Nations and contributes industry expertise to help the global health community find solutions that improve global health.

ACKNOWLEDGEMENTS
The production of this publication is the fruit of the labor of many individuals.
The project was managed by Nina Grundmann and Mario Ottiglio.
Layout: Inart Design Works

International Federation
of Pharmaceutical
Manufacturers & Associations

Campus Biotech
Chemin des Mines 9
P.O. Box 195
1211 Geneva
Switzerland

Tel: +41 22 338 32 00
Fax: +41 22 338 32 99
Email: info@ifpma.org

www.ifpma.org

IFPMA

ISBN 978-2-940498-45-1