The impact of antimicrobial resistance on enteric infections in Vietnam

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Outline

• The impact of antimicrobial resistance
• The drivers of antimicrobial resistance
• (Fluoro)quinolone resistance in typhoid
• ESBL producers
• Resistance in commensal organisms
• Carbepenemases
• Preventative measures
Microorganisms

We live in a microbial world
From the miracle……

1928……1942……1947
......To This

Are you ready for a world without antibiotics?
Antibiotics are a bedrock of modern medicine. But in the very near future, we're going to have to learn to live without them once again. And it's going to get nasty.

Sarah Boseley
The Guardian, Thursday 12 August 2010
Article history

In less than 50 years
Impact of resistance

• 70% of neonatal sepsis cannot be treated with antibiotics recommended by WHO due to resistance. Lancet 2005.

• 67% died with resistant bacteria as compared to 26% with sensitive. BMC Pediatrics 2010.

• Antimicrobial resistance has global health implications

• Pathogenic bacteria that exhibit antimicrobial resistance are a widespread phenomenon and arguably constitute an uncontrollable global epidemic.
Occurrence of antimicrobial resistance is associated with antimicrobial usage

Data for primary blood culture isolates of *S. pneumoniae* and *E. coli*
MRSA - Methicillin resistant
Staphylococcus aureus

S. aureus is a common bacterium that can be found on the skin of many healthy people. Typically, it causes only minor infections, such as “pimples” but can also cause serious diseases (e.g., pneumonia). First report of resistance to penicillin in 1947. MRSA is also resistant to ampicillin and other penicillins, erythromycin, tetracycline.

Can only be treated with Vancomycin. Vancomycin-resistant strains have already been found and isolated.
NHS superbug death rate doubles

The number of deaths in which the superbug MRSA has been cited as a cause has doubled in four years, official statistics show.

The Office for National Statistics said in 2003 MRSA was mentioned on 955 death certificates - up from 487 in 1999.

But the figures suggested some of the rise may be down to better reporting of the bug.

Other statistics revealed the number of HIV diagnoses seems to have levelled off after a decade of increases.

However, it was the MRSA figures which have proved most controversial.

Mortality rates were highest among older people with more men than women dying.
MRSA in the UK

Deaths per year

Source: Health Protection Agency
Antimicrobial development

Lack of development of new antimicrobial drugs: a potential serious threat to public health

Antimicrobial resistance is threatening the management of infections such as pneumonia, tuberculosis, malaria, and AIDS. In the past, resistance could be handled by development of new drugs active against resistant strains. However, the pharmaceutical industry has reduced its research efforts in infections; generic harmstruck the anticipated novel therapeutics; new regulatory requirements have increased costs and setbacks in early-stage drug development. The emergence of infections—eg, pneumococcal and staphylococcal, etc.—is questioned, and, compared with other drugs, return on investment is lower for antimicrobials. To avoid a serious threat to public health, academic, biotechnology, and pharmaceutical industry, regulatory, and health-care providers must find solutions to this problem. Academia should concentrate on technologies to unlock new drug targets, and industry on drug candidates. In addition, regulatory and pharmaceutical companies should focus on new clinical trial designs, so that information on prospective efficacy is generated in fewer patients—by studying pharmacodynamics of antimicrobials in patients with defined infections.

Since the development of methicillin in the 1960s and penicillin in the 1940s, many new classes of antibacterial compounds have been developed. Drugs active against fungi, parasites, and viruses have also been introduced. Within the field of anthelmintics, the emergence of resistance has been delayed to represent a considerably distinct problem. However, until the end of the 20th century, drug companies were consistently able to develop new antibiotics with activity against the most resistant bacterial strains.

During the past 10-15 years, antibiotic-resistant organisms have steadily increased, and now present a threat to illness management. Examples include methicillin-resistant Staphylococcus aureus, penicillin-resistant Klebsiella pneumoniae, methicillin-resistant Acinetobacter baumannii, vancomycin-resistant Enterococcus faecalis, and vancomycin-resistant Enterococcus faecium. The development of multidrug-resistant strains is new and is making monitoring more substantially to the problem. For instance, penicillin-resistant Streptococcus pneumonia is not a major problem until the same organism becomes resistant to macrolides. Viruses, particularly HIV, have also developed resistance. Fungi may become resistant but, by contrast with bacteria, resistance cannot be transmitted between fungal cells. Resistance has also become a major problem in the treatment of, and prophylaxis against, malaria.

The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) has noted with great concern that we are moving towards a new era when few new antimicrobial drugs are being developed. For example, the first new antibiotic introduced during the past decade or so is under development, none has improved activity against multidrug-resistant Gram-negative pathogens, or against bacteria (table 1). As a consequence of this lack of new drugs, resistance to more dormant antimicrobials may emerge. The result could be that common infections become untreatable, and even lethal.

http://www.lancet.com

The Lancet Infectious Diseases, February 2005
Targets of Antimicrobials

**Inhibition of Cell wall synthesis**
- Penicillins
- Cephalosporins
- Carbapenems
- Daptomycin
- Glycopeptides

**DNA synthesis**
- Fluoroquinolones

**RNA synthesis**
- Rifampicin

**Protein synthesis**
- Macrolides
- Chloramphenicol
- Tetracycline
- Aminoglycosides

**Folic acid synthesis**
- Sulfonamides
- Trimethoprim

A lack of novel targets for new antimicrobials?
Impact of resistance in Vietnam

- Lack of antimicrobial legislation
- Inappropriate community usage
- Inadequate therapy or therapy not required
- Forcing a selective pressure on bacterial populations
- Failing of hospital therapy for severe infections
- Prospect of antimicrobials becoming useless....
Emergence of Antimicrobial Resistance

**Prescribers**
- lack of time
- convenience
- patient expectations
- economic incentives
- advertisement
- lack of knowledge
- no updated guidelines

**Pharmacies**
- patient expectations
- economic incentives
- advertisement
- lack of knowledge
- no law enforcement

**Inappropriate antibiotic use**

**Resistant infections**
- Treatment failures
- Increased morbidity
- Increased mortality
- Increased costs
Important drivers of AB consumption

- High out-of-pocket health expenditure
- Mostly self-medication as is cheaper and quicker
- Despite regulation, AB dispensed without prescription
- No law enforcement
Important drivers of AB consumption

• Lack of knowledge: patient, pharmacist, doctor
• Financial incentives: patient, pharmacist, doctor
• Financial incentives health facilities
• Lack of time doctor
• Lack of good diagnostics
• Frequently used for mild ARI
• Advertising
Antibiotic use pattern is some pharmacies and hospitals in Vietnam

Source: GARP report 2010
Quinolones

- Family of broad-spectrum antibiotics.
- The majority of quinolones in clinical use belong to the subset of Fluoroquinolones (FQ).
- Inhibit topoisomerases/DNA synthesis
  - DNA gyrase/topo II (gyrA and gyrB)
  - Primary target in Gram-negatives
  - Topoisomerase IV (parC and parE)
  - Primary target in Gram-positives
Resistance to Quinolones

• Mutations in DNA gyrase and topoisomerase IV subunits
• Stepwise increase in resistance results from sequential mutations
  • Quinolone resistance determining region (QRDR) is a hotspot for mutation
  • gyrA codons 83 and 87 in Salmonella
  • Amino acid substitutions within QRDR
  • Hydroxyl group hydrophobic group
  • Changes in binding site conformation and/or charge
Plasmid-mediated FQ resistance

- Plasmid-mediated FQ resistance ($qnrA, B, S$)
- Significant as previously FQ resistance only spread vertically!
- Protects DNA gyrase from ciprofloxacin (CIP) inhibition.
- Nalidixic acid resistance, reduced susceptibility to FQ’s
- Association with ESBL producers ($qnrA, B$).
Fluoroquinolones in Typhoid in Vietnam
Fluoroquinolones in Typhoid
Clinical typhoid response

<table>
<thead>
<tr>
<th>Breakpoint value</th>
<th>Number successfully treated/total number treated (%)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ofloxacin MIC &lt; 0.06 µg/mL</td>
<td>148/152 (97.4 %) 144</td>
<td>5.47 (1.95-21.20)</td>
</tr>
<tr>
<td>Ofloxacin MIC ≥ 0.06 µg/mL</td>
<td>338/388 (87.1 %) 314</td>
<td></td>
</tr>
<tr>
<td>Ofloxacin MIC &lt; 0.12 µg/mL</td>
<td>406/423 (96.0 %) 80</td>
<td>11.05 (5.71-21.88)</td>
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<tr>
<td>Ofloxacin MIC ≥ 0.12 µg/mL</td>
<td>117 (68.4 %)</td>
<td></td>
</tr>
<tr>
<td>Ofloxacin MIC &lt; 0.25 µg/mL</td>
<td>417/435 (95.9 %) 69</td>
<td>12.09 (6.24-23.81)</td>
</tr>
<tr>
<td>Ofloxacin MIC ≥ 0.25 µg/mL</td>
<td>105 (65.7 %)</td>
<td></td>
</tr>
<tr>
<td>Ofloxacin MIC &lt; 0.50 µg/mL</td>
<td>432/455 (94.9 %) 54</td>
<td>10.78 (5.6-20.77)</td>
</tr>
<tr>
<td>Ofloxacin MIC ≥ 0.50 µg/mL</td>
<td>85 (63.5 %)</td>
<td></td>
</tr>
<tr>
<td>Ofloxacin MIC &lt; 1.00 µg/mL</td>
<td>466/502 (92.8 %) 20</td>
<td>11.65 (5.26-25.36)</td>
</tr>
<tr>
<td>Ofloxacin MIC ≥ 1.00 µg/mL</td>
<td>38 (52.6 %)</td>
<td></td>
</tr>
<tr>
<td>Nalidixic acid susceptible</td>
<td>417/434 (96.1 %) 69</td>
<td>13.15 (6.74-26.20)</td>
</tr>
<tr>
<td>Nalidixic acid resistant</td>
<td>106 (65.1 %)</td>
<td></td>
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</tbody>
</table>
Cephalosporins

1\textsuperscript{st} Generation
e.g. Cephalexin

2\textsuperscript{nd} Generation
e.g. Cefuroxime, cefoxitin

3\textsuperscript{rd} Generation
e.g. Cefotaxime, cefpodoxime, ceftriaxone, cefoperazone, ceftazidime

4\textsuperscript{th} Generation
Cefopime, Cefquinome
What Are ESBLs?

• Molecular class A or D b-lactamases
• Hydrolyse oxyiminio cephalosporins
• Have an active site serine
• Generally inhibited by b-lactamase inhibitors (clavulanic acid, sulbactam, tazobactam)
• Most often associated with *E.coli* and *Klebsiella pneumoniae* but can be produced by other enteric bacilli
• >170 types
**Extended-spectrum β-lactamases**

- Plasmid-mediated enzymes found in *Enterobacteriaceae*
- Hydrolyze 3rd generation cephalosporins
  - But not carbapenems or cephemycins (cefoxitin)
- Encoded on large plasmids (>100Kb)
  - Multi-drug resistance
- Mostly Ambler class A
  - TEM, SHV, CTX-M
- More rarely
  - Ambler Class D
  - OXA (can also be resistant to cefipime)
  - VEB, PER (resistant to β-lactamase inhibitors)
Laboratory Detection

• Increased global reporting of resistant Enterobacteriaceae
  – AmpC
  – ESBL
• Many labs still fail to routinely test for ESBLs
• No methodology without its problems
ESBL detection

- Double disc synergy
- Combination disc test
- E-test

>5mm = ESBL

Disc with cephalosporin and clavulanic acid

Disc with cephalosporin alone

3-fold reduction of MIC=ESBL
Laboratory detection

• Initial decreased susceptibility to oxyamino cephalosporins
  • Will not detect all ESBLs (TEM7, TEM12, SHV2)
• Further phenotypic (and genotypic) testing of isolates for ESBL production
• Testing with ceftazidime alone may miss CTX-M isolates
• Cefoxitin susceptibility will exclude the presence of AmpC-type beta-lactamase
Extended-spectrum $\beta$-lactamases in *Shigella* in Ho Chi Minh City
# Resistance in commensal enteric bacteria

<table>
<thead>
<tr>
<th>Antimicrobial tested</th>
<th>AMP</th>
<th>GEN</th>
<th>CHL</th>
<th>TET</th>
<th>SXT</th>
<th>CRO</th>
<th>FEP</th>
<th>KAN</th>
<th>TIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of resistant organisms (from 32) [n (%)]</td>
<td>23 (71.9)</td>
<td>21 (65.6)</td>
<td>18 (56.3)</td>
<td>15 (46.9)</td>
<td>15 (46.9)</td>
<td>6 (18.8)</td>
<td>5 (15.6)</td>
<td>2 (6.3)</td>
<td>2 (6.3)</td>
</tr>
<tr>
<td>Resistant <em>E. coli</em> (from 17) [n(%)]</td>
<td>13 (76.5)</td>
<td>9 (52.9)</td>
<td>13 (76.5)</td>
<td>8 (47.1)</td>
<td>8 (47.1)</td>
<td>1 (5.9)</td>
<td>1 (5.9)</td>
<td>2 (11.8)</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Resistant <em>K. pneumoniae</em> (from 15) [n(%)]</td>
<td>10 (66.7)</td>
<td>13 (86.7)</td>
<td>4 (26.7)</td>
<td>7 (46.7)</td>
<td>6 (40.0)</td>
<td>5 (33.3)</td>
<td>4 (26.7)</td>
<td>1 (6.7)</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td><em>p value a</em></td>
<td>0.6989</td>
<td>0.0605</td>
<td>0.0118*</td>
<td>1</td>
<td>0.7345</td>
<td>0.0755</td>
<td>0.1609</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Resistant organisms community (from 21) [n(%)]</td>
<td>15 (68.2)</td>
<td>11 (50.0)</td>
<td>17 (77.3)</td>
<td>12 (54.5)</td>
<td>11 (50.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>2 (9.1)</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Resistant organisms hospital (from 11) [n(%)]</td>
<td>8 (72.7)</td>
<td>10 (90.9)</td>
<td>1 (9.1)</td>
<td>3 (27.3)</td>
<td>4 (36.4)</td>
<td>6 (54.5)</td>
<td>5 (45.5)</td>
<td>0 (0.0)</td>
<td>1 (9.1)</td>
</tr>
<tr>
<td><em>p value b</em></td>
<td>1</td>
<td>0.0273*</td>
<td>0.0005*</td>
<td>0.2659</td>
<td>0.712</td>
<td>0.0004*</td>
<td>0.0019*</td>
<td>0.5417</td>
<td>1</td>
</tr>
</tbody>
</table>
Carbapenemases

- **Class A**
  - Chromosomally-encoded IMI, NMC-A and SME
  - Plasmid-encoded KPC and GES
  - Clavulanic acid-inhibited
- **Class B**
  - Metallo-β-lactamases (inhibited by EDTA)
  - IMP, VIM, NDM-1
  - Integron encoded (transposon and plasmid)
- **Class D**
  - OXA types (mostly *Acinetobacter baumannii*)
  - Sensitive to β-lactamase inhibitors
Figure 1: Numbers of carbapenemase-producing Enterobacteriaceae referred from UK laboratories to the UK Health Protection Agency’s national reference laboratory from 2003 to 2009
The predominant gene is bla_{NDM-1}, which was first identified in 2008. The other group includes diverse producers of KPC, OXA-48, IMP, and VIM enzymes.
Figure 2: 90% minimum inhibitory concentration (MIC$_{90}$) for Enterobacteriaceae from Chennai and Haryana, India, and the UK
Carbapenem resistance *P. Aeruginosa*

Cause of hospital pneumonia

(133 strains isolated in 6 hospitals - 2008)

- Emerging carbapenem resistance

Source: Dr Doan Mai Phuong, Bach Mai Hospital
Tools to control use and resistance

Surveillance
- Decrease the need for antimicrobials
- Reduce disease incidence
- Prevent the spread of bacteria

Monitor:
- Resistance patterns
- Antimicrobial usage

Use antimicrobials appropriately
- Improve diagnostics and usage

Non medical usage
- Environment
- Food, plants
- Etc.

Coordinate National activities

Knowledge
- Education, information research

International collaboration
What surveillance can be done now?

• **Antibiotic consumption surveillance**
  – main driving force for development of resistance
  – Surveillance provides data to implement interventions
  – Hospital, community, agriculture

• **Antibiotic resistance surveillance**
  – Monitor of prescribing practices and interventions
  – Early warning of important resistance trends
  – Helps prescribers to give the right antibiotic
  – Hospital, community, agriculture
Proposals to Combat Antimicrobial Resistance

- Speed development of new antibiotics
- Develop alternatives
- Track resistance data nationwide
- Restrict antimicrobial use
- Directly observe dosing (TB)
- Use more narrow spectrum antibiotics
- Use antimicrobial cocktails
In addition

- Education
- Guidelines and Pathways
- Antimicrobial cycling
- Antimicrobial order forms
- Combination therapy
- De-escalation of therapy
- Dose Optimisation
- IV/Oral
- Controlling community usage
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