

IN THE ABSENCE OF ALTERNATIVES – addressing the dual challenges of antimicrobial resistance and the failing antibiotic pipeline



Tracey Guise
CEO, British Society for
Antimicrobial Chemotherapy

Few of us alive today in high income countries can remember living without the unprecedented health benefits that antibiotics bring. In 1928, Sir Alexander Fleming's discovery of the antibacterial powers of *Penicillium* mould changed the face of human medicine. Within a few decades healthcare progressed more in the presence of these "wonder drugs" than in the two millennia prior to their discovery.

Antibiotics are now the mainstay of human health. They are lifesaving, life enhancing and life extending. Without them medicine as most of us know it would not exist. As consumers we have high expectations for

depleted antibiotic discovery and development pipeline. It poses a crisis to human health as critical as the AIDS pandemic in the 1980s and 1990s. It is not a pending crisis – it is already here.

developed. Coupled with the requirement to work within an increasingly complex, and in turn expensive, regulatory environment the development of antibiotics became a high-risk activity with diminished returns to shareholders. The effect has been tragic. The number of companies has diminished mainly due to mergers. Those producing new antibiotics have declined dramatically, and consequently so has the number of new antibiotics reaching the market. Only two systemic antibacterial agents were approved for use in humans from 2008-2012 compared to sixteen from 1983-1987. Those that have reached the patient have been

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our health and wellbeing, including treatment of infections allowing survival to adulthood and old age. They provide life extending treatments for those with chronic conditions such as cystic fibrosis, cancer chemotherapy regimens, organ transplant and joint replacement surgeries. In high income countries people expect to receive these treatments when required, and without exception, and this is an aspiration for everyone across the globe. Without effective antibiotics a simple scratch can prove fatal. It was therefore unthinkable that antibiotics would become ineffective, and yet this is the unprecedented health crisis we face. It is the dual crisis of antibiotic resistance and a

Physicians and scientists have been warning of the relentless rise in the numbers of antibiotic resistant bacteria for over 25 years. Between 1998 and mid-2013 over 90 enquiries, reports and recommendations, including some by the World Health Organisation, were published. These were laudably received, but political will to act has been

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lacking, and the public has remained largely unaware of the problem. However, one sector was listening, taking note and taking action. The pharmaceutical industry was acutely aware that antimicrobial resistance seriously reduced the life-span of the antibiotics they

predominantly active against Gram-positive bacteria such as MRSA, and this trend continues today. This is of critical concern when faced with the continued emergence of new types of resistance in Gram-negative bacteria including *Escherichia coli* and *Klebsiella pneumoniae*,



Laura JV Pidcock
Director, Antibiotic Action and
Professor of Microbiology, University
of Birmingham

for which there are few – and sometimes no – effective treatments. In April 2014 The World Health Organisation published its first report on antimicrobial resistance, indicating how widespread the problem is.

Until recently there was little evidence of progress or the necessary political impetus to bring about change. It is difficult to imagine how loud the outcry might be if there were so few new cancer treatments, yet the size of the antibiotic arsenal available to defeat a growing number of multidrug-resistant bacterial infections is small. Learned societies and

... magnitude of the burden of antibiotic resistance ...

organisations have worked tirelessly to influence those in the research, political, economic and public arenas through education and continued pressure for action. The Alliance for Prudent Antibiotic Use, CDDEP and the Pew Trust in the US, ReAct and Antibiotic Action in Europe are a few of the influential organisations providing resource. All are aware of the task ahead but hope that their messages are being heard.

There are signs that the landscape is at last changing with professional interest and campaign action helping accelerate change. The Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) was established by US Presidential declaration in 2009 and issued its first report in September 2012, identifying the need for intensified cooperation between the USA and the EU. The same month saw the USA Food and Drug Administration announce the formation of a task force to support

development of the Antibacterial Drug Development Task Force (ADDTF). This will assist in 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). The European Medicines Agency has been reviewing the requirements for clinical trials of antibacterial treatments. The World Economic Forum Global Risks Report 2013 and 2014 recognised the magnitude of the burden of antibiotic resistance by its inclusion on the risks register. In India publication of the Chennai Declaration led to

changes in Indian law aimed at ending the sale of over the counter antibiotics. The EU Innovative Medicines Initiative will soon announce the award of a multi-million grant 'Driving re-investment in R&D and responsible use of antibiotics'.

Recent political focus and activity has been especially high in the United Kingdom. The All Party Parliamentary Group on Antibiotics, chaired by Jamie Reed MP, Shadow Minister for Health, was established in June 2013 to ensure antibiotics remain high on the political agenda. 2013 saw publication of the UK Government's 5-year strategy on antimicrobial resistance. July 2014 was a landmark month: the House of Commons Science and Technology Select Committee reported on the findings of its inquiry into antimicrobial resistance; antibiotics won public support, and was voted the winning topic of the £10 million Longitude Prize; on 7 July the Prime Minister declared the

need for urgent action and announced the launch of a Commission on Antibiotic Resistance.

Interest is now high across international medical, scientific and political arenas. The next steps must be to go beyond public statements and reports

... Governments must respond ...

and take action. Governments must respond as they have to other public health crises such as Alzheimer's and obesity, and identify properly funded mechanisms that will further the scientific base for understanding the biology, clinical and societal impact of antibiotic resistance. Academic and small and medium-sized enterprises (SMEs) need to be enabled to work together and with Pharma to capitalise on their abilities, and accelerate discovery of new ways to prevent and treat bacterial infections. Regulators and economists must work together across international boundaries to examine and safely redefine the regulatory and financial models that govern the development and marketing of antibacterial agents to facilitate a return to this market.

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Lastly, it is imperative that all stakeholders – professional, political, public, industrial – have a clear understanding of the importance of ensuring antibiotics are used appropriately, and with the respect they deserve. Antibiotics are used in many settings. Discouraging use other than to treat infection is essential. Education on appropriate use will include instruction on curtailment of use where there is no bacterial infection and

restricting the purchase of antibiotics by the general public. This is widespread in some countries. Learned societies must work to ensure that prescribing of antimicrobial agents is included in the training and education of all who may prescribe these drugs. To assist

in this process the British Society for Antimicrobial Chemotherapy is working with colleagues to develop a Massive Open Online Course (MOOC) on Antimicrobial Stewardship.

The road ahead is challenging, but there are opportunities aplenty. Henry Kissinger said *"the absence of alternatives clears the mind marvellously"*. We must now be bold enough to invest in the infrastructure and innovation needed to protect and replenish the antibiotic 'treasure trove'. Governments and funders must put their money where the problem is. Regulators must protect public health while offering innovative frameworks. Reimbursement models for antibacterial treatments must be redefined. Most importantly,

there needs to be an acknowledgment by all stakeholders, politicians, scientists, funders, healthcare professionals and the general public, of the crossroad at which we stand.

Note: Extracts from this article were published online by CNN News in August 2014.