Antimicrobial resistance

Jonathan Iredell

In this issue, we present a series of short overviews on important topics with a common theme. In their paper, Djordjevic and Morgan point out the impact of antimicrobial resistance on food security and remind us of the importance of understanding the relationships between animals (including humans) and the environment when considering antibiotic resistance, particularly those elements of it that are part of normal genomic plasticity and readily transferable. This sentiment is echoed in a sobering description of the classic post-antibiotic opportunist, *Clostridium difficile*, in Australia and overseas, by Hong *et al*.

Patrick Murray, a doyen of clinical microbiology and well known to many of our readers, describes the move from the art of microbiology to the science of modern diagnostics and the need for modern laboratories to be responsive in clinically relevant timeframes. The improved diagnostic power of simple nucleic acid-based testing (NAT) has saved costs in laboratories under economic pressure and enormously increased our capacity to find cases, treat infection and to define infection reservoirs and chains of transmission. There is also little doubt that whole genome sequencing has revolutionised mycobacteriology, for example. Nicol and Cox describe the huge changes in the diagnosis and management of TB that modern genomic methods have brought about, in which modern sequencing technologies provide better and faster diagnosis of drug resistance and more efficient and precise management of outbreaks.

However, a cautionary note is also included. Culture-based surveillance is particularly important to develop a reliable phenotype when the ability to predict this from genomic data is limited. It is also the easiest way to facilitate high-resolution surveillance for certain pathogens (e.g. for determining the entire genome DNA sequence), notwithstanding the move to culture-independent genome sequencing, even direct from specimens. Sometimes it is employed as a 'reflex culture' when a NAT is positive, sometimes it is part of a planned surveillance and sometimes it is routine practice. Overreliance on NAT-only methods means that key phenotypic evolution may go unnoticed for too long, including the development of antibiotic resistance phenotypes in important pathogens. David Speers describes the successful embrace of molecular diagnostics in managing gonococcal infection and transmission but also reminds us that cultured pathogens remain essential for detailed analyses. Similarly, obtaining *C. difficile* organisms by culture remains essential for surveillance programs (Hong *et al.*). For many organisms, culture is still the best route to a finished genome, a reliable phenotype and a long-term store of reference strains. Thus, for sexually transmitted infections, culture-independent methods have been both our salvation (providing cost-effective accessible diagnosis) and our undoing (without a culture, it is much harder to monitor evolving phenotypes). We must now use the high-resolution molecular data we can derive from genome sequencing to develop better NAT, so as to sharpen our diagnosis and surveillance in turn. As microbiologists, it is our role to find the right compromise between high-resolution techniques and cheap fast methods for each of the important organisms and clinical syndromes.

An understanding of the state of the nation as a whole is essential and Coombs *et al*. describe the national bacteraemia surveillance program (AGAR) that started in Australia more than 30 years ago. This is the world's longest-running such system and AGAR is now embracing the genomic era, with routine sequencing of important isolates such as MRSA so that we have a clearer picture of the natural epidemiology of this pathogen around the country from year to year.

The point of all this is to better understand and manage infection risk – in this issue Stewart *et al*. describe some new agents for the high-risk Gram-negative bacteria, while Blaskovitch tempers this optimistic outlook by pointing out that antibiotic development is fundamentally unprofitable and that our current pipeline is producing barely a trickle. This need is reflected in part by some increased funding available for drug development, but new approaches are urgently required. Boyce *et al*. remind us that, despite their increasing importance as threat pathogens, fungal resistance to major agents such as polyenes (e.g. nystatin, amphotericin) remains poorly understood.

So what does all this mean for the workforce and for future planning? The research need is obvious and increasing but professional recognition and professional development is not unique to the academic sector. It is now increasingly embraced by Fellowship systems, some by formal examination, from the *Australian Society for Microbiology*, from the *Australian Institute for Medical Scientists*, and from the Faculty of Science of the *Royal Australasian College of Pathologists* as prime examples. Some of these began as recognition of academic and professional excellence and some are promoted as qualifications suited to senior positions in professional laboratories. How this evolves is yet to be seen but it is clear that the promotion of excellence and workforce development is core business for societies such as the ASM. There is a big challenge ahead of all of us as our diagnostic services pick up the powerful genetic and genomic tools that are clearly providing enormous utility but are not yet part of the usual workflow outside academic and major reference laboratories. The need to integrate the workforces and expertise of clinical and professional laboratories and the academy is greater now than ever and we may be able to look to new funding organs such as the Medical Research Futures Fund help us meet this need.

Finally, it should be noted that we did not discuss the importance of bacteria to the health of the planet and the evolved species that inhabit it. Indeed, the previous issue dealing with bacteriophages helps to highlight this. Among the many great challenges in bacteriophage therapy is the understanding of susceptibility and the plasticity of the relationships between predator and prey and how these relationships are shaping complex systems like the gut microflora. Bacteriophages and bacteria co-evolved for billions of years before we created new niches for both to exploit and we now look to these natural bacterial predators as potential allies in our fight against antibiotic-resistant bacteria. The proper use of these agents in the clinic, like that of the antimicrobial drugs and compounds we have developed, requires a deep understanding of their biology.

Antimicrobial resistance as a topic is necessarily taking a view of the bacterial world as a threat and here, we have dealt with adaptation of selected bacteria and fungi to the antibiotics that we rely on to protect us and our modern health systems. It is our hope that this issue highlights some of the most widely discussed themes and stimulates readers to pursue some of these topics in greater depth.

Biography

Jon Iredell is an Infectious Disease Physician and Microbiologist who divides his time between Westmead Hospital in a combined Infectious Diseases and Microbiology Department and his research, which is supported by the NHMRC at the University of Sydney. His major interests are in critical infection, including the study of bacterial septic shock, and in bacterial genetics and ecology. He is Director, Center for Infectious Diseases and Microbiology at Westmead Institute/Marie Bashir Institute, and conjoint Professor of Medicine and Microbiology at the University of Sydney.