UNIT NO. 2

ANTIMICROBIAL RESISTANCE: COMMUNITY AND HOSPITAL

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ABSTRACT

Antimicrobial resistance (AMR) increases the morbidity, mortality and costs of treating infectious diseases. (Hawkey and Jones, 2009)[1]. The threat from resistant organisms is now a global problem, both in the hospital and to some extent in the community. The key drivers are: medical care complexity; widespread antimicrobial use in animal husbandry; antimicrobial contaminated food distribution; international travel, and food distribution of food contaminated with multidrug resistant organism. Strategies for infection control are: good understanding of what needs to be done, consistent application of infection control measures, use of "search and destroy" techniques; and effective antimicrobial stewardship. This paper reviews the current issues and potential solutions.

Keywords: multidrug resistant organisms, infectious disease

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ANTIMICROBIAL RESISTANCE

Illustrative cases

Three cases are used to illustrate the pervasiveness of multidrug resistant organisms in present day Singapore.

CASE 1 – Multidrug resistant E coli

An elderly Chinese female with no travel history, who was deskbound and watched her stocks and shares on a laptop was admitted for urinary tract infection. She was found to have a multidrug resistant E coli Infection. The profile of the causative organism was:

- Resistant to ampicillin, augmentin, ceftriaxone, cefeprime, gentamicin, amikacin, ciprofloxacin, bactrim, doxycycline, piperazine/ tazobactam.
- Resistant to ertapenem.
- Sensitive to imiprenem/ meropenem.

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CT abdomen showed bilateral pyelonephritis. She stayed many weeks in hospital for her multidrug resistant E coli infection to be brought under control.

CASE 2 – Multidrug resistant Klebsiella pneumoniae

An elderly Malay man with no travel history is seen for benign enlarged prostate. He is found to have an urinary tract infection. Isolates from the urine culture and sensitivity showed multidrug resistant Klebsiella pneumoniae. He was ill and had to be admitted to ICU. The profile of the causative organism was:

- Resistant to ampicillin augmentin, ceftriaxone, cefepime, gentamicin, amikacin, ciprofloxacine, Bactrim, doxycycline, piperacillin/ tazobactam, impenem, eropenam.
- Resistant to polymyxin B.
- Intermediate resistance to aztrenam.

CASE 3 - Several multidrug resistant organisms

An elderly Singapore female patient went to Mumbai for holiday. She was knocked down by a bus and sustained an open wound. She was admitted to a Mumbai hospital for a day and subsequently flew back to Singapore for treatment. She was found to have several organisms isolated from her wound that were resistant to carbepenem as shown in Table 1. Blood culture was positive for multidrug resistant Klebsiella pneumoniae. She stayed many months in hospital before she was fit for discharge.

TABLE 1. ISOLATES FROM PATIENT ADMITTED TO MUMBAI HOSPITAL

Organism	Site	Carbapenem	Resistance Gene
Pseudomonas aeruginosa	Wound	Resistant	NDM-1
Pseudomonas putida	Wound	Resistant	NDM-1
Enterobacter cloacae	Wound	Resistant	NDM-1
Citrobacter sediakii	Wound	Resistant	NDM-1
Stenotrophomonas maltophilia	Wound	Resistant	Other
Acinetobacter baumannii	Wound	Resistant	OXA-23
Klebsiella pneumonia	Blood	Resistant	NDM-1

Footnotes

NDM-1 stands for New Delhi metallo-beta-lactamase, an enzyme produced by bacteria like E.coli and Klebsiella pneumonia that confers antibiotic resistance to all common penicillins, cephalosporins and the carbapenems. The only drug that has been shown to be reasonably effective is colistin, an antibiotic that has not been used in the past few decades because of its toxicity. Essentially, we do not have the capability to treat our patients with effective antibiotics if they were to have this infection.

Multidrug resistant organisms (MDROs)

Table 1 shows the major antibiotic resistant bacteria contributing to the burden of resistance.

TABLE 2. MAJOR ANTIBIOTIC-RESISTANT BACTERIA CONTRIBUTING TO THE BURDEN OF RESISTANCE

Gram-positive bacteria		
Staphylococcus aureus	Staphylococcus aureus showing resistance to meticillin (MRSA) cause potentially life-threatening infections in hospitals and other healthcare facilities. They have also been found among patients with no obvious exposure to a healthcare facility. An increasing number of reports of MRSA in food-producing animals and companion animals is a cause for concern. Community-acquired MRSA (not related to hospital acquired MRSA) is also increasing.	Ref. Hogberg, 2010[2]; Hawkey, 2009[1]; Woodford, 2009[3]
Enterococcus species	Enterococci are a normal component of human bowel flora and are rarely problematic in healthy individuals, but are responsible for opportunistic infections in hospitalized patients. Enterococci might acquire resistance to many antibiotic classes, but of greatest clinical concern are those that have acquired resistance to aminoglycosides and glycopeptides, which are frequently reported as causing significant outbreaks in healthcare facilities. Recent reports of clones resistant to linezolid are of particular concern.	Ref. Hogberg, 2010[2]; Woodford, 2009[3]; Hawkey, 2009[1]
Gram-negative bacteria		
Escherichia coli and Klebsiella pneumoniae resistant to third-generation cephalosporins	Accumulating evidence suggests that resistance to third-generation cephalosporins in E. coli and, in particular, K. pneumoniae, has become a worldwide problem. ESBL-production in Enterobacteriaceae has been demonstrated to have a significant impact on mortality and length of treatment in hospital. Dissemination of ESBL-producing Enterobacteriaceae in the community poses a new threat because it may become a powerful reservoir for the continued influx of resistant strains into hospitals. In healthcare settings, Klebsiella spp and E coli what are carbapenem-resistant (CPRE) are seen in patients who are treated with conditions that require devices like ventilators, urinary catheters or intravenous catheters, and patients who are on long courses of antibiotics.	Ref. Hogberg, 2010[2]; Livermore, 2009[5] Giske, 2008[4];
Acinetobacter baumannii	Acinetobacter baumannii is an important nosocomial pathogen, and hospital outbreaks have been described from various geographic areas. Drug resistance is a major problem in Acinetobacter infections, and the bacteria are often multi-resistant, leaving few treatment options. They rarely occur outside of healthcare settings. They can cause pneumonia, septicaemia, wound infections, or be colonisers of tracheostomy sites and open wounds.	Ref. Hogberg, 2010[2]; Livermore, 2009[5]
Pseudomonas aeruginosa	Pseudomonas aeruginosa is one of the leading Gram-negative organisms associated with nosocomial infections. The increasing frequency of multidrug-resistant Pseudomonas aeruginosa strains is concerning because efficacious antimicrobial options are severely limited.	Ref. Hogberg, 2010[2]; Hawkey, 2009[1]; Boucher, 2009[6]

Resistance in Gram positive bacteria

Methicillin resistant Staph aureus is widely distributed globally and increasing with levels of MRSA reaching 30% in many countries. There is now the emergence of community-associated MRSA (CA-MRSA) which are genetically unrelated to the hospital acquired strains of MRSA. Cases of CA-MRSA usually present in younger patients without underlying risk factors, and typically cause skin and soft tissue infections (SSTIs). (Hawkey, Jones, 2009)[1].

Resistance in Gram negative bacteria

Resistance in Gram negative bacteria is commonly acquired through beta-lactamases which are acquired by horizontal gene transfer. (ESBLs) are enzymes that inactivate and confer resistance to most beta-lactam antibiotics, including penicillins, cephalosporins, and the monobactam aztreonam. They are found exclusively in gram-negative organisms, primarily Klebsiella pneumoniae, Klebsiella oxytoca, and Escherichia coli. Many different varieties of ESBL exist. They differ in their activity against particular beta-lactam substrates and in their geographical distribution. Surveillance data report high levels of ESBL-producing strains of Klebsiella pneumonia and E coli in Australasia, Japan, Singapore and China. (Hawkey, Jones, 2009)[1].

Fortunately, most ESBLs do not break down cephamycins or carbapenems and are susceptible to beta-lactamase inhibitors. The best therapeutic option for severe infections caused by ESBL-producing organisms is a carbapenem (imipenem, meropenem, doripenem, andertapenem). Cefepime may be effective against ESBL-producing organisms that test susceptible if administered in high doses (ie, 2 g every eight hours). Use of other cephalosporins and piperacillin-tazobactam has been associated with treatment failures. (Munroz-Price, 2014)[7].

The emergence of metallo-beta-lactamases with activity against carbapenems has now occurred and compromised the clinical utility of this class of antibiotics. Rising fluoroquinolone resistance is also present in Europe. (Hawkey, Jones, 2009)[1] The spread of ESBL-producing organisms within institutions can be slowed by the use of barrier protection and restriction of later generation cephalosporins. (Munroz-Price, 2014)[7].

Community acquired MRSA (CA-MRSA)

What are the criteria for distinguishing community-associated MRSA (CA-MRSA) from healthcare-associated MRSA (HA-MRSA)? Persons with MRSA infections that meet all the following criteria likely to have CA-MRSA infections (CDC, 2007)[8]:

- Diagnosis of MRSA was made in the outpatient setting or by a culture positive MRSA within 48 hours after admission to hospital.
- No medical history of MRSA infection or colonisation.
- No medical history in the past year of hospitalisation; admission to a nursing home; skilled nursing facility, or hospice; dialysis; surgery.
- No permanent indwelling catheters or medical devices that pass through the skin into the body.

DRIVERS IN THE DEVELOPMENT OF ANTIBIOTIC RESISTANCE

Several drivers acting in concert result in the development of antibiotic resistance. The interrelationships are shown in Figure 2.

(a) Medical care complexity.
(b) Antimicrobial use in farming and animal husbandry.
(c) Microbe contaminated food distribution, and
(d) Resistant organisms dissemination through international travel.

Medical care complexity as a driver

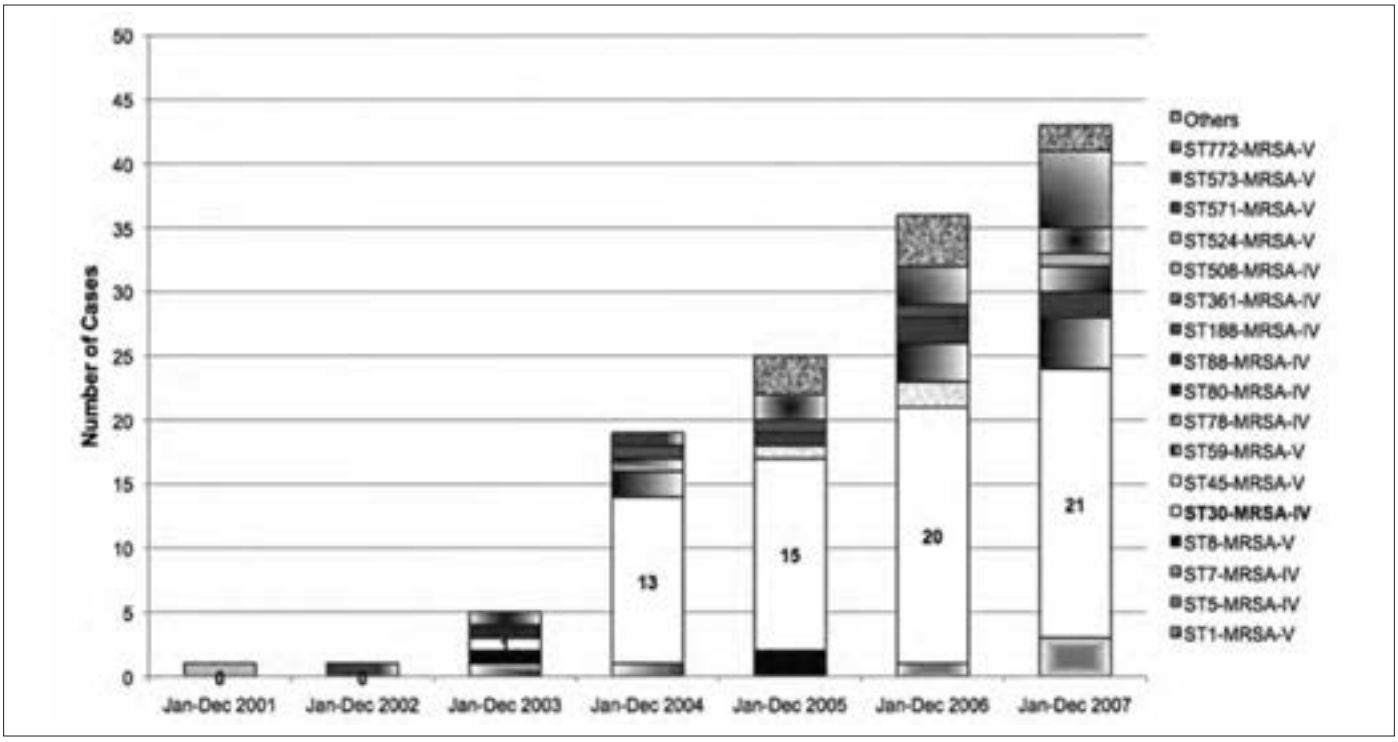
Medical care complexity is contributed by the older population, more chronic diseases, inter-connected healthcare system allowing acquisition in high risk settings, as well as antibiotic-resistant bacteria laden food. The risk of bacteria acquiring drug resistance are highest in intensive care unit; moderate risk in prolonged hospitalisation, major surgery (not requiring ICU care), transfer to metropolitan tertiary hospital; and low to negligible risk in outpatient clinic visit, community hospital short stays, and community residence.

Spiralling drug resistance. In high risk healthcare settings, the vicious cycle of demand for stronger and stronger antibiotics is kept going by the following spiralling factors:

- A new broad spectrum antibiotic is required because of rising trends of antimicrobial resistance trends to existing antibiotics.
- There is continuing pressure for empirical therapy of the new broad spectrum antibiotic to save lives.
- More of the broad spectrum antibiotic is then prescribed resulting in greater antibiotic selection pressure.
- Higher resistance rates then occur, and
- The need for a new broad spectrum antibiotic is now created and the vicious cycle goes on.

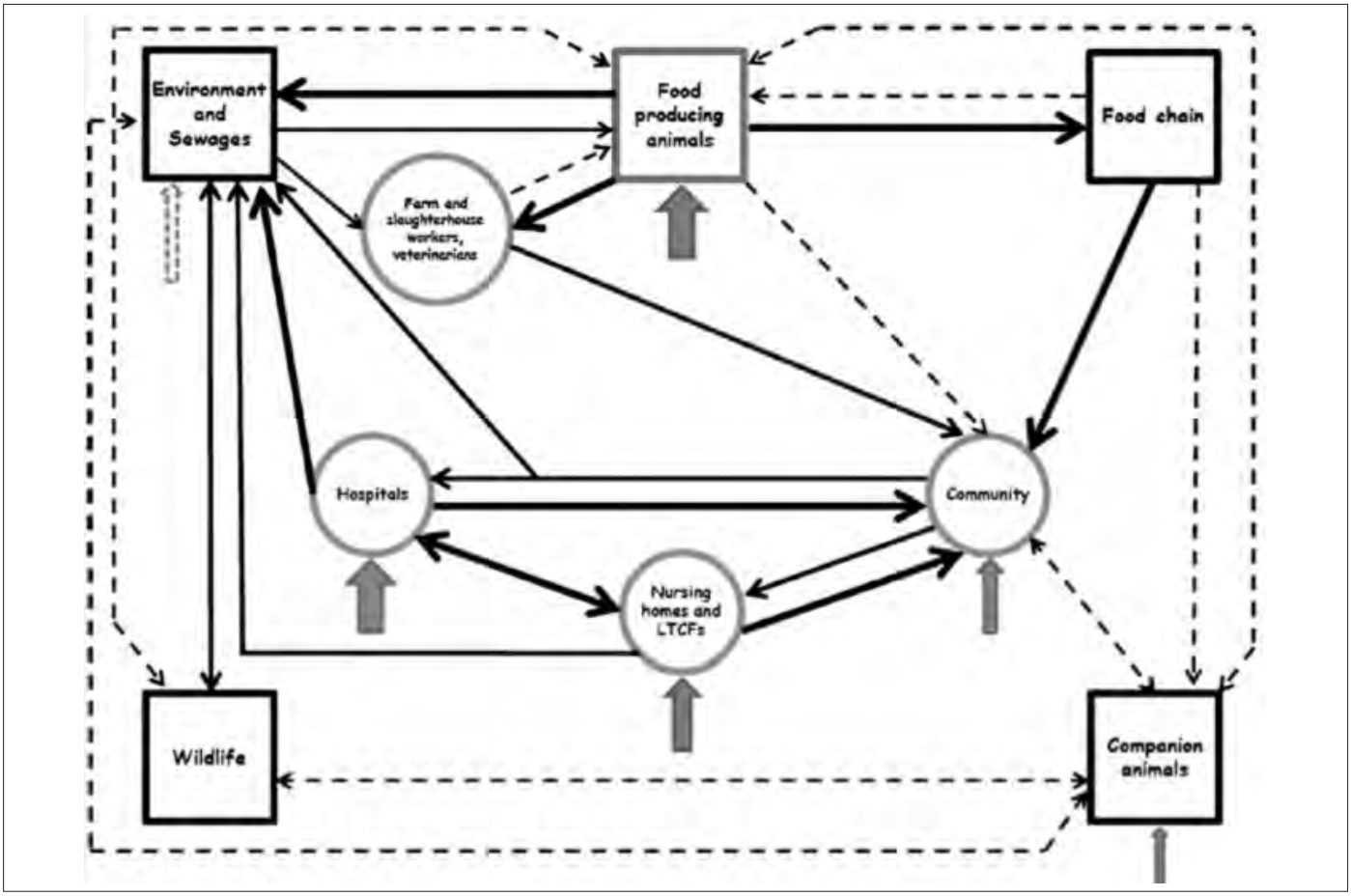
The arms race. There is a need to develop effective antibiotics in healthcare fast enough to beat growing antimicrobial resistance. The phenomenon can be compared to an arms race against multidrug-resistant organisms. Winning the fight against infectious bacteria requires staying ahead of the organisms' uncanny ability to flank our frontal assaults (Karyn Hede, 2014)[10]. This has been called the Red Queen phenomenon or the Red Queen's race taken from the story of Alice in Wonderland's encounter with the Red Queen and what she said. Table 3 shows the results of this infectious arms race since the days of penicillin.

FIGURE 1: CA-MRSA SKIN/SOFT TISSUE INFECTIONS (SSTI) IN SINGAPORE



Source: Wijaya, Limin, and Li Yang Hsu (2010)[9]

FIGURE 2. SETTINGS CONTRIBUTING TO THE POOL OF ANTIMICROBIAL RESISTANCE



Source: Seiffert et al 2013[11]

Footnote. The up arrows show the use or presence of antibiotics in each specific setting of hospital, nursing homes, and long term care facilities; as well as in the raising of food producing animals. The continuous arrows connecting the human settings (circles) and animal settings (squares) show the spread of organism between human and animal settings.

TABLE 3. AN INFECTIOUS ARMS RACE

As new antibiotics come on the market, resistance develops, but the drugs continue to be used. The growing collection of antibiotics over time is offset by the increasing resistance. Winning the fight against infectious bacteria requires staying ahead of the organisms' uncanny ability to flank our frontal assaults.

Antibiotic introduced	Antibiotic resistance appearing	Observations and actions
Penicillin – 1943	Staphylococcus resistance developed before penicillin was approved Resistance in pneumonia developed 22 years after the drug went on the market	1940 – Antibiotic resistance to penicillin was discovered before the drug went on the market 1945 – Alexander Fleming warns about the misuse of antibiotics
Tetracycline – 1950	Shigella resistance 9 years later	
Erythromycin – 1953	Staphylococcus resistance 15 years later	1959 – Discovery of the way bacteria swap resistance genes
Methicillin – 1960	Staphylococcus resistance 2 years later	
Gentamycin – 1967	Enterococcus resistance 12.5 years later	
Vancomycin – 1972	Enterococcus resistance 16 years later	1978 – First reports of drug-resistant tuberculosis in Mississippi
Ceftazidime – 1985	Enterobacteriaceae resistance 2.5 years later	
Imipenam – 1985	Enterobacteriaceae resistance 11.5 years later	1995 – Denmark starts banning the use of antibiotics to promote growth in farm animals
Levofloxacin – 1996	Pneumococcus resistance 0.5 year later (Quick onset of resistance)	
Linezolid – 2000	Staphylococcus resistance 1.5 years later (Quick onset of resistance)	2001 – The European Union establishes cooperation in surveillance, prevention and research on antibiotic resistance
Deptomycin – 2003		2006 – The European Union bans growth-promoting anti-microbials in farm animals
Ceftaroline – 2010	Staphylococcus resistance 1.5 years later (Quick onset of resistance)	2013 – US Food and Drug Administration proposes action plan on antibiotic overuse in farm animals

Source: Hede, 2014 (adapted)[10]

The empty pipeline. To add to the woes of antibiotic resistance is the paucity of new antibiotic development efforts by pharmaceutical firms is a serious challenge. A world economic forum in 2013 lamented that no new classes of antibiotics have been discovered since 1987 (WEF, 2013)[11].

(b) Antimicrobial use in farming and animal husbandry

The need to stop using antibiotics on farm animals to promote growth is now clearly lrecognised and world action is taking place (See Table 3). Essentially, antibiotics should only be used to treat infections.

(c) Microbe contaminated food distribution

Distribution of contaminated food is another driver of resistant organisms. Surveillance is all important. Thus, Our Agriculture and Food service in Singapore routinely checks for common and emerging food-borne pathogens such as Salmonella, Shigella, Vibrio, Yersinia, Clostridium, Campylobacter, Listeria, Escherichia coli O157:H7 and Vancomycin Resistant Enterococci, to minimise the transmission of antimicrobial resistance and the development of illness when food is consumed. (Agri, Food, and Veterinary Authority of Singapore, 2014)[12]

(d) Resistant organisms dissemination through international travel

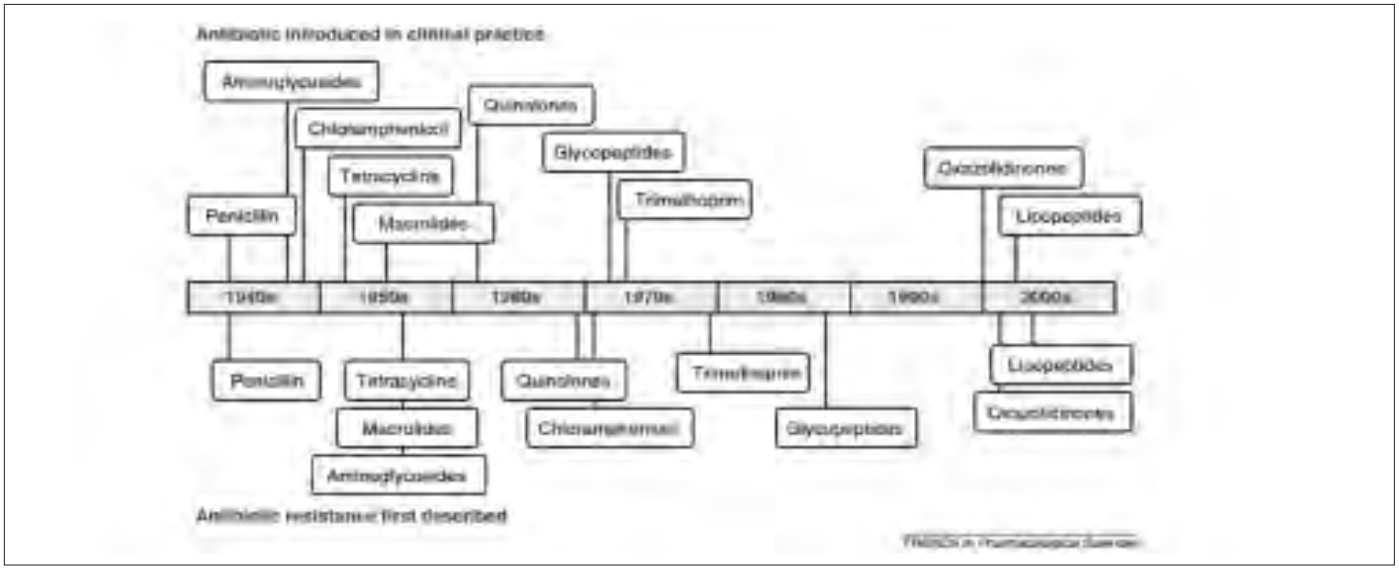
This is another driver. A study of 226 travellers by Peirano et al (Peirano et al, 2011)[13] in Canada confirmed the findings of 2 earlier Swedish studies that foreign travel, especially to the Indian subcontinent and Africa were major risks for rectal colonization with CTX-M-producing E coli through contaminated food intake and these events were most likely to contribute to the worldwide spread of these bacteria (Peirano et al, 2011)[13]. CTX-M producing E coli are bacteria that acquired beta-lactamase enzymes not by mutation but by plasmid acquisition of beta-lactamase genes from environmental bacteria (Munroz-Price, 2014)[7]. Overall, Periano et al found that 24/52 (46%) of travellers with diarrhoea returning to Canada from travel to India, Africa, or Asia were colonized with ESBL-producing organisms. (Peirano et al, 2011)[13].

INFECTION CONTROL

Principles of infection control

Infection control begins with asking the questions in Tables 4, 5 and 6. These principles have been embodied in the Ministry of Health's MDRO Infection Control Guidelines, 2013[16] .

FIGURE 3. PAUCITY OF ANTIBIOTICS ENTERING THE MARKET IN RECENT YEARS



Source: Hogberg et al, 2010[2]

TABLE 4. WHAT DRIVES ANTIMICROBIAL RESISTANCE (AMR)?

- Inadequate national commitment to a comprehensive and coordinated response, ill-defined accountability and insufficient engagement of communities.
- Weak or absent surveillance and monitoring systems.
- Inadequate systems to ensure quality and uninterrupted supply of medicines.
- Inappropriate and irrational use of medicines, including in animal husbandry.
- Poor infection prevention and control practices.
- Depleted arsenals of diagnostics, medicines and vaccines as well as insufficient research and development on new products

Source: World Health Organisation – World Health Day 7 April 2011[13]

TABLE 5. WHAT IS BLOCKING PROGRESS?

- Complex problem requiring a comprehensive response among and between Member States across different sectors
- Actions needed are clear – but there is a failure of commitment, implementation and accountability
- Preventing AMR is a "public good" which strengthens health security – but financing is insufficient

Source: World Health Organisation – World Health Day 7 April 2011[14]

TABLE 6. KEY TIERED RECOMMENDATIONS FROM THE HEALTHCARE INFECTION CONTROL PRACTICES ADVISORY COMMITTEE TO CONTAIN MULTIDRUG-RESISTANT GRAM-NEGATIVE BACTERIA

Tier 1 recommendation	Example	Examples of Tier 2 recommendation	Example
Administrative control and adherence monitoring	Obtain and document administration support	Obtain expert consultation	Use of real-time feedback to enhance adherence
Education	Focus on best prevention and practices for HCWs	Intensified educational program	Increase frequency of education and provide timely feedback
Antibiotic control program	Monitor susceptibility patterns	Target key antibiotic restrictions	Increase frequency of feedback susceptibility to clinicians
Surveillance for MDR-GNB	Estimate MDR-GNB burden stratified by units at risk	Implement Active surveillance culture	Active surveillance culture and track patients with MDR-GNB (e.g. use of line listing)
Infection control (e.g., contact isolation and hand hygiene)	Monitor adherence to basic infection control measures	Intensified program with monitoring and feedback	Use of cohort section together with real-time feedback
Environmental measure	Implement policy and monitor cleaning practice	Monitor cleaning performance using checklist or special approaches	(e.g. environmental cleaning) Use of nontouch technology (e.g. ultra-violet light, hydrogen preroxide vapour)

Source: Apisarnthanarak A et al (2013)[15]

Search & Destroy strategies

Search & Destroy strategies have been introduced in the hospitals and also in the community. The practices in Hospitals in the Eureigo MRSA elimination initiative which is a collaboration between Holland and Germany across a section of the Dutch German border. The initiative consists of isolation and screening of high risk patient groups; screening of low risk groups; strict isolation of carriers; decolonisation of carriers (Friedrich et al, 2008)[17]. Similarly there is a search and destroy initiative in the community conducted by Bartels et al (Bartels, 2010)[18]. The authors were able to eliminate the MRSA carrier state in persons in 8 households.

ANTIBIOTIC STEWARDSHIP

There is a need for an antibiotic stewardship programme to conserve existing antibiotics. The activities have been described by Dellit et al, (Dellit, 2007)[19]. These are:

- Prospective audit and feedback.
- Antibiotic restriction through (a) permission required for prescription, and (b) antibiotic cycling.
- Other elements (a) education of providers, (b) guidelines, and (c) computerised clinical decision support.

CONCLUSIONS

- Antimicrobial resistance (AMR) is now a global problem, both in the hospital and in the community.
- Key drivers of AMR need to be addressed.

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LEARNING POINTS

- **Antimicrobial resistance (AMR) is now a global problem, both in the hospital and to some extent in the community too.**
- **The key drivers for this development are medical care complexity; widespread antimicrobial use in farming and animal husbandry; contaminated food distribution; and resistant organisms dissemination through international travel.**
- **Strategies for infection control are: good understanding of what needs to be done; consistent application of infection control measures; use of "search and destroy" techniques; and effective antimicrobial stewardship.**