Antimicrobial resistance – a public health issue?

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With any decision to label a disease a public health issue comes an implicit understanding that action must be taken and that there should be a government intervention or management plan – but there is no standard definition of what constitutes a public health issue. Most often the factors considered are the number of cases, the vulnerability of the affected group and rapidity of spread, and the levels of morbidity and mortality caused. The cost to the community – either directly in managing the disease or in loss of work or productivity – is also an important factor. We can all think of infectious diseases that fit these criteria; meningococcal meningitis, because it kills young healthy adults and children rapidly; pandemic influenza because it has the potential to kill many rapidly; sexually transmitted diseases carrying with them social stigma and the potential to cause sterility; tuberculosis with its transmissability and protracted and potentially lethal course; and food borne infections causing large outbreaks. Where does antimicrobial resistance (AMR) fit in this and is it a public health issue? To answer this question we must look at the evidence.

Are there large numbers of infections due to antimicrobial resistant organisms?

Although it is recognised that there are many infections due to antimicrobial resistant organisms, with many anecdotal reports and case series, validated prevalence or incidence data are sparse. There are even less data available on burden of disease caused by AMR organisms. However, there are surveillance data showing proportions of isolates from clinical disease that exhibit resistance. The following table attempts to consolidate what information is available for Australia and other countries for comparison, when appropriate*.

Do antimicrobial resistant organisms cause increased morbidity and mortality?

A number of publications show an association between AMR in Staphylococcus aureus, enterococci and gram-negative bacilli

Table: Resistance rates in clinical isolates from Australia, USA and Asia-Pacific region.

<table>
<thead>
<tr>
<th></th>
<th>HA-MRSA % S. aureus</th>
<th>CA-MRSA % S. aureus</th>
<th>N. gonorrhoea FQ R</th>
<th>ESßL K. pneumoniae</th>
<th>VRE E. faecium</th>
<th>XDR TB % of MDR</th>
<th>S. pneumoniae penicillin non susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia (overall)</td>
<td>31.9%</td>
<td>15.3%</td>
<td>28.6%</td>
<td>8.8%</td>
<td>7.2%</td>
<td>0%</td>
<td>28%</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>95.1%</td>
<td>11.6%</td>
<td></td>
<td></td>
<td></td>
<td>60.8%</td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>76.9%</td>
<td>10%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>59.5% (ICU)</td>
<td>13.3%</td>
<td>20.6% (ICU)</td>
<td>28.5% (ICU)</td>
<td>3%</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Singapore</td>
<td></td>
<td></td>
<td>35.6%</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

HA-MRSA = hospital associated methicillin-resistant Staphylococcus aureus; CA-MRSA = community associated methicillin resistant Staphylococcus aureus; FQ = fluoroquinolone; R = resistant; ESßL = extended spectrum ß lactamase; VRE = vancomycin resistant enterococcus; XDR TB = extensively resistant Mycobacterium tuberculosis; MDR TB = multidrug-resistant Mycobacterium tuberculosis.

*As there may be variations between the states of Australia, overall data only are given. The source documents will provide greater detail if required. European data have not been included as it is not possible to give any representative figure. There are wide variations between member states and non-EU countries. Data can be obtained through the Euro Surveillance website (www.eurosurveillance.org).
and increases in mortality and morbidity. There is debate on the method chosen for measuring such outcomes, but when controlled for disease severity and other confounding variables a significant increase in mortality can be demonstrated. This has been shown for methicillin-resistant *Staphylococcus aureus* (MRSA) relative to methicillin-susceptible *S. aureus* (MSSA) for bacteremia (OR 1.93; P<0.001) 14, and surgical site infection (OR 3.4 P 0.003) 15, and for patients infected with vancomycin-resistant *Enterococcus* (VRE) compared with non-infected patients (RR 2.1 P 0.04) 16. Emergence of resistance during therapy for gram-negative infections has also been shown to increase mortality; for *Pseudomonas aeruginosa* (RR 3.0 P 0.02) 17 and *Enterobacter* species developing resistance to third generation cephalosporins (RR 5.02 P 0.01) 18.

Studies in various parts of the world have demonstrated greater morbidity and mortality associated with antimicrobial resistant organisms associated with food borne disease. In the USA, FoodNet studies have shown that patients infected with antimicrobial resistant non-typhoidal salmonella are more likely to have bloodstream infection and to be hospitalised than patients with susceptible infection. Similarly, in Canada 21 patients infected with ciprofloxacin-resistant *Campylobacter* infection had a longer duration of diarrhoea than those with ciprofloxacin-susceptible infection. Similarly, in Canada 21 patients infected with *S. enterica* serotype *typhimurium*, both DT104 and non-DT104, had higher hospitalisation rates if the organisms were resistant to the main therapeutic agents. In a Danish study 22, patients with infection with *S. typhimurium* with multiresistance were 4.8-times more likely to die than the general population, and 10.3-times more likely to die if quinolone resistance was present.

*Mycobacterium tuberculosis* is of enormous public health importance. Globally it kills more than 2 million people each year and is the second leading cause of death due to infectious disease after HIV/AIDS. Most cases potentially can be treated with current antituberculous drugs – imagine if this were not the case. What if not only our first line drugs were ineffective as with multidrug resistant TB (MDR-TB) but also our second line. This is a reality. Extensively drug resistant tuberculosis (XDR-TB) has now been reported throughout the world, with the highest rates in Korea, Eastern Europe and Russia 23. This signals the potential for a return to outcomes that were seen in the pre-antimicrobial era when almost 50% of patients with the disease died. We are fortunate that in Australia we have not yet seen XDR-TB 24 but with high prevalence in countries in the Asia Pacific region, together with the prevalence of air travel and increased exchange (e.g. students), it is inevitable that we will.

**Is there rapid transmission?**

Whenever an infectious disease that can cause severe infection spreads rapidly within a community there are cries for public health action. Consider the attention given to meningococcal disease, pandemic influenza, and legionella outbreaks. We are seeing the rapid spread of community associated MRSA (CA-MRSA) in all states of Australia. Many of the strains of CA-MRSA also possess a toxin, Panton-Valentine leukocidin (PVL) that is associated with severe disease such as necrotising pneumonia, necrotising fasciitis, severe skin and soft tissue infections, and osteomyelitis. These types of infections are being reported more frequently 2 and mortality or severe morbidity have occurred in the Australian community 24-26. A number of PVL positive CA-MRSA strains have been identified, with the most common, the Queensland clone, also being the most widely distributed 2. In the USA, CA-MRSA was reported for the first time in 1999 with the death of four previously healthy children. Within a few years the predominant CA-MRSA strain (USA300), which is PVL positive, has spread across the USA. In a study reported in 2006 27, adult patients presenting to emergency departments with skin and soft tissue infection were enrolled in eleven states in the USA. The prevalence of MRSA was 59%, of which 97% were the USA300 strain. This same strain has recently been reported in Canada 28, Denmark 29 and now Australia (Gram-Positive Laboratory, PathWest Laboratory Medicine Royal Perth Hospital. Six monthly report July 2006-December 2007.) In Western Australia the public health threat of PVL positive CA-MRSA has been recognised and a program to control spread is underway. The emergence of staphylococci, both resistant to methicillin and possessing additional toxin genes, has been described as a convergence of antimicrobial resistance and virulence 30. Therefore, we also should be greatly concerned about the increasing number of reports 2,31 indicating that these more virulent strains are entering our hospitals and causing infections in our more vulnerable patients. We have been fighting hospital associated MRSA for many years and the prospect of a more virulent opponent is certainly a major public health issue. In addition, fatal or severe post-influenza community associated MRSA pneumonia has recently been documented 2,32 indicating that these more virulent strains are entering our hospitals and causing infections in our more vulnerable patients. We have been fighting hospital associated MRSA for many years and the prospect of a more virulent opponent is certainly a major public health issue.

**Are vulnerable groups involved?**

The young, the elderly and the immunocompromised are all targets for infections by AMR organisms. These are the groups in whom antimicrobial usage is greatest and hence where selective pressure for AMR is greatest. VRE and MRSA infections in hospitals are common in intensive care and transplant units. Drug resistant *Streptococcus pneumoniae* and CA-MRSA are noted for causing infection in children. The development of an effective conjugate
vaccine for *S. pneumoniae* has reduced invasive pneumococcal disease in children in areas where there has been high vaccine uptake. However, there is now the emergence of invasive disease due to non-vaccine serotypes. One of these serotypes, 19A, reported in the USA states of Massachusetts 59 and Texas 61, has resistance to penicillin and ceftriaxone. The vulnerable, under two years age group, will potentially have a resurgence of invasive infections that will pose therapeutic challenges. New vaccines will undoubtedly be developed but selection of non-vaccine strains will almost certainly re-emerge. The first cases of CA-MRSA in the USA were recognised in children and there is now a very large body of literature devoted to CA-MRSA infections in children in many areas of the world. Adults are also infected but it is often when disease affects young healthy children that a public health issue is first recognised.

**Is there increased cost to the community?**

Costs due to AMR have mostly been measured as increased costs associated with therapeutic management of the patient – usually of drug therapy; increased length of stay in hospital – or as costs incurred in controlling the organisms in the hospital environment. There is a lack of research on costs due to loss of work or productivity. Also, control of resistance in the community is rarely undertaken although there is an intervention in Sweden for penicillin-resistant *S. pneumoniae*. Hospital studies show increased costs for infections due to MRSA 15,57,98 vancomycin-resistant enterococci and resistant gram-negatives 17,18,40-42. The cost of infection control within a hospital to eradicate an organism such as VRE can be high. In my own hospital, eradication of VRE cost AU$2.7 million 97. The Swedish experience in the community also had societal costs with exclusion of children from daycare centres until negative for DRSP 91.

**What then the conclusion?**

Yes – infections due to AMR organisms do occur in significant numbers. Yes – infections due to AMR organisms cause increased morbidity and mortality. Yes – infections due to AMR organisms can be rapidly transmitted. Yes – AMR organisms cause infections in the vulnerable members of society. Yes – the overall the cost of AMR in Australia and globally is huge and probably in the many billions of dollars.

Based on the evidence, there is only one conclusion. Yes – AMR is a very significant public health issue.

**References**

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