Is the cupboard bare?
The threat of antimicrobial resistance

Antimicrobial resistance is one of the greatest threats to health that we have faced in recent history. As the rate of resistance grows, fewer antibiotics remain in the arsenal to fight common infectious diseases. These illnesses have the potential to once again become untreatable, as they were in the days before antimicrobial medicines existed. It is estimated that there are currently 630 000 cases of multiple drug resistant tuberculosis worldwide.[1] This accounts for 3.7% of new cases and 20% of previously treated cases of tuberculosis.[1] Resistance varies globally, and in some countries more than 18% of new cases of tuberculosis are now multiple-drug resistant.[1] There is widespread resistance to antimalarial medicines, such as chloroquine and mefloquine, in most countries in which malaria is endemic.[1] Resistance to newer antimalarial medicines (artemisinin-combination treatments) is now emerging in South-East Asia,[1] and it is likely that fully resistant malaria parasites will start to become widespread.

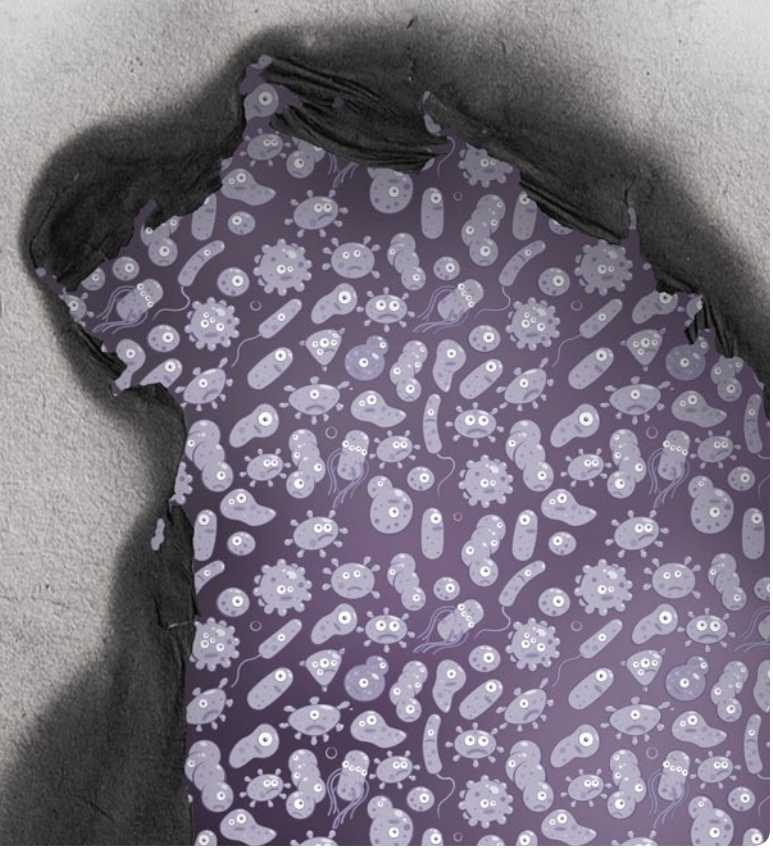
Many multiple drug resistant organisms are found to be clonal, i.e. from the same origin, and are spread widely as people are increasingly mobile. For example, most methicillin-resistant *Staphylococcus aureus* (MRSA) isolates in New Zealand have originated from overseas. There was an epidemic MRSA in New Zealand hospitals in 2000, from a strain imported from the United Kingdom, most likely by both patients and staff. Traditionally, MRSA was mainly associated with hospital-acquired infections, but it is now increasingly being seen in the community. A recent study in New Zealand found that MRSA is now more commonly associated with infections in the community than in hospitals.[2] Latest ESR surveillance data from 2011 showed that 1020 patients had laboratory confirmed MRSA, of which 44% were from hospital-acquired infections and 56% were from community-acquired infections.[3] There was a 37% increase in MRSA prevalence between 2010 (17.3 people with MRSA per 100 000 population) and 2011 (23.7 per 100 000), which is the largest yearly increase in the last ten years.[3] Prevalence varied by DHB region, and was highest in the Tairawhiti (64.4 per 100 000), Counties Manukau (57.4 per 100 000) and Hawke's Bay (50.1 per 100 000) DHBs. The MRSA prevalence in the Tairawhiti DHB was almost five times higher than in 2010.[3] Community-acquired strains of MRSA have historically been distinct from hospital-acquired strains, however, crossover is now being seen.[3] This shift to a dominance of community MRSA infections follows a similar pattern to that seen in other countries.

There are increasingly limited options for treating MRSA infections. Vancomycin has been the antibiotic of choice for MRSA in a hospital setting, however, this has now resulted in the emergence of vancomycin-resistant enterococci. Multiple drug resistant extended-spectrum beta-lactamase-producing enterobacteriaceae (ESBL-E) are also spreading in both

Why should we care about antimicrobial resistance?

According to the World Health Organisation, antimicrobial resistance poses the following threats:[1]

- Standard antibiotics are often ineffective when used to treat infections caused by resistant bacteria, resulting in prolonged illness and an increased risk of mortality
- Resistance causes the effectiveness of treatment to be reduced, increases the amount of time that a person is infectious and increases the spread of resistant microorganisms to others
- Infections which were previously easily managed may become untreatable and uncontrollable, as seen in the pre-antibiotic era
- The costs of treating resistant infections (to healthcare, individuals and societies) is increased due to the need to use more expensive second-line treatments, longer treatment periods and a greater need for hospital care
- Resistant infections are detrimental to the success of "modern medicine" treatments such as major surgery, chemotherapy and organ transplantation



hospitals and the community, mostly due to quinolone and cephalosporin use, and are increasingly becoming a concern.

We are down to our last line of defence (parenteral ceftriaxone) in the treatment of gonorrhoea, due to increasing resistance to oral ciprofloxacin. Latest surveillance data from ESR show that resistance to fluoroquinolones was at 40.8% in 2011,[4] which means that ciprofloxacin can no longer be considered an appropriate first choice antibiotic for gonorrhoea. There is considerable local variation in resistance rates, with some areas reporting an even higher resistance rate to fluoroquinolones.

As we discard the last of the useful antibiotics, what is left in the cupboard? The Infectious Diseases Society of America (IDSA) has called for a worldwide commitment to develop at least ten new systemic antibiotics by 2020; the 10 × '20 initiative. The IDSA says that pharmaceutical research and development needs to urgently focus on new agents to fight multiple drug resistant Gram-negative bacilli infections (e.g. ESBL-E). However, at this time, many pharmaceutical companies are withdrawing from antibiotic research and development, rather than increasing resources in this area. In the five year period from 1983 – 1987, 16 new systemic antibiotics were approved in the United States, however, this has steadily declined, with only two new antibiotics approved between 2008 and 2012.[5]

Pharmaceutical companies are reluctant to invest in developing antibiotics because it has now become scientifically difficult to develop a new, effective and safe antibiotic, and the cost involved in this development cannot be recouped. Most antibiotics are only used for a short amount of time, and prescribers are encouraged to limit their use of these medicines. This is coupled with the fact that due to the natural process of resistance, a new antibiotic has a relatively short "life-span" before it becomes obsolete in clinical practice. All of these factors deter investment.[6]

There are currently seven parenteral antibiotics active against Gram-negative bacilli in advanced clinical development (Phase 2 or 3) in the United States, but not all will make it through the approval process, and not all in time for the 2020 deadline.[5] In addition, none of these seven medicines are active against all clinically relevant resistant Gram-negative bacilli.[5] Six of the seven antibiotics are being developed for the treatment of complicated urinary tract infection or intra-abdominal infection, and one for acute bacterial skin infection. There are no antibiotics currently in development in the United States for the treatment of community-acquired or hospital-acquired bacterial pneumonia or bloodstream infection, which are considered by the IDSA to be important conditions for which to find new antibacterial treatments.[5]

In Europe, the European Commission has collaborated with the pharmaceutical industry, to help drive the development of new and safer medicines, including antibiotics, and increase the rate in which these medicines are available to patients. The Innovative Medicines Initiative has an ongoing focus on combating antimicrobial resistance, which includes the programme "New Drugs for Bad Bugs". There are currently only a few antibiotics targeting resistant strains of bacteria in an advanced stage of development in Europe.[6]

If waiting for a wave of new antibiotics is not the immediate solution, what can we do? The development of antimicrobial resistance is a natural process of evolution, however, certain behaviours that we are responsible for can accelerate the emergence and spread of resistance.[1] This includes the inappropriate use of antimicrobials in both medicine and veterinary care, and the use of antimicrobials for non-therapeutic purposes, e.g. food and animal feed additives, preservatives and disinfectants, which also results in environmental contamination.[6] The key lies in optimising use of our currently available antimicrobial medicines by preserving them for only when they are absolutely required, prescribing the right antibiotic for the right condition and susceptibility, at the right dose and duration, educating patients to follow instructions for use and improving surveillance and access to resistance data. Adequate infection prevention and control measures underpin all of these interventions.

Work is currently being done in New Zealand to develop a coordinated strategy for addressing antimicrobial resistance at a national level and across all health care sectors. The main players in health care policy and education have expressed a strong willingness to collaborate on this strategy. In the meantime, individual clinicians and healthcare organisations need to make a concerted effort to work towards the common goal of preserving the effectiveness of the antibiotics that we still have.

Watch this space We are currently in the final process of updating our 2011 guide: "Antibiotic choices for common infections". Printed copies of the booklet will be distributed soon, and an interactive version of the guide will also be available on our website: **www.bpac.org.nz**

"Antibiotic resistance as a phenomenon is, in itself, not surprising. Nor is it new. It is, however, newly worrying, because it is accumulating and accelerating, while the world's tools for combating it decrease in power and number."

—**JOSHUA LEDERBERG**, Nobel Prize laureate

References

1. World Health Organisation (WHO). Antimicrobial resistance. Fact Sheet no. 194. WHO, 2013. Available from: www.who.int (Accessed Jun, 2013).
2. Williamson D, Roberts S, Ritchie S, et al. Clinical and molecular epidemiology of methicillin-resistant Staphylococcus aureus in New Zealand: Rapid emergence of sequence type 5 (ST5)-SCCmec-IV as the dominant community-associated MRSA clone. PLoS ONE 2013;8(4):e62020.
3. Heffernan H, Bakker S. Annual survey of methicillin-resistant Staphylococcus aureus (MRSA), 2011. Institute of Environmental Science & Research Ltd (ESR); Wellington, 2013. Available from: www.surv.esr.cri.nz (Accessed Jun, 2013).
4. Public Health Surveillance. Antimicrobial resistance data from hospital and community laboratories, 2011. Institute of Environmental Science & Research Ltd (ESR); Wellington, 2013. Available from: www.surv.esr.cri.nz (Accessed Jun, 2013).
5. Boucher H, Talbot G, Benjamin D, et al. 10 x '20 progress – development of new drugs active against Gram-negative bacilli: an update from the infectious diseases society of America. Clin Infect Dis 2013;56(12):1685-94.
6. European Commission. Communication from the Commission to the European Parliament and the Council. Action plan against the rising threats from antimicrobial resistance. Brussels, 2011. Available from: http://ec.europa.eu (Accessed Jun, 2013).