An overview of emerging community based antimicrobial resistance

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The development of community antimicrobial resistance should not surprise any budding microbiologist. Bacteria are highly adaptable and mutations are acquired or selected in response to any number of stresses. In the 21st century the major ‘stressor’ is profligate human and veterinary antibiotic use, and inappropriate antimicrobial use in food and agricultural sectors. Worldwide, resistance in the community has been well described in many bacterial species (Table 1). In this overview, we focus on community resistance in three bacterial species – *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Neisseria gonorrhoeae*. In all three human antibiotic use provides the greatest selection pressure.

**Streptococcus pneumoniae**

Worldwide *S. pneumoniae* is the major bacterial cause of community acquired pneumonia, upper respiratory tract infections, (including sinusitis and otitis media), and childhood and adult meningitis. Resistance has implications for empiric treatment; in turn empiric respiratory prescribing, whether uncontrolled or through local guidelines, impacts on continuing community antibiotic resistance selection pressures.

Penicillin resistant isolates of *S. pneumoniae* were first detected independently in the 1970s, from South Africa, Papua New Guinea and Australia. In Australasia these were sporadic cases, though it led to a labelling of Australia on the *S. pneumoniae* resistance map. In the early 1990s, penicillin non-susceptibility emerged rapidly, with resistance rates of up to 30–50% reported from Europe, the United States and East Asia in particular. In some settings penicillin resistance was linked to a shift to the use of oral cephalosporins. Susceptibility rates have varied widely according to reporting countries, site of infection (e.g. invasive vs non-invasive), and to pneumococcal serotype. However, resistance has not been confined to β-lactam antibiotics and of concern is the evolution of resistance in other antibiotic classes, especially macrolides and fluoroquinolones, multi-drug resistance and the potential to compromise treatment availability.

Recently penicillin non-susceptibility appears to have stabilised in many western countries, however macrolide resistance continues to increase. Macrolide resistance has been linked to usage, particularly of longer-acting macrolides. Penicillin and macrolide resistance rates continue to reside at high levels in parts of Asia. In Vietnam as example; in 2000/01, 92% penicillin non-susceptibility was reported, of which 71% was high level resistance.

Key to interpretation of the data is an understanding of the clinical implications of resistance and worldwide trends. Despite resistance, there have been no bacteriologically confirmed reports of failure of intravenous penicillin therapy in pneumococcal pneumonia. In pneumonia, worsened outcomes have been retrospectively reported when penicillin MICs were ≥4 mg/L. In Australia strains with an MIC ≥4 mg/L remain uncommon, in the 2005 AGAR study, 1.6% had MICs ≥4 mg/L (Figure 1). Hence despite in vitro pneumococcal resistance, intravenous penicillin and high-dose oral amoxicillin remain the currently recommended antibiotics in Australia. Conversely, even low level

Figure 1. *S. pneumoniae* – Etest MICs: AGAR 2005 studies.
penicillin resistance has an adverse impact on penicillin therapy for meningitis. In contrast to β-lactams, there is a confirmed association between macrolide resistance and therapeutic failures in bacteraemic *S. pneumoniae* 10,11. Newer fluoroquinolones, (e.g. moxifloxacin, levofloxacin) are effective drugs, particularly for infection by multi-drug resistant strains. Rising resistance rates have been documented (France 3% 12, Hong Kong 14% 13), and correlate with increasing levels of use. Resistance has been linked with therapeutic failures 14.

National surveillance studies aid the formulation of therapeutic guidelines in monitoring their ongoing relevance and to link in with vaccination strategies. The Australian Group on Antimicrobial Resistance (AGAR), a national laboratory network, has performed periodic studies of *S. pneumoniae* susceptibility since 1989, the last in 2005 8.

In the AGAR studies, penicillin non-susceptibility has continued to increase, albeit at a slower rate than first observed in the early 1990s, reaching a national level of 28% in 2005 (Figures 2 and 3). This increase has occurred in both penicillin intermediate and resistant categories. In 1989, 1% of strains tested were penicillin non-susceptible (intermediate resistance). By 2005 the penicillin intermediate group had increased to 16.3% and this level of resistance has remained steady over the past six years. However, the rate of *S. pneumoniae* high-level resistance nationally has increased from 0% in 1989, to 5.9% in 1999 and 11.7% in 2005, and resistance in non-invasive isolates with an MIC ≥2 mg/L rose from 6.9% to 13.3%. The higher rates in non-invasive infection may relate to differing serotypes involved in invasive and bloodstream infections and the selective pressure of community antibiotic use in upper respiratory tract infections.

In 2005 erythromycin resistance was documented in 22.7% of isolates, a rise of 5% since 1999. Similarly, increases were primarily in non-invasive isolates. A macrolide-lincosamide-streptogramin B (MLSB) phenotype, suggestive of an ermB (high-level) resistance mechanism was present in 62.6%. The AGAR study data suggests that macrolides should not be used as sole empiric therapy for invasive respiratory tract infections.

There were extremely low levels of fluoroquinolone resistance (0.1%). The low fluoroquinolone resistance levels are likely to relate to restrictions placed on their use. To date, Australian guidelines have not endorsed fluoroquinolone use as first line therapy in community acquired pneumonia. Tetracycline resistance in invasive isolates was below 10% and trimethoprim-sulphamethoxazole resistance fell from 37.8% in 2002 to 31.0% in 2005. It is notable that the tetracycline and folate synthesis inhibitor drugs were the two classes of antibiotics to show a >50% reduction in community prescribing over the past fourteen years 15.

Regular AGAR surveillance studies of *S. pneumoniae* resistance have allowed a much clearer picture of changing susceptibility and provide an indirect measure of our prescribing policies. Although resistance appears to have reached a stable threshold, rates of ‘high-level’ penicillin resistance and multi-resistance continue to rise worldwide 16.

### Staphylococcus aureus

As a major human pathogen causing significant mortality and morbidity *S. aureus*, with its constantly evolving antimicrobial resistance, continues to be a challenge for scientists, microbiologists and clinicians.

Whilst methicillin-resistant *S. aureus* (MRSA) has been a well-established pathogen in hospitals and healthcare settings, its emergence as a community pathogen has only been recognised in more recent times. Since the 1990s, multiple community epidemics of infections caused by MRSA occurred worldwide, including the USA 17, Canada 18, New Zealand 19 and Australia20. The foci of these infections (often necrotising skin and soft tissue infections) within communities included the paediatric population 21, indigenous peoples and within community institutions such as prisons 22.

Figure 3 *S. pneumoniae*: penicillin and macrolide resistance by region – AGAR 2005 study.

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**Figure 2. Trends in national *S. pneumoniae* resistance – AGAR 1994–2005.**

![Graph showing trends in national *S. pneumoniae* resistance from 1994 to 2005](image)
The isolates causing these community onset staphylococcal infections have been commonly called ‘community MRSA’ (cMRSA), in an attempt to distinguish them from hospital or healthcare associated infections. However, apart from the community acquisition of these infections, there are several features that distinguish them from traditional MRSA infections. These include the lack of usual risk factors for MRSA acquisition, susceptibility to a wider range of non beta-lactam antimicrobials, and the presence of specific virulence factors. Of note is the presence of the toxin Panton-Valentine leukocidin (PVL), which is associated with the skin and soft tissue infections and primary necrotising pneumonias. At a molecular level, MRSA isolates harbour the mec gene (encoding for beta lactam resistance) as part of a mobile genetic element staphylococcal chromosome cassette mec (SCCmec). In cMRSA isolates, these cassettes (designated as class IV or V) are smaller and suggest the potential for easy transfer between and amongst staphylococci.

In Australia, the evolution and spread of cMRSA has been well documented. First observations in the 1990s of community acquired MRSA infections in Western Australia (WA-MRSA) were followed soon after by reports in the eastern states. Some of these strains appear to have originated from the Pacific Islands (‘Western Samoan Phage Pattern’ (WSPP-MRSA)), and in 2000, another strain emerged in Queensland (QLD-MRSA). Concurrently, there was recognition of community-onset infections with healthcare associated non-multiresistant MRSA strains (such as the ‘epidemic’ MRSA or EMRSA-15 strain originally from the United Kingdom). National surveillance by the AGAR network of laboratories has provided ongoing data in the form of alternate-year community surveys of S. aureus (Staphylococcus aureus Surveillance Programme), whereby one hundred consecutive, non-duplicate S. aureus isolates are collected by each of the participating laboratories from non-hospitalised patients (including those in long-term care facilities but excluding day surgery and dialysis patients). Information on antimicrobial susceptibility, epidemiology and typing for the years 2000, 2002 and 2004 has been analysed and reported.

In summary, these community surveys show that:

- The percentage of S. aureus isolates that are methicillin resistant has increased from 11.7% in 2000 to 15.3% in 2004.
- The percentage of cMRSA isolates as a proportion of all S. aureus isolates has increased from 4.7% in 2000 to 7.3% in 2004.
- Geographical differences were noted with some states reporting lower percentages of cMRSA (Tasmania and Victoria 2%) than others (Northern Territory 20% and Western Australia 11%).
- In 2004, twelve cMRSA clones were identified with the predominant being WA-1 MRSA, QLD-MRSA and WSPP-MRSA.
- Overall, 46.4% of cMRSA were positive for PVL.

The information from these surveys demonstrates that cMRSA is becoming a common pathogen in many regions of Australia. In the 2004 AGAR survey, cMRSA isolates accounted for >10% of all clinical outpatient isolates in Darwin, Brisbane and Perth. This has significant implications for local antibiotic prescribing practices for the treatment of staphylococcal infections in the community. It has been suggested that an arbitrary threshold of 10% or more of S. aureus isolates with methicillin resistance be used for consideration of specifically tailoring empiric antibiotic treatment strategies to account for cMRSA infections.

Whilst obtaining specimens for culture and susceptibility testing was often not considered to be part of routine management for community infections in the past, the increasing prevalence of cMRSA has made this practice more important. Antibiotic susceptibility profiles can assist the clinician in the appropriate choice of antibiotics to treat these infections. At present S. aureus isolates with multiple resistances to non beta-lactam antibiotics does not appear to be a significant problem in Australia, with 60.3% of cMRSA isolates being resistant to beta-lactam agents only, and only 1.5% with resistance to three non beta-lactams. However, a recent study based within an ambulatory care centre in the USA, suggests that multi-drug resistance is emerging in cMRSA (USA 300 strain). High rates of resistance to erythromycin (96%), clindamycin (57%), levofloxacin (85%) and tetracycline (30%) were demonstrated. In addition, 18% of the isolates were resistant to all four of these non-beta-lactams. These developments are concerning as they suggest that the acquisition of antibiotic resistance in cMRSA occurs readily with continued antibiotic use and selection pressure. The potential spread of a multi-resistant cMRSA would greatly limit the clinician’s options for therapy.

**Neisseria gonorrhoeae**

The causative agent of gonorrhoea, *N. gonorrhoeae* is a well-known human pathogen whose importance is often forgotten, given its antiquity. However, it continues to cause significant morbidity with increasing antimicrobial resistance the focus of concerns in managing the scope of this global public health issue. Surveillance of antimicrobial resistance is important in the development of local empiric treatment regimens, which in turn affects disease outcomes for individuals, and in addition importantly impacts upon ongoing transmission of infection.

The World Health Organisation (WHO) Western Pacific Gonococcal Surveillance Programme has documented over the last decade or so, the spread of quinolone resistant gonococci.
throughout our Asian and Pacific neighbours. In 2005, countries such as China and Korea were reporting rates in excess of 90% of *N. gonorrhoeae* isolates being resistant to the fluoroquinolone ciprofloxacin.\(^{31}\)

Locally, data on gonococcal antimicrobial resistance is collected and reported on quarterly by the Australian Gonococcal Surveillance Programme (AGSP). On the home front, increasing rates of antimicrobial resistance among local isolates are a concern. Figures 4 and 5,\(^{32}\) demonstrate the significant percentages of isolates with penicillin and quinolone resistance, and the regional differences in susceptibility results. Nationally in 2006, 34% and 37.8% of gonococci were resistant to penicillin and quinolones respectively; increases from the preceding two years. Of great concern, the most recent data from the AGSP in the first quarter of 2007 supports an ongoing upward trend in resistance rates with record rates of quinolone resistance nationally (51.6% of all *N. gonorrhoeae* isolates). Once again, New South Wales carries the burden of resistance with 66.8% isolates tested as quinolone resistant.\(^{33}\)

The WHO recommends that once resistance to an antimicrobial of 5% or more in isolates obtained from the community is demonstrated, that treatment programs be modified to account for this.\(^{34}\) Given the above data, the evidence is that quinolones cannot be used reliably to treat gonococcal infections (the exception being perhaps in the Northern Territory). Unfortunately, this leaves injectable agents such as ceftriaxone as the mainstay for treatment in Australia. Currently, 0.6% of surveyed *N. gonorrhoeae* isolates have raised ceftriaxone minimum inhibitory concentrations (in the range 0.06–0.25 mg/L).\(^{32}\) The rates for ceftriaxone resistance have remained low and stable since 2001, but it is notable that such isolates are in general also resistant to both penicillin and quinolones. Thus,

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**Table 1. Examples of emerging community bacterial resistance.**

<table>
<thead>
<tr>
<th>Source</th>
<th>Bacterial species</th>
<th>Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td><em>Streptococcus pneumoniae</em></td>
<td>β-lactam (penicillin, cephalosporin), macrolide, fluoroquinolone, MDR</td>
</tr>
<tr>
<td></td>
<td><em>Haemophilus influenzae</em></td>
<td>β-lactam</td>
</tr>
<tr>
<td></td>
<td><em>Mycobacterium tuberculosis</em></td>
<td>rifampicin, isoniazid (MDR) + quinolones, others (XDR)</td>
</tr>
<tr>
<td>Gastrointestinal / Urinary</td>
<td><em>Enterobacteriaceae</em> (e.g. <em>E. coli</em>), ESBL+ <em>Enterococcus faecalis</em> <em>Salmonella typhi</em></td>
<td>amino-penicillins, trimethoprim 3rd gen cephalosporin, fluoroquinolone, vancomycin (VRE), amino-penicillins TMP-SMX, fluoroquinolone</td>
</tr>
<tr>
<td>Genital Tract</td>
<td><em>Neisseria gonorrhoeae</em></td>
<td>penicillin, fluoroquinolones</td>
</tr>
<tr>
<td>Skin / Soft tissue</td>
<td><em>Staphylococcus aureus, Strepococcus pyogenes</em></td>
<td>methicillin (β-lactam), macrolide</td>
</tr>
<tr>
<td>Zoonotic</td>
<td><em>Salmonella sp</em></td>
<td>β-lactam, TMP-SMX, fluoroquinolones</td>
</tr>
<tr>
<td></td>
<td><em>Campylobacter jejuni</em></td>
<td>3rd gen cephalosporin (ESBL), MDR fluoroquinolones MDR</td>
</tr>
<tr>
<td></td>
<td><em>Yersinia pestis</em></td>
<td>MDR</td>
</tr>
</tbody>
</table>

MDR = multi drug resistant; XDR = extremely drug resistant; TMP-SMX = trimethoprim-sulphamethoxazole
with limited treatment options and ongoing antibiotic selection pressure, it would appear inevitable, that with time rates of resistance to ceftriaxone will also increase.

In this review we have briefly covered issues of antimicrobial resistance in three pathogens which are common causes of community acquired infections. The evolution of antimicrobial resistance in all three is a dynamic process, and thus continued surveillance in the form of local, national and global surveys are important in providing data that can be utilised to appropriately guide antimicrobial prescribing guidelines and formulate public health strategies. Introduction and maintenance of effective vaccination programs as well as continuing promotion of prudent community prescribing are crucial to maintaining effective control on resistance.

Acknowledgments

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References

33. Tapsall J, for The Australian Gonococcal Surveillance Programme. First Quarter Report for 2007; publication pending.

Figures 1–3 are presented with the permission of the Australian Group on Antimicrobial Resistance (http://antimicrobial-resistance.com/).