The changing landscape of antimicrobial resistance in New Zealand

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Abstract
Antimicrobial resistance is one of the biggest health threats of the modern age, threatening the routine treatment of many common infectious diseases. Resistance to many common antimicrobials is now endemic in New Zealand, in both community and healthcare settings. Over the past two decades, the landscape of antimicrobial resistance has changed considerably in New Zealand, with the emergence and spread of pathogens such as community-associated methicillin-resistant Staphylococcus aureus, extended-spectrum β-lactamase-producing Enterobacteriaceae and multi-resistant Neisseria gonorrhoeae.

Factors contributing to the emergence and spread of antimicrobial-resistant pathogens in New Zealand include the use and overuse of antimicrobials, transmission of resistant organisms in community and healthcare settings, and importation of resistant pathogens from areas where multi-resistant pathogens are endemic.

In this review, we provide a summary of major antimicrobial-resistant bacteria in New Zealand, with a specific focus on those pathogens that pose major threats to human health.

Antimicrobial resistance (AMR) is one of the greatest global health threats of the modern age.1,2 As the prevalence of antimicrobial resistance rises, treatment of common infectious diseases, such as respiratory infections and urinary tract infections, becomes increasingly challenging, and advances made in complex medical therapy, such as organ transplantation, neonatology and intensive care, are also threatened.

Compounding this threat is the scarcity of new antimicrobial compounds in the research and development pipeline.3 Moreover, the treatment of infections due to antimicrobial–resistant organisms places a substantial burden on healthcare systems, and has a major societal and economic impact.1,4

For many bacterial pathogens, resistance to major antimicrobial classes, such as penicillins, fluoroquinolones and third-generation cephalosporins, is now commonplace in New Zealand hospitals, and is increasingly found in the community setting. Examples of such resistant pathogens include Staphylococcus aureus (S. aureus), Escherichia coli (E. coli), and Neisseria gonorrhoeae (N. gonorrhoeae). A timeline of significant events related to AMR in New Zealand is shown in Figure 1.
The factors responsible for the emergence and spread of antimicrobial resistance are complex, but the key drivers in New Zealand are likely to include:

- The use and overuse of antibiotics in both human and animal populations;\(^5^,^6\)
- Transmission of antimicrobial-resistant organisms in community and healthcare settings;\(^7^,^8\) and
- Increasing globalisation, resulting in the importation of antimicrobial-resistant pathogens.\(^6^,^9^,^10^\)

One of the key components of efforts to combat the emergence and spread of antimicrobial-resistant pathogens is comprehensive and consistent surveillance.\(^12\)

Although surveillance *per se* does not reduce antimicrobial resistance, effective surveillance can provide valuable information that can be used to formulate local antibiotic guidelines, to inform policy recommendations, to identify high-priority areas for interventions, and to monitor the impact of interventions designed to prevent or reduce antimicrobial resistance.

Surveillance of antimicrobial-resistant pathogens should occur at multiple levels, including local, national and supranational, and can be structured according to factors such as the specific purpose of surveillance, available resources and testing capacity, and the likely prevalence and threat of certain resistant pathogens. Often, a number of complementary surveillance approaches are required and may involve a combination of routine surveillance, targeted phenotypic and molecular surveys, and clear pathways for the rapid identification of resistant pathogens of major public health significance (e.g. carbapenemase-producing Enterobacteriaceae, vancomycin-resistant *S. aureus* or extensively drug-resistant *Mycobacterium tuberculosis* [M. *tuberculosis*]).

In this review, we provide a contemporary overview of the epidemiology of antimicrobial resistance in New Zealand, with a particular focus on those antimicrobial-resistant pathogens that pose a major threat to human health.
Antimicrobial resistance in specific medically important bacteria

Methicillin-resistant S. aureus (MRSA)—Over the past two decades, the global clinical and molecular epidemiology of S. aureus disease has changed dramatically, predominantly due to the emergence and spread of community-associated MRSA (CA-MRSA) clones, most notably the USA300 CA-MRSA clone in North America. Similarly, in New Zealand, there has been a considerable change in the epidemiology of S. aureus disease, with a significant increase in S. aureus skin and soft tissue infections, particularly in Māori and Pacific Peoples, and in the under-5 year age group.

In New Zealand, the majority of S. aureus disease is due to methicillin-susceptible S. aureus (MSSA), with recent aggregate national antimicrobial susceptibility data showing a stable MRSA prevalence of approximately 8–10%, although the prevalence of MRSA differs between regions, with a generally lower prevalence in the South Island compared to the upper North Island. However, despite this relatively stable national MRSA prevalence, there have been marked changes in the molecular epidemiology and antimicrobial resistance patterns of MRSA in New Zealand during the past decade.

Throughout the 1990s and early 2000s, the South West Pacific (SWP) clone (also known as Western Samoan Phage Pattern, ‘WSPP’) was the predominant CA-MRSA in New Zealand. Belonging to multilocus sequence type (ST) 30, this clone was first isolated in 1992 from patients in the Auckland community who had contact with Western Samoa.

Similar to CA-MRSA clones in other parts of the world, the SWP ST30 clone is generally resistant only to β-lactam antimicrobials, and harbours the lukF-PV/lukS-PV genes encoding the Panton Valentine leucocidin (PVL) toxin. In 2005, a newly emerged ST5 MRSA clone (the ‘AK3’ clone) was identified in the Auckland region, and since then, this clone has rapidly displaced SWP ST30 as the predominant CA-MRSA clone in New Zealand (Figure 2).

Although the reasons for the remarkable success of this clone in New Zealand are as yet undetermined, it is notable that, in addition to resistance to β-lactams, this clone is usually also resistant to fusidic acid, and in New Zealand, topical fusidic acid is widely used for a number of dermatological conditions.

Indeed, recent data suggest that community dispensing rates of topical fusidic acid have increased significantly over the past decade (Williamson DA, Monecke S, Heffernan H, et al. A cautionary tale: high usage of topical fusidic acid and rapid clonal expansion of fusidic acid-resistant Staphylococcus aureus. Clin Infect Dis. 2014 Aug 18. pii: ciu658. [Epub ahead of print]), and it is likely that a key factor driving the emergence of the AK3 ST5 MRSA clone has been high and sustained usage of topical fusidic acid in the New Zealand community.
Figure 2. Annual point-prevalence rates of methicillin-resistant *Staphylococcus aureus*, 2003–2012, showing the relative prevalence of the AK3 MRSA strain, South West Pacific clone and EMRSA-15 strain

![Graph showing annual point-prevalence rates of MRSA strains from 2003 to 2012.](image)

**Note:** Data based on annual 1-month national surveys and rates calculated using the mid-year population estimates.

In addition to these two major CA-MRSA clones, a number of prominent global clones have been detected in New Zealand, such as the ST8 (‘USA300’), ST93 (‘Queensland’) and ST772 (‘Bengal Bay’) clones. Furthermore, a recent study described the isolation of clonal complex (CC) 398 MRSA from nine patients in the South Island. In other settings, particularly in Europe, the CC398 clone has been strongly associated with exposure to livestock, most commonly swine.

In contrast to the diverse range of CA-MRSA clones, MRSA clones in the hospital setting are more genetically restricted and more commonly resistant to a wide range of antimicrobial agents, with the predominant healthcare-associated MRSA (HA-MRSA) clone being ST22 ‘EMRSA-15’, which is typically resistant to several non-β-lactam antimicrobials, particularly ciprofloxacin and erythromycin.

In keeping with other countries, recent data suggest an infiltration of CA-MRSA clones into the healthcare setting in New Zealand, and it has been suggested that due to an increasing community reservoir, CA-MRSA clones will ultimately replace HA-MRSA clones in the hospital setting. This is of concern given the apparent high transmissibility of CA-MRSA clones, and highlights the need for ongoing systematic molecular surveillance to track MRSA clones in the New Zealand setting.

**Resistance in Enterobacteriaceae**—Enterobacteriaceae, particularly *E. coli* and *Klebsiella pneumoniae* (*K. pneumoniae*), are major human pathogens in both community and healthcare settings, and over the past decade, the prevalence of
Antimicrobial-resistant Enterobacteriaceae has increased dramatically in many parts of the world.\(^2\)

In particular, resistance in Enterobacteriaceae to third-generation cephalosporins (e.g. ceftriaxone, ceftazidime) due to extended spectrum β-lactamase (ESBL) production, or to carbapenems (e.g. ertapenem, meropenem) due to carbapenemase enzymes, has reached disturbing levels in several regions.\(^2\) For example, data from the Asia-Pacific region collected as part of the Study for Monitoring Antimicrobial Resistance Trends (SMART study) reported an ESBL prevalence of \(\geq 60\%\) in *E. coli* urinary tract isolates from China and Vietnam.\(^{25}\)

Of even greater concern are reports of the widespread dissemination of carbapenemase-producing Enterobacteriaceae (CPE) in certain geographic regions, most notably the Indian subcontinent.\(^{26}\)

Data from national surveillance demonstrates an increase in the incidence of ESBL-producing Enterobacteriaceae (ESBL-E) isolation over the past decade in New Zealand (Figure 3), with marked geographic variation in incidence rates, such that ESBL-E isolation rates are consistently higher in the greater Auckland region.\(^{27}\)

However, these geographic differences are likely to be due, in part, to regional variation in infection control screening policies, differences in patient case mix and any concurrent local outbreaks.

**Figure 3. Annualised point-prevalence rates of extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-E), 2003-2012**

![Annualised point-prevalence rates of ESBL-E](image)

**Note:** Data based on annual 1-month national surveys with rates calculated using mid-year population estimates.\(^{27}\)

Based on aggregate susceptibility data,\(^{28}\) the overall prevalence of ESBL production in *E. coli* bloodstream isolates has remained stable in New Zealand over the past
decade at <5%, whereas the reported prevalence of ESBL production in *K. pneumoniae* bloodstream isolates is higher at 10–15%.

In keeping with these aggregate national data are recent data from Auckland demonstrating an ESBL prevalence of 5.6% in *E. coli* bloodstream isolates, and an ESBL prevalence of 5.1% in Enterobacteriaceae from faecal samples submitted to a community pathology laboratory.

Several studies have attempted to identify specific epidemiological associations for ESBL-E colonisation and/or infection in New Zealand. Such information may be useful in informing decisions around infection control practices and empiric therapy. A case-control study conducted in Auckland in 2003-2004 identified residence in a long-term care facility (LTCF) (odds ratio (OR) 6.1, 95% confidence interval (CI) 1.6–23.2) and concurrent chronic obstructive pulmonary disease (COPD) (OR 10.6, 95% CI 1.04–107.7) as strong independent risk factors for ESBL-E infection in the community setting. These authors postulated that the association of ESBL-E isolation and COPD might reflect frequent exposure to healthcare and/or multiple prior courses of antimicrobials.

Another study conducted in the Auckland community in 2009 also identified LTCF residence as an independent risk factor for ESBL-E colonisation (OR 19.8, 95% CI 7.0–56.2). In addition, a retrospective case-control study conducted between 2003 and 2007 in South Auckland identified known colonisation with an ESBL-E as a particularly strong risk factor (OR 46.2, 95% CI 3.5–619) for subsequent bloodstream infection with ESBL-E. The authors of this study suggested the importance of considering ESBL-E colonisation status when choosing empiric therapy in such patients.

Throughout the 1980s and 1990s, the most common reported types of ESBL were either TEM- or SHV-type ESBLs. However, during the 2000s, the CTX-M-type ESBLs rapidly emerged and spread to become the most commonly identified ESBL type worldwide. In particular, CTX-M-15 has emerged to become the most globally prevalent CTX-M enzyme, and in keeping with these findings, a molecular epidemiological study conducted in 2006 identified CTX-M-15 as the most common ESBL type in New Zealand. In this study, 81/83 (98%) of ESBL-E isolates produced CTX-M enzymes, with the most common CTX-M types being CTX-M-15 (63/81; 78%) and CTX-M-14 (11/81; 14%).

A strong association has been described between CTX-M-15 producing *E. coli*, and a global ‘pandemic’ clone of *E. coli* known as ST131. This clone is notable for its ability to harbour numerous genes associated with both antimicrobial resistance and virulence, and in addition to resistance to β-lactam resistance, it is also commonly resistant to fluoroquinolones. The ST131 clone has been identified as a cause of bloodstream infections in the Auckland region, most notably following prostate biopsy in patients who had recently been treated with a fluoroquinolone antimicrobial.

The endemicity of ESBL-E in New Zealand is posing an ongoing therapeutic challenge to the treatment of infections caused by such organisms, particularly community-onset urinary tract infections. In particular, suitable oral antimicrobial options may be limited to agents such as fosfomycin and mecillinam, although the latter is not routinely available in New Zealand.
In contrast to ESBL-E, it is fortunate that the isolation of CPE continues to be relatively infrequent in our setting. In addition to hydrolysing penicillins and cephalosporins, CPE hydrolyze carbapenems such as ertapenem and meropenem, and similar to ESBL-E, CPE usually harbour genes conferring resistance to other classes of antimicrobials such as aminoglycosides and fluoroquinolones.

As a result, there are little or no available treatment options for infections caused by such organisms. To date however, all CPE in New Zealand have been isolated from patients who have recently returned from areas in which CPE are endemic. For example, one study between 2009 and 2010 described the identification of New Delhi metallo-β-lactamase (NDM)-producing Enterobacteriaceae from four patients in New Zealand hospitals, all of whom had received recent medical care in India. Similarly, an OXA-181-producing K. pneumoniae was isolated in 2010 in Auckland from a patient who had recently been hospitalised in Asia. These reports highlight the requirement for vigilance, both in surveillance and infection prevention and control policies, in monitoring the importation of such extensively resistant organisms.

Mycobacterium tuberculosis—Tuberculosis (TB) remains a significant global public health issue, with an estimated 8.6 million people developing TB in 2012 and a global incidence rate of 122 per 100,000 population. One of the most challenging problems in TB control is drug-resistant M. tuberculosis, specifically multidrug-resistant TB (MDR-TB, defined as M. tuberculosis that is resistant to at least isoniazid and rifampicin), and extensively drug-resistant TB (XDR-TB, defined as MDR-TB plus resistance to a fluoroquinolone and a second-line injectable agent).

TB is a notifiable disease in New Zealand, and the 2012 notification rate was 6.6 per 100,000 population, with the highest notification rate in the Asian ethnic group (41.4 per 100,000 population). Methods for the laboratory diagnosis of drug-resistant TB have changed considerably over the past decade, with a shift towards rapid genotypic detection of resistance-conferring mutations. In particular, the Cepheid Xpert® MTB/RIF assay, which simultaneously identifies M. tuberculosis and common mutations in the rpoB gene that are used as a surrogate marker for MDR-TB, has been widely adopted globally. This assay is also used in New Zealand, and was useful in detecting four cases of MDR-TB that were not identified by conventional phenotypic testing.

Fortunately, MDR-TB remains relatively rare in New Zealand. Between 1995, when national antituberculosis-drug resistance surveillance began, and 2013, a total of 48 MDR-TB cases were identified, with the vast majority of cases occurring in patients born overseas. In keeping with the predominantly overseas origin of MDR-TB in New Zealand are recent molecular epidemiological data demonstrating an association between distinct phylogenetic lineages of MDR-TB and patient country of origin, although the clinical relevance of this finding has not yet been determined.

Importantly, the first reported case of XDR-TB in Australasia was identified in 2010 in Otago, New Zealand. This patient, an emigrant from Myanmar, had no reported history of TB or prior receipt of anti-tuberculous therapy, suggesting that XDR-TB strains are circulating within Myanmar.

Of particular concern in the New Zealand setting was the approximate 2-month delay between specimen collection and final reporting of XDR-TB. Fortunately this
patient did not have active pulmonary TB, although this case highlights the value of risk-based laboratory testing algorithms and emphasises the importance of cohesive laboratory networks.

**Neisseria gonorrhoeae**—Antimicrobial-resistant *N. gonorrhoeae* has been identified as an ‘urgent threat’ to public health.\(^4\) Over the past four decades, *N. gonorrhoeae* has developed resistance first to the penicillins, and subsequently to macrolides, tetracyclines and fluoroquinolones.\(^45\)

Currently, the recommended empiric treatment of *N. gonorrhoeae* infection in many countries, including New Zealand, is ceftriaxone (intramuscularly, 250–500 mg) plus azithromycin (orally, 1 g).\(^45\) Beyond third-generation cephalosporins such as ceftizime and ceftriaxone, treatment options are extremely limited. Of concern therefore, are worldwide reports of *N. gonorrhoeae* strains displaying decreased susceptibility to third-generation cephalosporins, typically with minimum inhibitory concentrations (MICs) of $\geq 0.06 \text{ mg/L}$, with sporadic reports of treatment failures in patients infected with such strains.\(^46,47\) In these strains, decreased susceptibility is due to the presence of mosaic penicillin-binding proteins, which have reduced affinity for extended-spectrum cephalosporins such as ceftriaxone.

More alarming is the description of two multi-drug resistant *N. gonorrhoeae* strains (H041 and F89) from Japan in 2009 and France in 2010 respectively.\(^48–50\) In addition to displaying resistance to almost all classes of antimicrobials, both strains exhibited high-level resistance to ceftriaxone, with a ceftriaxone MIC of 2 mg/L.

In New Zealand, sexually transmitted infections, including gonorrhoea, are not notifiable diseases, and monitoring of gonorrhoea cases is performed predominantly by laboratory-based surveillance. Aggregate susceptibility data indicates that, during the 10 years 2003–2012, rates of penicillin resistance in *N. gonorrhoeae* increased only modestly from 5.1% to 11.3% compared to fluoroquinolone resistance which increased from 8.1% to 40.6%.

Fortunately, no ceftriaxone-resistant *N. gonorrhoeae* strains (MIC $\geq 0.25 \text{ mg/L}$) have recently been detected in New Zealand to date; however, isolates with decreased susceptibility to ceftriaxone (MIC 0.06–0.25 mg/L) have been detected in the Auckland region.\(^51\)

Currently, one of the major challenges in monitoring the emergence and spread of antimicrobial resistance in *N. gonorrhoeae* is the shift from culture-based to molecular diagnostics, using nucleic acid amplification tests (NAAT). Although NAAT assays are rapid, sensitive and specific, bacterial culture is still required to provide information on antimicrobial susceptibility.

In New Zealand, as in other settings, it is vital that regular, systematic monitoring of antimicrobial resistance in *N. gonorrhoeae* is undertaken to inform empiric therapy guidelines and to track the inevitable emergence of resistant strains.

**Clostridium difficile**—*Clostridium difficile* (*C. difficile*) is the commonest cause of healthcare-associated diarrhoea, and *C. difficile* infection (CDI) has been associated with increased morbidity and mortality in overseas settings.\(^52,53\) Although acquired antimicrobial resistance in *C. difficile* is not a problem per se, its intrinsic resistance to many common antimicrobials, typical occurrence after exposure to antimicrobial agents, and propensity for transmission in healthcare settings poses a major challenge.
Over the past decade the clinical and molecular epidemiology of CDI has changed considerably with several important observations from other developed countries. These include:

- An increase in infection rates in younger populations;\(^{54}\)
- The emergence of “epidemic” ribotypes of \emph{C. difficile}, most notably ribotype 027, which has been associated with increased morbidity and mortality;\(^{55}\) and
- Infections in patients who would not previously have been considered to be “at risk” for CDI, most notably patients with no prior healthcare exposure.\(^{54}\)

At present, there are no formal systems in place for coordinated surveillance of CDI in New Zealand. To date, two national “snapshot” surveys have been conducted, one in 2009 and the second in 2011.\(^{56}\) These surveys indicated a diverse range of circulating ribotypes, with no single dominant strain.

Although these ad-hoc surveys provided useful information on the molecular epidemiology of circulating \emph{C. difficile} ribotypes in New Zealand, minimal accompanying clinical metadata were obtained. As such, relatively little is known about the clinical epidemiology or prevalence of CDI in New Zealand. Such information is crucial in determining the most appropriate strategies for prevention and control of this important infection.

Other antimicrobial resistance threats—In addition to the pathogens above, there are numerous other bacteria in which antimicrobial resistance poses a major threat. For example, vancomycin-resistant enterococci (VRE) continue to be regularly isolated from patients in New Zealand,\(^{57}\) often as the result of importation from overseas settings. Reassuringly however, the prevalence of VRE in New Zealand has not reached the concerning levels seen in some Australian healthcare settings.\(^{58}\)

Penicillin non-susceptibility is prevalent among \emph{Streptococcus pneumoniae} in New Zealand, with 17.2% of invasive isolates recorded as penicillin resistant (MIC \(\geq 0.12\) mg/L) and 25.1% of non-invasive isolates recorded as penicillin non-susceptible (MIC \(\geq 0.12\) mg/L) during 2012.\(^{59}\)

It is disappointing that there has been little change in penicillin or cefotaxime susceptibility among pneumococci since the addition of pneumococcal conjugate vaccine to the childhood immunisation schedule in 2008, given that the pneumococcal serotypes covered by the conjugate vaccines are those types that were most commonly associated with resistance to penicillin and third-generation cephalosporins in the pre-vaccine era. However, as has been observed globally, non-vaccine serotypes have in part replaced vaccine types, and in New Zealand one of the two most common replacement serotypes, 19A, is often penicillin resistant.\(^{59}\)

Finally, despite the large agricultural sector in New Zealand, relatively little is known about the contemporary prevalence and epidemiology of antimicrobial resistance in zoonotic bacteria in animals.

A study conducted in New Zealand over a 12-month period in 2009 and 2010 found that the prevalence of antimicrobial resistance among potential human pathogens isolated from food-producing animals (including very young calves, pigs and broiler poultry) was comparatively less than that reported for human isolates of the same bacterial species, especially for antibiotics of particular importance in human medicine, such as third-generation cephalosporins and fluoroquinolones.\(^{60}\)
However, a study assessing antibiotic sales in the veterinary sector in New Zealand between 2009 and 2011 identified increasing use of third-generation cephalosporins as a potential antimicrobial resistance threat at the human-animal interface.\(^6\) Of particular concern was the finding of a 26% increase in sales of cefovecin, a long-acting third-generation cephalosporin used in the companion animal population. The authors of this study suggested that overuse of such compounds could result in significant antimicrobial resistance in bacteria infecting companion animals.

### Identifying knowledge gaps

Although recent data from the 2014 World Health Organization (WHO) Global Antimicrobial Resistance report indicate that New Zealand has comparatively low rates of antimicrobial resistance (particularly when compared to countries in neighbouring regions such as South-East Asia), New Zealand is not immune to the threat of antimicrobial resistance, and we should not become complacent.\(^2\) Although there are existing programmes of antimicrobial resistance surveillance, there remain a number of important ‘knowledge gaps’ and ‘action gaps’ around antimicrobial resistance in New Zealand.

Importantly, there are few New Zealand data on the extent and impact of antimicrobial usage, both in hospital and community settings. Such information may permit benchmarking comparisons at national or international levels; guide the development of treatment guidelines and formularies; assess the public health consequences of antimicrobial use (and misuse) and evaluate the impact of any educational or regulatory interventions that encourage prudent antimicrobial prescribing.

In addition, there are no data available on the clinical and economic impact of antimicrobial resistance in New Zealand; this information is particularly important in informing policy decisions around health and research funding for antimicrobial resistance-related activities.

Notably, a recent UK study analysing infection-related research funding between 1997 and 2010 found that only 5.5% of such funding was allocated to the area of antimicrobial resistance.\(^6\) These authors highlighted the importance of prioritising such funding, given the potentially devastating public health consequences of increasing antimicrobial resistance.

### Conclusions

Antimicrobial resistance is one of the biggest man-made public health threats of modern times, and similar to other settings, New Zealand must confront this challenge. Noteworthy contemporary issues in New Zealand include fusidic acid-resistant S. aureus, the endemicity of ESBL-E in the community setting, and the alarming global reservoir and importation of drug-resistant TB.

It is imperative that, in the face of the threats and realities of antimicrobial resistance, New Zealand builds on existing linkages and infrastructure, and adopts a cohesive, proactive and multi-regional approach that combines expertise from across the medical, academic, and veterinary sectors.
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