

Note

26



Antibiotic Resistance: Not Just a Problem of Patents

April 2017

EXECUTIVE SUMMARY

01 INTRODUCTION

02 HUMAN AND ECONOMIC COST

03 INEFFICIENT MARKETS

04 THE CHALLENGE OF CREATING THE RIGHT INCENTIVES

05 CONCLUSION

06 BIBLIOGRAPHY

This report was written by Elena Villanueva (Independent Consultant) and Gonzalo Fanjul (Policy Director, ISGlobal)

The authors gratefully acknowledge the comments and input received from Clara Ballesté, Jordi Vila and Oriana Ramirez.

Design by Mucho.



Obra publicada bajo la licencia de Creative Commons. Reconocimiento -No comercial- Sin obras derivadas 3.0

The inflexible and disproportionate rules governing intellectual property are clearly responsible for some of the obstacles that prevent millions of patients worldwide from accessing the medicines they need, whether because of the high prices imposed by patents or the way the system determines incentives for innovation. Nonetheless, the parameters of the problem extend far beyond the regulation of patents. The global model for innovation and access to medicines has numerous grey areas that are responsible for the fact that issues of immense importance to public health and the treatment of disease do not receive the resources and research effort they deserve.

One of the most alarming consequences of this flawed system is the failure to develop new antibiotics to combat multidrug-resistant bacteria. Paradoxically, these essential medicines, which are crucial to the efficacy of other therapies and the control of infectious diseases, offer only modest or unpredictable profits to the companies that make them. Several key factors greatly limit the interest of the private sector in producing antimicrobials, including the difficulty of predicting resistance, the size and characteristics of the population that would benefit from a drug effective against a resistant strain, and the short duration of a course of antibiotic treatment.

The problem of antimicrobial resistance calls attention to the pressing need to reform our outdated model of pharmaceutical innovation. Further evidence of its shortcomings can be found in the lack of drugs for neglected diseases and the exorbitant prices that put essential treatments out of the reach of the patients who need them. Our aim in this report is to review the current situation and propose some solutions.

01 Introduction

In 1928, Alexander Fleming discovered penicillin, the first antibiotic used to treat bacterial infections. His discovery marked a turning point in the treatment of infectious diseases such as pneumonia and tuberculosis, which until then had been the implacable enemies of public health worldwide. Since then, other antibiotics have been developed, and antimicrobials have become indispensable in the treatment of all kinds of infections and in preventing and treating infections in immunocompromised patients, including transplant recipients and patients receiving cancer chemotherapy.

However, antibiotic treatment favours the growth of bacteria that have acquired resistance to the agent used, which explains why the overuse and misuse of existing antibiotics has increased the prevalence of drug-resistant bacteria (especially pathogens). This resistance complicates treatment and can even render existing antimicrobial agents useless. Furthermore, owing to the lack of incentives, the poor return on investment and the scientific challenges involved in discovering new antibiotics, the pharmaceutical industry is doing very limited research in this area with the result that there have been almost no new discoveries in the last twenty-five years.

With no new antibiotics to provide alternatives to the ones that have been in use for decades, we are starting to lack the tools we need to deal with the resistant infections that often occur in the course of common procedures and treatments, such as caesarean sections, hip replacements and chemotherapy. The fact that resistant strains can emerge and become consolidated much more rapidly than we can create new drugs to combat them has set off alarms for governments and global health organizations alike.

02 **Human and Economic Cost**

Antimicrobial-resistant (AMR) pathogens have a high risk of prolonging and complicating the course of disease, and may eventually cause death. Length of stays in hospital are prolonged by drug-resistant infections, and these same infections are often acquired in hospitals. One European study estimated the number of additional hospital days attributable to infections with three resistant bacteria to be 4 million in 2012, increasing the financial burden on the affected health care systems by approximately €1.5 billion a year.¹ In the United States and Europe alone, over 50,000 people die every year as a result of resistant infections.² Even more alarming is the case of India, where almost 60,000 newborn babies die from infections resistant to treatment with existing antibiotics every year.³

The far reaching implications of this threat have started to capture the attention of those involved in the global public debate. Former British Prime Minister David Cameron launched an initiative in 2014 to seek solutions to the problem of antimicrobial resistance. In one of their first reports, the UK commission stated that—if resistance were to continue to increase at the current rate—the number of deaths caused by drug-resistant infections would be 10 million a year by 2050, a tenfold increase over current figures. This would be higher than the death rate attributable today to cancer and other diseases (see Figure 1), representing one death every three seconds. In the same time frame, the economic burden would rise to 100 billion dollars.⁴

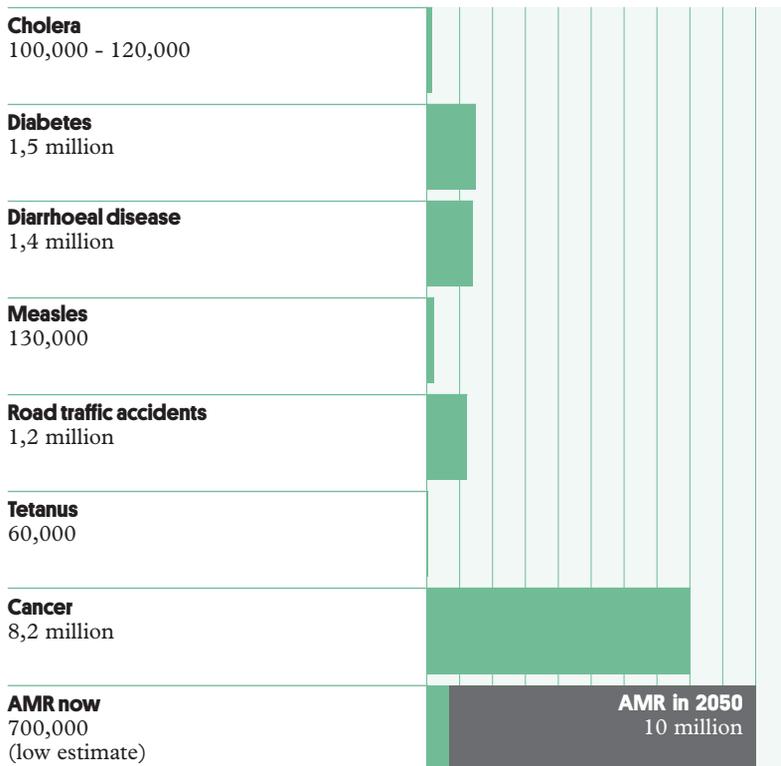
1 KPMG. The global economic impact of anti-microbial resistance. 11 November, 2014. <https://www.kpmg.com/UK/en/IssuesAndInsights/ArticlesPublications/Documents/PDF/Issues%20and%20Insights/amr-report-final.pdf>

2 The Review on Antimicrobial Resistance. Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations. December 2014; http://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf

3 Laxminarayan R, Duse A, Wattal C, Zaidi AKM, Wertheim HFL, Sumpradit N, et al. Antibiotic resistance—the need for global solutions, The Lancet Infectious Diseases Commission, 2013; 13: p.1057-98.

4 The Review on Antimicrobial Resistance. Tackling drug-resistant infections globally: Final report and recommendations. May 2016. http://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf

Figure 1
Deaths attributable to antimicrobial resistance in 2050 compared to the number caused by other diseases today



Source The Review of Antimicrobial Resistance. Tackling Drug Resistant Globally. March 2016. http://amr-review.org/sites/default/files/Tackling%20drug-resistant%20infections%20-%20An%20overview%20of%20our%20work_IncHealth_LR_NO%20CROPS.pdf

If this catastrophe is to be averted, our public institutions must take urgent action to encourage and support the better use of antimicrobials. That means ensuring greater adherence to the full course of treatment when antibiotic treatment is indicated and preventing overuse. That is, the prescription of antimicrobials when they are not indicated—to a patient with a viral infection, for example.

At the same time, it is also essential to develop new antibiotics to compensate for the limitations of those currently on the market. In the last 30 years, only two compounds from new classes of antibacterial drugs have been approved (linezolid and daptomycin). All the other antibiotics on the market today were developed earlier (see Figure 2). Without looking any further, this situation highlights a failure of market forces that could lead to a serious public health problem.

Figure 2
Discovery of new classes of antibiotics throughout the 20th century

1930s	Sulfonamides
1940s	Aminoglycosides Beta-lactams*
1950s	Chloramphenicol Tetracyclines Macrolides Glycopeptides
1960s	Streptogramins Quinolones Lincosamides
1970s	Trimethoprim
1980s	
1990s	
2000s	Cyclic lipopeptides Oxazolidinones

Source World Health Organization. The evolving threat of antimicrobial resistance: Options for action. 2012.

03 Inefficient Markets

The market for antibiotics, unlike those of other drugs, has certain characteristics that make it an unattractive option for private sector investment. First, predicting when and where resistance will develop is difficult and in the absence of such resistance older products can be just as effective as new ones that have just entered the market. As a result, physicians have no objective motive for prescribing the newer drug. The market for a new antibiotic is generally limited to the subgroup of patients with resistant infections because clinicians will try to reserve novel agents for the treatment of cases for which there is no other option. As a result, the financial return from a new antibiotic is not immediate, and this greatly reduces its market potential.

Duration of treatment is another factor limiting the return on investment in these drugs. A course of antibiotics, which lasts between one and two weeks, is very short compared to that of drugs used to treat chronic or semichronic conditions, such as diabetes, hypertension and high cholesterol. Total annual sales worldwide of all types of antibiotics is US\$40 billion.

While undoubtedly a considerable amount of money, this sum is only equivalent to the annual sales of just one of the more successful anticancer drugs.⁵ Financial reward is a crucial factor in determining corporate research priorities, and pharmaceutical companies prefer to invest in the development of drugs that will return a profit while the product is still in patent, irrespective of their therapeutic value.⁶

In 2004, only 1.5% of all the drugs in development by the world's 15 largest pharmaceutical companies were antibiotics.⁷ Today, despite the urgent need for new antimicrobials, fewer than 5 of the 50 major pharmaceutical companies have an antibiotic in development.⁸ In 2014, some 800 cancer medicines were in clinical testing, of which about 80% are expected to be successful, but there were only 50 new antibiotics in the pipeline.⁹

5 The Review on Antimicrobial Resistance. Tackling Drug-resistant Infections Globally: Final report and recommendations. May 2016

6 The Review on Antimicrobial Resistance. Securing new drugs for future generations: The pipeline of antibiotics. May 2015. http://amr-review.org/sites/default/files/SECURING%20NEW%20DRUGS%20FOR%20FUTURE%20GENERATIONS%20FINAL%20WEB_0.pdf

7 Smith, RD; Coast, J. The economic burden of antimicrobial resistance: Why it is more serious than current studies suggest. Technical Report. London School of Hygiene & Tropical Medicine. 2012. London.

8 MSF Access Campaign. Lives on the Edges Time to Align Medical Research and Development with People's Health Needs. Medecins Sans Frontieres. May 2016. http://www.msfaccess.org/sites/default/files/MSF_assets/Innovation/Docs/R&D_report_LivesOnTheEdge_ENG_2016.pdf

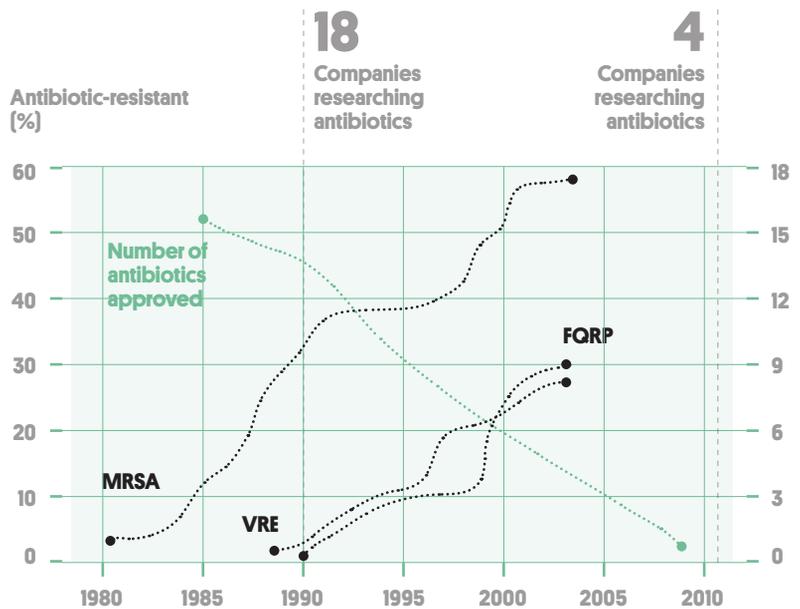
9 Pharma, Medicines in Development in 2014: Cancer, Pharma 2014 <http://www.phrma.org/sites/default/files/pdf/2014-cancer-report.pdf>

04 The Challenge of Creating the Right Incentives

Figure 3
**Antimicrobial
Resistance – A Crisis
in Waiting**

MRSA Methicillin-resistant
Staphylococcus aureus
VRE Vancomycin - resistant
enterococci
FQRP Fluoroquinolone-Resistant
Pseudomonas Aeruginosa

Source Report of the United
Nations Secretary-General's High
Level Panel on Access to Medicines.



Given the situation described above, it is unlikely that market forces alone can provide a solution to the problem of antimicrobial resistance. The vicious circle of low profitability and meagre incentives for innovation can only be broken by an ambitious and urgent public intervention.

At least that is the opinion of several international bodies and governments, which are beginning to react to the problem. At its General Assembly in 2015, the World Health Organization (WHO) approved a global action plan on multidrug-resistant bacteria, which recognizes the urgent need to develop new products. The plan states that the private sector (primarily the major pharmaceutical companies) “is no longer doing any research in the area”. It goes on to emphasise the need to invest in the development of new antibiotic agents and calls on member countries to develop national plans to ensure, among other things, R&D funding that prioritises basic research and promotes agreements between research centres in developed and developing countries.¹⁰

In other words, the WHO action plan calls for the same thing as the Expert Commission convened by David Cameron: public intervention to ensure sufficient investment in R&D related to antibiotics. The UK commission proposed the creation

¹⁰ WHO. Global Action Plan on Antimicrobial Resistance. 27 March 2015 http://apps.who.int/gb/ebwha/pdf_files/WHA68/A68_20-en.pdf?ua=1

¹¹ The Review on Antimicrobial Resistance. Securing new drugs for future generations: The pipeline of antibiotics .

¹² See link to the priorities set at the G7 summit in June 2015. https://www.g7germany.de/Webs/G7/EN/G7-Gipfel_en/Agenda_en/agenda_node.html

of a global innovation fund to support antimicrobial research, with an initial budget of 2 billion dollars to assure the necessary resources.¹¹ They propose that the pharmaceutical industry should contribute to this fund since it is clearly in their interest that society should have new antibiotics so that infections will not compromise the effectiveness of more profitable treatments, such as cancer therapies.

Germany has made AMR a priority in its public health agenda, highlighting the seriousness of the problem and the urgent need for an approach that treats antimicrobial resistance as a supra-national problem requiring global solutions.¹² To further this approach, the German government persuaded the world's seven largest economies (G7) to commit to implementing the WHO's Global Action Plan and to incorporate it into the G20 meeting agenda that will take place this year in Germany.

One of the most encouraging messages we can take from this joint initiative is that both the new Global Action Plan on Antimicrobial Resistance and the report of the British Commission agree, as do other actors (for example, Doctors Without Borders), on the need to delink the cost of research from the final price of medicines.¹³ Even the High Level Panel convened to advise the Secretary General of the United Nations on improving access to medicines, which published its recommendations in June 2016, agrees that the idea that new antibiotics can or will be developed on the basis of a free market model is unrealistic and that research models that separate the cost of research from the final price must be explored.¹⁴ In a new report published ends of 2016, the OECD recognizes the health and economic threat posed by the lack of new antibiotics and the need to explore new alternatives to accelerate their development.¹⁵

This position, which differs from the stance of the same G7 governments regarding the development of other essential drugs, opens the door to creative business models that can more effectively meet the needs of research than those used to date. Eighty-five pharmaceutical companies have signed a declaration presented at the 2016 World Economic Forum, which recognises, for the first time, the need to explore new models, although without directly endorsing the delinkage of final price from R&D costs. While this is not enough, it is undoubtedly a first step in the right direction.¹⁶

13 WHO. Global Action Plan on Antimicrobial Resistance. 27 March 2015.

14 Report of the United Nations Secretary-General's High-Level Panel on Access to Medicines. Promoting innovation and access to health technologies. June 2016, <https://static1.squarespace.com/static/562094dee4b0d00c1a3ef761/t/57d9c6ebf5e231b2f02cd3d4/1473890031320/UNSG+HLP+Report+FINAL+12+Sept+2016.pdf>

15 Antimicrobial resistance. Policy Insights. OECD, Noviembre 2016. <http://www.oecd.org/health/health-systems/AMR-Policy-Insights-November2016.pdf>

16 Declaration by the Pharmaceutical, Biotechnology and Diagnostics Industries on Combating Antimicrobial Resistance. January 2016. http://amr-review.org/sites/default/files/Industry_Declaration_on_Combating_Antimicrobial_Resistance_UPDATED%20SIGNATORIES_MAY_2016.pdf

05 Conclusion

The challenge of AMR exposes the limitations of the current global model of innovation and access to medicines. The problem will only get worse in the coming years unless there is a decisive public intervention to compensate for the lack of incentives to drive private sector innovation in this field.

Over the last decade, the idea of a biomedical fund or a binding R&D agreement that would ensure public funding for antimicrobial research has been debated under the umbrella of the WHO. This agreement could include a model for the development of antibiotics that would delink the cost of R&D from the price of the final product.¹⁷ This is the direction being taken by the Global Antibiotic Research and Development (GARD) Partnership, a recently launched joint initiative of the WHO and the Drugs for Neglected Diseases initiative (DNDi).¹⁸

In the meantime, the Global Action Plan on Antimicrobial Resistance endorsed by the World Health Assembly together with the interest of the members of the G7 and the G20 should accelerate progress towards an agreement on biomedical R&D with funding to guarantee its sustainability coming from both governments and pharmaceutical companies.

At ISGlobal, we believe that it makes no sense to deal with the case of antibiotics as a separate issue since they are not the only drugs affected by the failure of the market-driven model. In our opinion, there are other drugs, vaccines and diagnostic tools that are similarly affected, for example, the treatments and vaccines for Ebola and other neglected diseases.

What the case of antibiotics does clearly demonstrate is that the rules governing intellectual property are only part of the problem and that the market can fail patients for other reasons. Whatever the reason for the failure, financial intervention and regulatory support by the public sector are preconditions for any sustainable solution.

We can—and should—take advantage of the current political conjuncture now that the validity of the prevailing model for biomedical R&D is, for the first time, being called into question by many different actors. International organisations such as the United Nations, the European Union, the WHO and the Organisation for Economic Co-operation and Development (OECD) have already openly acknowledged the failure of the market in

¹⁷ WHO. Follow-up of the report of the Consultative Expert Working Group on Research and Development. <http://www.who.int/phi/documents/CEWG-WP/en/>

¹⁸ WHO and DNDi. Investing in the development of new antibiotics and their conservation: A proposal for a Global Antibiotic Research and Development Facility to promote research, responsible use, and access to new antibiotics. December 2015. http://www.dndi.org/wp-content/uploads/2016/03/Global_Antibiotic_RD_Facility_Concept_Note.pdf

biomedical R&D. Those institutions are currently consulting diverse stakeholders to draw up a list of possible improvements that could ensure the sustainability of health systems while giving patients access to essential drugs.

06 Bibliography

- 1** Declaration by the Pharmaceutical, Biotechnology and Diagnostics Industries on Combating Antimicrobial Resistance. Enero 2016.
- 2** KPMG. The Global Economic Impact of Anti-microbial Resistance. Noviembre 11, 2014.
- 3** Laxminarayan R, Duse A, Wattal C, Zaidi AKM, Wertheim HFL, Sumpradit N, et al. Antibiotic resistance – the need for global solutions, *The Lancet Infectious Diseases* 2013; 13: p.1057-98.
- 4** MSF Access Campaign. Lives on the Edges Time to Align Medical Research and Development with People’s Health Needs. *Medicins Sans Frontieres*. May 2016.
- 5** Organización Mundial de la Salud. Follow-up of the report of the Consultative Expert Working Group on Research and Development.
- 6** Organización Mundial de la Salud. Plan de Acción Global contra la resistencia Antimicrobiana. 27 de Marzo del 2015.
- 7** Organización Mundial de la Salud. The evolving threat of antimicrobial resistance: options for action. *Options for action*. 2012.
- 8** OMS y DNDI. Investing in the development of New Antibiotics and their conservation: a proposal for a Global Antibiotic Research and Development Facility to promote Research Responsible Use and Access to New Antibiotics. Diciembre 2015.
- 9** Pharma, *Medicines in Development in 2014: Cancer*, Pharma 2014.
- 10** Smith, RD; Coast, J. The economic burden of antimicrobial resistance: Why it is more serious than current studies suggest. *Technical Report*. London School of Hygiene Tropical Medicine. 2012. London.
- 11** The Review of Antimicrobial Resistance. Securing new drugs for future generations: the pipeline of antibiotics. May 2015.
- 12** The Review of Antimicrobial Resistance. *Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations*. Diciembre 2014.
- 13** The Review of Antimicrobial Resistance. *Tackling Drug Resistant Globally*. March 2016.
- 14** The Review on Antimicrobial Resistance. *Tackling Drug-Resistant Infections Globally: final report and recommendations*. May 2016.

ISGlobal Barcelona
Institute for
Global Health

A partnership of:



"la Caixa" Foundation

