

## The dual crises of antibiotic resistance and the failing antibiotic pipeline

# Avoiding the doomsday predictions

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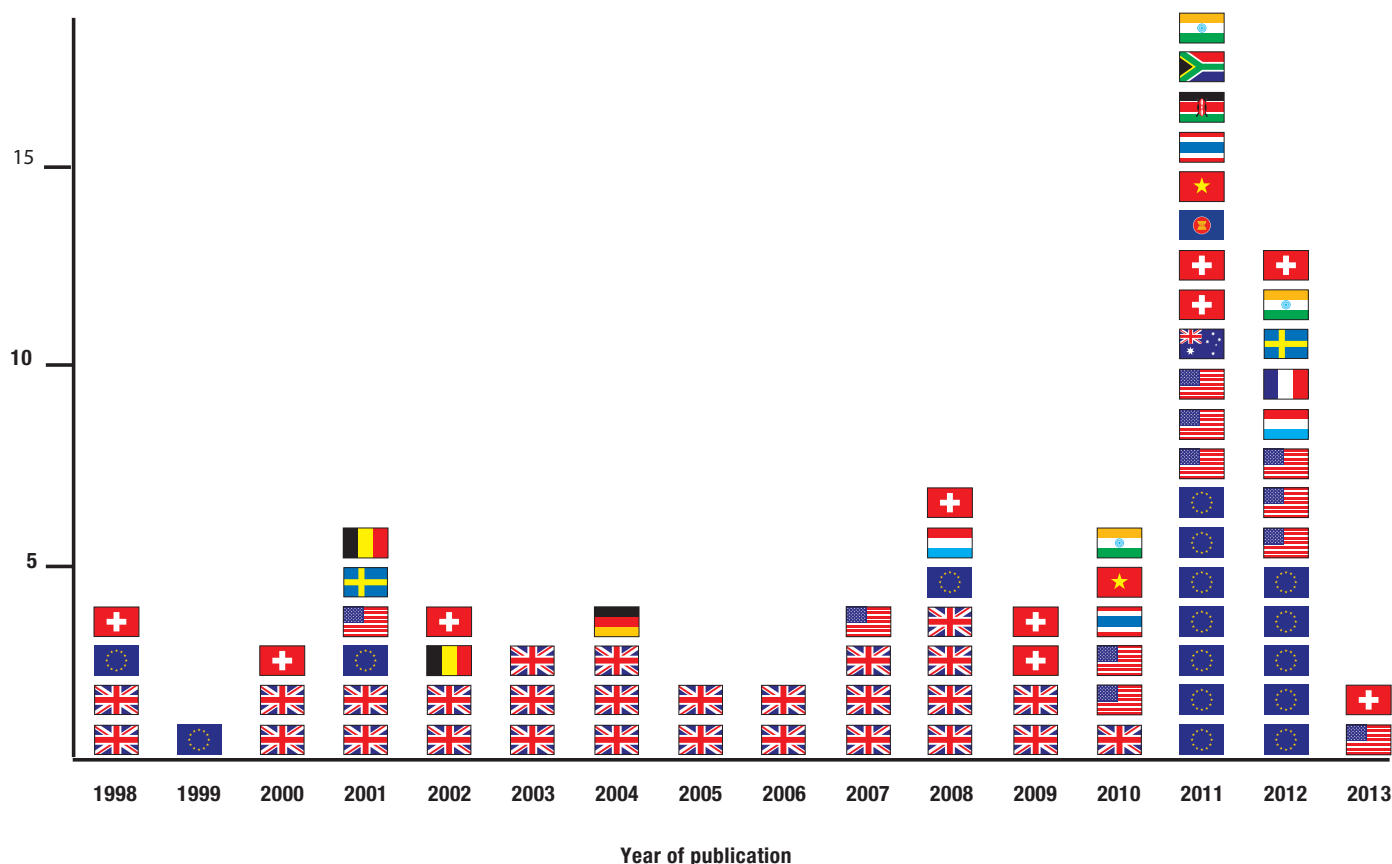
The introduction of antibiotics in the 1940s led to a revolution in healthcare, saving millions of lives around the world and facilitated modern day care of cancer patients, organ transplants and commonplace orthopaedic surgery such as knee and hip replacements. Although public expectations for improved healthcare remain high, there are global concerns over the urgent need to secure the long-term availability of effective treatments for bacterial infections. There is a perfect storm on the horizon, fed by the exorable rise in the numbers of antibiotic-resistant bacteria, the continuing emergence of new types of resistance is particularly in Gram-negative bacteria including *Escherichia coli* and *Klebsiella pneumoniae*, and a market failure in antibiotic development. The number of pharmaceutical companies producing new antibiotics has declined dramatically, with the new drugs that have reached the patient being predominantly those active against Gram-positive bacteria such as MRSA. The combination of antibiotic resistance and the near empty antibiotic pipeline poses a crisis to human health globally as critical as the AIDS pandemic in the 1980s and 1990s.

Concern about antibiotic resistance is not new. Between 1998 and 2008 over 20 enquiries, reports and recommendations were published from the UK alone, with at least another 70 reports published across the globe between 2008 and mid-2013 (Figure 1). Until recently, and despite these sustained attempts, there was little evidence of progress or political impetus necessary to bring about change. It is difficult to imagine how loud the outcry might be if there were only two new cancer treatments in the pipeline globally, yet this is the potential size of the antibiotic arsenal available to defeat a growing number of multidrug-resistant bacterial infections.

The combined problems of antibiotic resistance and the diminishing antibiotic pipeline are complex and the solutions are myriad. Solving these problems at a global level requires partnerships between governments and various departments from health, to business, to overseas aid. The first challenge is to gain a better

understanding of antibiotic resistance. The World Economic Forum's decision in January 2013 to place antibiotic resistance on the global risk register was based on a handful of studies that are considered by many to represent an underestimate of the true burden. We need to fully understand how resistance occurs, how it is spread and the magnitude of the true cost to society if those engaged in antibacterial discovery, research and development are to find and produce new treatments. Academia and small and medium-sized enterprises (SMEs) have much to offer in increasing understanding of antibiotic resistance and discovering new molecules and ways to combat bacterial infection. A dedicated funding mechanism for research will not only further the scientific base for understanding the biology of antibiotic resistance and facilitate drug development, but will also stimulate economic development.

A next step will be to examine and redefine the regulatory and financial models that govern the development and marketing of antibacterial agents. Simply put, there has been a market failure. Companies are faced with the high costs of development, uncertainties over regulatory success and obtaining a product licence, expectations that antibiotics are low-cost treatments and uncertainties over duration of efficacy before their drugs become ineffective due to resistance. The risks are just too high for some. Discussions held at the European Medicines Agency and the USA Food and Drugs Administration will hopefully bring about changes in the clinical trial paradigm. An ideal outcome would be new and clear guidelines that mean requisite studies to obtain a licence are feasible and not subject to change during the research and development process, thus helping incentivize companies return to this product area. It is also imperative that the chances of successful antibiotic development are maximized by learning lessons from the past successes and failures, and by drawing on the experience of those in 'big Pharma' who have a track record in antibiotic discovery, research and development. The antibiotic void seen since the 1980s



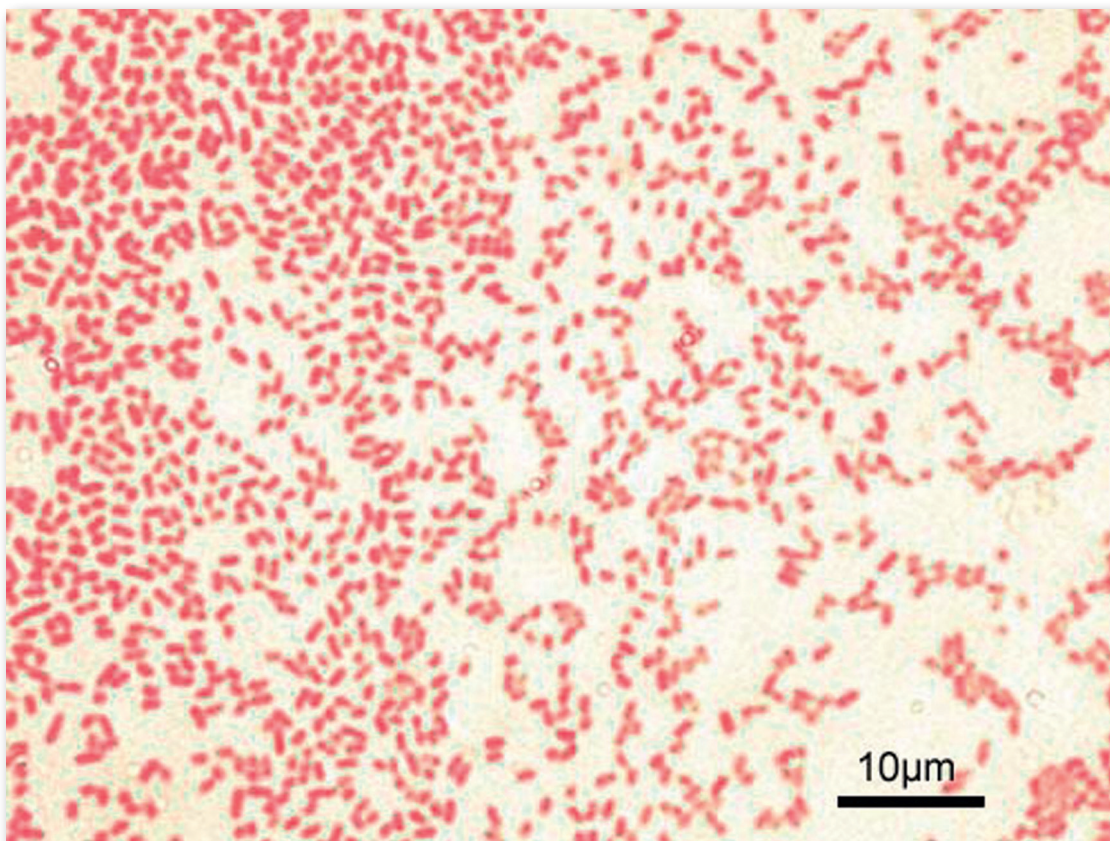
**Figure 1.** Number of reports on antibiotic resistance and lack of new drugs to mid-2013

means many of those most experienced in the field have retired and we risk, but cannot afford, losing the legacy they can offer.

It is important that all from the general public to healthcare professionals to politicians and policy makers have a clear understanding of the importance of ensuring antibiotics are used appropriately, and with the respect of which they so deserve. Antibiotics are used widely in many settings and so discouraging use other than to treat infection is essential. This includes curtailment of use where there is no bacterial infection and restricting the purchase of antibiotics by the general public, which is widespread in some countries. Royal Colleges and likewise bodies internationally must work to ensure training in prescribing of antimicrobial agents is included in national curricula of all who may prescribe. The key to appropriate use is reducing public expectation to receive an antibiotic through education and supporting interventions, such as ‘Start Smart Then Focus’<sup>1</sup> that enable UK healthcare professionals to make appropriate and informed prescribing choices.

Professional societies such as the British Society for Antimicrobial Chemotherapy (BSAC) have contributed their expertise in national and international fora. To

exemplify BSAC’s contributions, 2011 saw publication of the report of a BSAC working party ‘The Urgent Need (TUN): regenerating antibacterial drug discovery development’<sup>2</sup> that examined research<sup>3</sup>, regulatory<sup>4</sup> and economic<sup>5</sup> barriers to effective antibiotic discovery and development. The action plan of TUN is being carried forward by Antibiotic Action<sup>6</sup>, the UK-led global initiative to educate all of the need for effective treatments for bacterial infections available for all who need them, and which was established in November 2011. Antibiotic Action has engaged widely and been quoted more than 7000 times in the lay and specialist print, broadcast and electronic media. Amongst its many activities, Antibiotic Action organized the ‘Lessons to be learnt’ interactive 1-day symposium held in May 2013 and supported by the BSAC, the Biotechnology and Biological Sciences Research Council (BBSRC), the Medical Research Council (MRC) and the Wellcome Trust. The interdisciplinary workshop brought together key individuals from academia, the biotech and pharmaceutical sectors, and clinical practice to discuss why antibiotic development has stalled and what can be done to restart it. The free report of the meeting<sup>7</sup> and podcasts<sup>8</sup>



**Figure 2.** Microscopic image of *Pseudomonas aeruginosa* (ATCC 27853)

adds helpful insight to the complexity of the problems faced and the innovation needed to reinvigorate the antibiotic pipeline. The BSAC is one of many like-minded societies and organizations [e.g. Action on Antibiotic Resistance (ReAct), Infectious Disease Society of America (IDSA), Alliance for the Prudent Use of Antibiotics (APUA), World Alliance Against Antibiotic Resistance (WAAAR) and Global Antibiotic Resistance Partnership (GARP)] and Antibiotic Action works closely with these and others to provide a network of initiatives working collaboratively across the globe, each calling for and supporting the professional and political action necessary to effect change.

So what hope is there for the future? The signs are hopeful with indications that the landscape is at last changing. We hope that professional interest and heightened political awareness will accelerate the pace of change both nationally and internationally. In 2009, at the annual summit between the EU and US presidencies, by Presidential declaration the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) was established; the first report was published in September 2012<sup>9</sup> and identified urgent antimicrobial resistance issues that could be better addressed by intensified cooperation between the USA and the EU. That month,

the USA Food and Drug Administration announced the formation of a task force to support development of the Antibacterial Drug Development Task Force (ADDTF), which will assist in developing and revising guidance related to antibacterial drug development, as required by the Generating Antibiotic Incentives Now (GAIN) and Food and Drug Administration Safety and Innovation Act (FDASIA), that was signed into law on 9 July 2012. The European Medicines Agency has also been reviewing the requirements for clinical trials of antibacterial treatments. Further afield, colleagues in India published the Chennai Declaration<sup>10</sup>, a roadmap to tackle the challenge of antimicrobial resistance, and the WAAAR published the Paris Declaration calling for moves to safeguard antibiotics. The latter was supported by 600 stakeholders from 50 countries.

The UK has taken a global leadership role in tackling the issue of antibiotic resistance in addition to Antibiotic Action, Dame Sally Davies, the UK Chief Medical Officer (CMO) has done much during 2013 to promote the need to address the issue, through her annual report, presentations to the G8 Summit and addressing the UK All Party Parliamentary Group (APPG) on Science and Technology meeting in June 2013, where she outlined the size of the problem and

the societal and financial costs to UK citizens and 'UK plc'. Publication of the UK Government's 5-year Strategy on Antimicrobial Resistance in September 2013 was also led by the CMO, who will remain instrumental in pushing forward implementation of its recommendations via the four UK administrations and in collaboration with healthcare professionals, researchers, scientists and their professional societies.

Further significant support in the UK for addressing the issue long term is the establishment of the APPG on Antibiotics, for which the secretariat is BSAC. The group held its inaugural meeting on 12 June, chaired by the Shadow Health Minister, Jamie Reed MP. Kevin Barron MP is Deputy Chair, Zac Goldsmith MP is Treasurer and Baroness Masham is secretary; all high profile parliamentarians working to ensure the APPG provides a vibrant forum in which cross-party members can hear evidence, contribute to debate and identify solutions that the UK can offer to the Grand

Challenge of antibiotic resistance and will further support delivery of the UK 5-Year Antimicrobial Resistance Strategy 2013–2018.

The road ahead is long, but peppered with opportunity if we are bold enough to invest in ideas and innovation. Governments and funders must put their money where the problem is, regulators must protect public health while offering innovative frameworks and reimbursement models for antibacterial treatments, which must be redefined. Most importantly, there needs to be a global acknowledgment by all stakeholders, politicians, scientists, funders, healthcare professionals and the general public, of the crossroad at which we stand. Inaction is not an option if we are to preserve the health of nations. If we are to address the problem of antibiotic resistance the solutions are something in which all, corporate, political and individual, must play their part. ■

#### Societies and organizations referred to in this article

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Action on Antibiotic Resistance	<a href="http://www.reactgroup.org/">http://www.reactgroup.org/</a>
Infectious Diseases Society of America	<a href="http://www.idsociety.org/topic_antimicrobial_resistance/">http://www.idsociety.org/topic_antimicrobial_resistance/</a>
Alliance for the Prudent Use of Antibiotics	<a href="http://www.tufts.edu/med/apua/">http://www.tufts.edu/med/apua/</a>
World Alliance against Antibiotic Resistance	<a href="http://www.waaar.org/">http://www.waaar.org/</a>
Global Antibiotic Resistance Partnership	<a href="http://www.cddep.org/projects/global_antibiotic_resistance_partnership">http://www.cddep.org/projects/global_antibiotic_resistance_partnership</a>
Transatlantic Taskforce on Antimicrobial Resistance	<a href="http://ecdc.europa.eu/en/activities/diseaseprogrammes/tatfar/">http://ecdc.europa.eu/en/activities/diseaseprogrammes/tatfar/</a>

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