

AVOIDING THE PERFECT STORM: MEETING THE NEED FOR NEW ANTIBIOTICS



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THE IMPENDING CRISIS

Global concerns are growing within medical and academic circles over the urgent need to secure the long-term availability of effective antibiotic treatments. Modern healthcare is facing a perfect storm. The inexorable rise in antibiotic resistance, the continuing emergence of multidrug-resistant infections and a market failure of antibiotic development leading to a near depletion of the antibiotic pipeline could have devastating effects on global health. The magnitude of the crisis we face becomes apparent when we note that sixteen new antibacterial agents were approved and brought to market between 1983-1987, compared with an estimated two to four agents between 2008-2012¹. It is by no means clear if even these can, or will, address the clinical issues we currently face.



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Over the past 80 years human health has enjoyed the unprecedented benefits brought about by the discovery, development and widespread use of antibiotics. There are few people alive today in the developed world who can remember what it was like to live in a world without them. We have high expectations – survival to adulthood is expected, treatment of common and less common infections is expected, as is a productive work force and an ability to live into old age. Antibiotics play a defining and key role in ensuring these expectations are met.

Twenty-first century medicine delivers increasingly complex treatments and health benefits to many, from improved quality of life and increased life expectancy for cystic fibrosis sufferers, to joint replacements, life-saving transplants and chemotherapy treatments. Whilst such advances are to be applauded, governments, health

professionals and society must acknowledge that they are only possible in the presence of effective antibiotic treatments. The dearth of new antibiotics reaching the marketplace potentially threatens not only the management of the much reported “superbugs” such as MRSA, but also many routine treatments and procedures across all branches of medicine. A return to a pre-antibiotic era is an all-too-real possibility and living with the spectre of untreatable infections could be a reality within our lifetimes.

ACTION TO DATE – PAST AND PRESENT

In 2009 the World Health Organisation² declared antibiotic resistance as one of the three greatest threats to human health, acknowledging the gravity of the situation through World Health Day in April 2011 – ‘Antimicrobial Resistance: No Action Today and No Cure Tomorrow’³. There have been

many attempts to bring the grave concerns about the lack of new antibiotics to the attention of government agencies, healthcare professionals and the public. Between 1998 and 2008 over twenty enquiries, reports and recommendations were published from within the UK alone (www.antibiotic-action.com/resources). Despite these sustained attempts there is little evidence of progress and efforts have failed to generate interest adequate to stimulate action or bring about change. It is difficult to imagine similar lethargy were it publicly reported that only two new cancer agents were under consideration, or there were only three new cardiology drugs in the pipeline. One would expect a rightful outcry from cancer and heart patients and their representative groups, and it is difficult to envisage there not being one.

The past two years have seen a gathering of pace within Europe and the US. Both the

European Union⁴, through ReAct, and the Infectious Diseases Society of America (IDSA)⁵ established initiatives to raise awareness of the problems of resistance and the need to replenish the antibiotic pipeline. The IDSA also lobbied the US Government in an attempt to gain its urgent attention and re-stimulate drug development⁶ and ReAct arranged an event in March 2010 at the European Parliament which raised the issue and discussed potential solutions, and followed in May with a seminar on this topic in Brussels. In July 2009 the British Society for Antimicrobial Chemotherapy (BSAC) established an initiative called 'The Urgent Need to Regenerate Antibacterial Drug Discovery and Development' (TUN), which included advisors from the American Society for Microbiology (ASM), IDSA and ReAct. Taking a different route from the norm, the working party chose to steer clear of rehearsing the known evidence or arguments for containing resistance; instead a decision was made to develop a framework for action (www.bsac.org.uk/News/TUN) that would identify opportunities for collaboration and action.

In developing its framework for action, TUN explored the status of research from basic through to translational, ie from small molecule inhibitors of potential new or novel targets through to isolation or synthesis of such inhibitors to drugs, and made proposals to maintain a pipeline of novel inhibitors for development as drugs⁷. Secondly, the initiative explored the regulation of antibiotics; the problems specific to antibiotic drug development and how these could be overcome; being always mindful that regulation exists to safeguard public health and accepting that this premise

cannot be compromised⁸. The working party questioned whether there were lessons from the past, such as the accelerated approval processes that brought antiviral therapies for the treatment of HIV/AIDS so speedily to market, that could be trialled and adopted for antibiotic agents. Lastly, the group explored the economics of antimicrobial drugs⁹. This topic provoked the most controversy, and may ultimately prove the most challenging to resolve. There are pre-existing tensions that need to be addressed – the widespread introduction of antimicrobial stewardship programmes is contributing to attempts to contain resistance and improve appropriate use. It is important to ensure that such stewardship is itself used appropriately and not perceived to be, or indeed used as, a budgetary lever. Raising the value of life-saving antibiotics to match that of other life-saving treatments is a challenge most aptly addressed in a recent article¹⁰ by Professor Richard Wise, who chaired TUN. Proposals to overcome this hurdle included different guidelines for both regulation and licensing antibiotics (due to the very different properties of these drugs), licensing new drugs via the 'orphan drug route', and public-private partnerships where both development costs and profits are shared.

Combined international efforts are also in place, with the report of a transatlantic taskforce (EU and US) on antimicrobial resistance (TATFAR) due for publication in autumn 2011. TATFAR's remit was, ringing by now familiar bells, the exploration of the need to re-invigorate the research and development pipeline for novel antibiotics.

The conclusions of these initiatives are the same – antibiotic resistance and the

urgent need for new antibiotic agents is a global problem requiring urgent redress by multi-agency, multi-stakeholder, multi-disciplinary action.

SO WHAT WAY FORWARD?

It is imperative that the profile of this issue is raised if progress is to be made. In September 2011 BSAC launched 'Antibiotic Action' (<http://antibiotic-action.com>), comprising a worldwide alliance of groups including IDSA, ReACT and UK/international charities and not-for-profit agencies. Antibiotic Action aims to engage all with a vested interest in antibiotics, especially agencies that represent patients who are reliant upon effective antibiotics. Antibiotic Action will be the catalyst through which this issue is moved from the medical arena to the public arena, calling on individuals and organisations – be they health related or lay – to sign either a UK or international petition calling for urgent action in this area. Viral communications have been initiated via Twitter and Facebook, a mobile phone app is in the pipeline, and the Antibiotic Action website is a rich repository of information, including stories from patients for whom antibiotics are or have been essential.

A Parliamentary launch meeting is being held on 9 November at the House of Commons, immediately following which the UK petition will be presented to the Prime Minister at 10 Downing Street. It is essential that all stakeholders, and particularly politicians, become involved and engaged in this issue so that ways to stimulate antibiotic discovery, research and development are found so that new drugs are available to treat infections in patients of the 21st century.

Antibiotic Action, with the support of UK politicians, hopes to be the global platform by which this is achieved.

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