Investing in antimicrobial resistance research

The problems of antimicrobial resistance are rapidly increasing, but there are large gaps in our knowledge and the research has been lacking.

The challenge of antimicrobial resistance

Antimicrobial resistance is a large and rapidly worsening public health burden, both in the UK and globally. In 2013, the UK Chief Medical Officer declared that antimicrobial resistance 'poses a catastrophic threat', and the 2013 annual report includes a comprehensive overview of the threat of antimicrobial resistance (Department of Health, 2013).

The Centers for Disease Prevention and Control (2013) have taken the unprecedented step of publishing a 'threat report' that gives a snapshot of the burden and threats posed by resistant bacteria and fungal pathogens (viral and parasitic diseases are outside the remit of their report), describes the 'potentially catastrophic consequences of inaction', and highlights the dwindling pipeline of new antibiotics.

The US National Institutes of Health and European Commission have published action plans about how best to approach antimicrobial resistance. Groups such as Antibiotic Action and initiatives including European Antibiotics Awareness Day (November 18 each year) have highlighted the threat to public health of antibiotic resistance. There are also concerns about the mass administration of antibiotics in animals (Centers for Disease Control and Prevention, 2013). These measures demonstrate that major stakeholders are very concerned about what the future holds for the management of infectious diseases.

Antimicrobial resistance research

Research into antimicrobial resistance is critical if the emerging challenges are to be addressed and risks mitigated. Pre-clinical research can investigate the discovery and development of new agents, clinical trials can help ascertain the efficacy of potentially effective new chemical entities and test treatment regimens and combinations, and implementation research can ascertain the impact of antimicrobial resistance in populations.

An earlier study on the funding awarded to UK institutions for antimicrobial resistance research, published in 2013 (Head et al, 2013a), analysed comprehensively the awards made by public and philanthropic funders of research (there were very limited publicly available funding data from the private sector). The study estimated that there had been £2.6 billion of funding between 1997 and 2010 across all infectious diseases (Head et al, 2013b); of this, just £102 million (3.9%) was allocated to antimicrobial resistance-related research.

Given the potential adverse impact of antimicrobial resistance, the authors argue that there is inadequate funding allocated to antimicrobial resistance-related research. Much of this research was focused on resistance in staphylococci (arguably a success story, given the timescales of the research and development investments under analysis here coincide with the peak and subsequent fall in rates of meticillin-resistant *Staphylococcus aureus*), with malaria and HIV the next most-studied diseases. There was virtually no investment specifically for resistance in gonorrhoea or *Escherichia coli* (or indeed Gram-negative bacteria generally), and few studies investigating drug-resistant tuberculosis. There was very little research into the adverse economic impact of antimicrobial resistance in the UK.

The lack of publicly available data on private sector investments for development of new therapeutics and vaccines means there are data gaps in this analysis. To have a full picture of investments in antimicrobial resistance, private sector data should be made available without compromising commercial sensitivities.

There is also an urgent need to pool research and development data from other research-intensive countries and the European Union to see if research gaps in the UK portfolio are being covered elsewhere. Availability of global data will enable identification of global research gaps, and local and national areas of strength and expertise. Duplication of research can be reduced and multidisciplinary collaborations enabled.

Wisely investing in research and development

Further to mapping the research landscape, there needs to be targeted investment in priority areas. Since 2010, there has been much progress in the UK in strategic investments in antimicrobial resistance-related research via initiatives such as the UK Clinical Research Collaboration Translational Infections Research Initiative and the Health Innovation Challenge Fund. Following the UK Chief Medical Officer's 2013 report, the National Institute for Health Research (2013), which mostly has a focus on translational research, issued a themed call for antimicrobial resistance research across all of its research streams. There have also been reports by the Joint Working Group of Defra Antimicrobial Resistance Coordination and Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infections entitled 'ESBLs: A Threat to Human and Animal Health?' (Department of Health, 2012).

The National Institutes of Health (2013) also announced the creation of a clinical research network, with specific focus on antibacterial resistance; funding for this project may eventually rise to $62 million, and the network will enable research into early-stage clinical evaluation of new antibacterial drugs, clinical trials to optimize currently licensed antibacterial drugs, testing diagnostics, and examining best practices in infection control programmes. Large-scale investments of this nature, which are concentrated into centres of excellence with outreach to

collaborating partners both locally and internationally, could be an effective model for public and philanthropic research and development policymakers to follow.

The paucity of a pipeline of new antibiotics indicates, as in other priority areas of underinvestment where there could be substantial health gains, the need to create push and pull incentives to attract private sector investment or public–private partnerships (Fisk and Atun, 2008). Public–private partnerships, such as the Innovative Medicines Initiative, supported jointly by the European Union and the European Federation of Pharmaceutical Industries and Associations, provide useful platforms for collaborative research. These novel collaborations involve both public funds and private investment, and can help to reduce the financial risk for pharmaceutical companies (Goldman et al, 2013).

Part of the Innovative Medicines Initiative is concentrated on identifying novel lead molecules for antibiotic development and this collaboration could be particularly important, in terms of highlighting the best direction for efficient antibiotic development research and development programmes and appropriate models of how the private and public sectors can best work together (Head et al, 2013a). Other legislative issues surrounding the difficulties of carrying out trials, patents and licensing could most likely be tailored towards encouraging pharmaceutical companies to invest, rather than acting as a barrier.

Policy and politics

Antimicrobial resistance is a global problem and a threat to Europe, given the rising burden and weak health systems in the countries with burden of drug-resistant infections that surround Europe, requiring concerted efforts in surveillance and action. However, global cooperation and leadership across nations with vastly different healthcare and surveillance systems (which may be woefully under-developed) is challenging, as is securing approval of a large number of politicians and health departments.

In health policy terms, the powerful actors globally (including senior politicians, senior scientists and influential individuals such as Bill Gates) can make a difference – there are success stories of worldwide collaboration involving countries and organizations such as the Global Fund, World Health Organization and Joint United Nations Programme on HIV/AIDS in fighting HIV/AIDS or malaria, or for a number of neglected tropical diseases but these successes are not universal. Philanthropic institutions such as the Bill and Melinda Gates Foundation have revitalized the fight against malaria and polio, and it is through similar partnership-based approaches that we should pursue greater investments in antimicrobial resistance research and development, as well as more immediately required attention in policy and health care (for example, in antibiotic prescribing and stewardship).

Priority areas for research investment

So many pathogens require urgent attention, including several Gram-negative bacteria (such as *E. coli*), *Mycobacterium tuberculosis*, *Clostridium difficile* and *Neisseria gonorrhoeae*. How can we develop new therapeutics, as well as management and best use of existing agents?

Alongside this, disciplines such as epidemiology, modelling, economics, policy and behavioural research, intervention studies aimed at reducing resistance and further pre-clinical research using new technologies (such as whole genome sequencing) and health systems research are areas to invest in (Head et al, 2013a). However, addressing a global problem will require concerted effort globally, and innovative models of investment and partnership with the private sector, with international political leadership, global recognition of the antimicrobial resistance problem and cooperation across nations. **BJHM**

KEY POINTS

- Antimicrobial resistance is now widespread and very much a global problem.
- The pipeline of new antibiotics is dwindling.
- Historically, there has been a lack of investment in research into antimicrobial resistance. In 2013, there has been an increased focus in this very important area from major stakeholders in the UK and USA.
- Is this focus too late? Probably not, but such urgency would have been better directed 15–20 years ago.
- Gram-negative bacteria (such as *Escherichia coli, Mycobacterium tuberculosis, Clostridium difficile* and *Neisseria gonorrhoeae* are some of the pathogens with the greatest resistance to existing therapeutics.

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