Current Epidemiology of Antimicrobial Resistance in South and SouthEast Asia

David Tribble, MD, DrPH
Professor and Science Director
Infectious Disease Clinical Research Program,
Department of Preventive Medicine & Biostatistics
Uniformed Services University of the Health Sciences

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Antibiotics: Resistance Movements
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Conflict of Interest/Disclosure/Disclaimer

Conflict of Interest: None
Disclosures: None Declared
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Objectives

- To review community- and hospital-based antibiotic resistance surveillance data from South/SE Asia
- To provide an overview of risk of antimicrobial resistance (AMR) in South/SE Asia for pathogens that are likely to affect travelers

AMR Focus for Talk

- Antimicrobial resistance covers reduced microbial susceptibility to antimicrobial drugs (such as antibiotics, antifungals, antivirals, antiparasitic agents)
- Pathogens not covered
  - Mycobacteria (TB – MDR/XDR)
  - Rickettsia (e.g. doxy resistance in scrub typhus)
  - Fungi (e.g. Candida auris)
  - Viruses (e.g HIV, Influenza)
  - Parasites (e.g. Plasmodium falciparum with emergent artemisin resistance)
- Focus for talk
  - Bacteria (hospital and community common pathogens)

Why South Asia & SE Asia?

- Frequently an epicenter for AMR emergence
- International travel and trade – global crossroads
- Regional considerations for travel medicine practice

Metallo-β-lactamases (MBLs), Zn-requiring for β-lactam hydrolysis-producing Enterobacteriaceae
- Discovery (2008) of an ST14 K. pneumoniae with a new MBL gene, blaNDM-1, from a Swedish patient with a UTI who received healthcare in New Delhi, India.
- Global dissemination of NDM MBLs with rapid gene transfer between species – most commonly Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, and gram-negative non-fermenters, Pseudomonas spp. and Acinetobacter baumannii
- Endemic regions (Indian subcontinent), NDM-type MBLs the predominant carbapenemase.
- Most other regions (except Middle East and Balkan countries), NDM-type MBLs sporadic
- Asian continent - major reservoir of NDM producers, with around 58% abundance of NDM-1 variant distributed mostly in China and India
- NDM-1 hydrolyzes a wide range of β-lactam antibiotics, including carbapenems

Khan et al. BMC Microbiology 2017
Logan and Weinstein. JID 2017
Key drivers in the spread and emergence of AMR

Progression of international travels per year, in million (source: UNWTO)

 Concurrent human exposures and contributions to environmental reservoirs of antibiotic-resistant bacteria, antibiotic residues, and resistance genes in lower and middle-income countries

• Nadimpalli et al. CID 2018:66

Networks contributing to surveillance efforts for AMR in Southeast Asia

- Global Antimicrobial Resistance Surveillance System (GLASS; WHO)
- VINARES: Vietnam Resistance
- Asia WT-MOPs: Welcome Trust Major Overseas Programmes
- GAR: Global Antimicrobial Resistance Partnership/2008
- PulseNet Asia Pacific (2000)
- AMRCP: Thailand AMR Containment and Prevention

Risk Assessment for Antibiotic Resistance in SE Asia

Rationale: Weak surveillance systems with incomplete data limits estimation of AMR in the WHO South East Asia region

Method: qualitative risk assessment (combined hazard, exposure, and context assessment) to evaluate relative effects of main determinants leading to risk estimate of AMR emergence and spread.

Likelihood of occurrence (risk) of each event (acquisition, selection, AMR transmission) rated as follows:

- Negligible—the event occurs under exceptional circumstances
- Low—the event occurs some of the time
- Moderate—the event occurs regularly
- High—the event occurs in most circumstances

Clinically Relevant and Prevalent AMR Threats in South/SE Asia

- Community pathogens:
  - Penicillin- or macrolide-resistant Streptococcus pneumoniae
  - Methicillin-resistant Staphylococcus aureus (MRSA)
  - Multidrug-resistant (MDR) enteric pathogens
  - Neisseria gonorrhoeae
  - Salmonella spp.

- Hospital-associated pathogens:
  - MRSA or glycopeptide-resistant S. aureus (vancomycin-intermediate or resistant S. aureus, VISA or VRSA)
  - Glycopeptide-resistant enterococci (vancomycin-resistant enterococci, VRE)
  - Extended-spectrum beta-lactamase (ESBL)-producing and carbapenem-resistant (CRE) Enterobacteriaceae
  - MDR nonfermenters (such as Pseudomonas and Acinetobacter spp.)

Chereau and colleagues, BMJ 358:Suppl1; 2017

Chool-in Kang and Jae-Hoon Song, Infect Chemother 2013

Open Forum Infectious Diseases® 2019;6(S1):S23–S33
Clinically Relevant and Prevalent AMR Threats in South/SE Asia

Community pathogens
- Penicillin- or macrolide-resistant Streptococcus pneumoniae
  - Resistance rates: EMYCIN > 70%, PCN 0.7% (nonmeningeal) 207.5% (meningeal)
  - India report (Singh, Vaccine 2017): resistance rates: TMP/SMX (31%), EMYCIN (29%), PCN (10%), chloramphenicol (6%), LEVO (6%), cefotaxime (4%), and VANC (none)
- Methicillin-resistant Staphylococcus aureus (MRSA)
  - MRSA accounted for 26% of community-associated (CA) S. aureus infections and 67% of healthcare-associated (HA) [ANSORP]
- Multidrug-resistant (MDR) enteric pathogens
  - Diarrheagenic E. coli (mainly ETEC/EAEC)
  - Campylobacter jejuni/coli
  - Shigella spp.
  - Nontyphoidal Salmonella spp.
- Neisseria gonorrheae
  - Gonococcal urethritis highly prevalent; increasingly resistant
  - Enhanced Gonococcal Antimicrobial Surveillance Programme (EGASP; Bangkok) 2015-16: all isolates susceptible cefixime/ceftriaxone; MICs < 2 μg/mL AZM; FQ 92% resistant
- Salmonella typhi/paratyphi (Typhoid fever)
  - Indian subcontinent – high proportion of global burden
  - Emergent AMR also common – older agents → FQ → 3rd gen Cephalosporins (still uncommon; with ESBLs) → AZM (primarily case reports)
  - Emergent, spreading internationally, genotype H58 with origin in South Asia associated with MDR and high level FQR

Hospital-associated pathogens
- MRSA or glycopeptide-resistant S. aureus (vancomycin-intermediate or resistant S. aureus, VISA or VRSA)
- Glycopeptide-resistant enterococci (vancomycin-resistant enterococci, VRE)
- Extended-spectrum beta-lactamase (ESBL)-producing and carbapenem-resistant (CRE) Enterobacteriaceae (such as Klebsiella pneumoniae, E. coli, and Enterobacter spp.)
- MDR nonfermenters (such as Pseudomonas and Acinetobacter spp.)

Prevalence of ESBL-producers among E. coli and K. pneumoniae isolates causing urinary tract infections by country in the Asia-Pacific region

Antibiotic Susceptibility Profile (% resistance) in Priority Healthcare-associated GN Bacteria in India

<table>
<thead>
<tr>
<th></th>
<th>Cephalosporin</th>
<th>Carbapenem</th>
<th>Colistin</th>
</tr>
</thead>
<tbody>
<tr>
<td>F. coli</td>
<td>Up to 70</td>
<td>Up to 10</td>
<td>8</td>
</tr>
<tr>
<td>K. pneumoniae</td>
<td>Up to 60</td>
<td>Up to 40</td>
<td>37</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>Up to 25</td>
<td>Up to 25</td>
<td>&lt;5</td>
</tr>
<tr>
<td>A. baumannii</td>
<td>Up to 70</td>
<td>Up to 70</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

Veeraraghavan et al. Indian J Med Microbiol 2018
To provide an overview of risk of antimicrobial resistance (AMR) in South/SE Asia for pathogens that are likely to affect travelers

- Several clinical syndromes/diseases associated with specific bacterial pathogens complicated by current and/or emerging AMR
- Of these, which ones are ‘likely to affect travelers’
  - Traveler’s diarrhea
  - URI/LRI
  - Typhoid fever
  - Very likely to occur with unknown ‘affect’ on the traveler
    - Asymptomatic colonization in gut flora
    - Risk for UTI
    - Risk of transmission

Acquisition rates of multidrug-resistant Enterobacteriaceae (MRE) depending on the destination of travel

Estimated rates of ESBL producers among E. coli clinical isolates

- CTX-M group ESBLs are the most common ESBLs globally
- Strong association between E. coli sequence type (ST) 131 and production of CTX-M group ESBL

Can epidemiological surveys documenting emerging regional resistance be extrapolated to inform treatment recommendations?

- Interpretative criteria for susceptibility testing
  - Clinical breakpoints – what defines S, I, R
  - Monitoring (epidemiological cut-off values)

- Needed for clinical breakpoint development
  - Antimicrobial susceptibility data generated by standardized in vitro susceptibility testing
  - Pharmacological parameters
  - Clinical outcome studies "often the missing piece"

Evolution of antimicrobial resistance in enteroaggregative E. coli and enterotoxigenic E. coli causing traveler’s diarrhea

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>EAEC Period 1</th>
<th>EAEC Period 2</th>
<th>ETEC Period 1</th>
<th>ETEC Period 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>52 (256)</td>
<td>62 (128)</td>
<td>43 (4)</td>
<td>53 (32)</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>64 (256)</td>
<td>76 (256)</td>
<td>57 (128)</td>
<td>59 (128)</td>
</tr>
<tr>
<td>TMP/SMX</td>
<td>48 (0.75)</td>
<td>56 (128)</td>
<td>50 (32)</td>
<td>67 (64)*</td>
</tr>
<tr>
<td>Nalidixic acid</td>
<td>6 (4)</td>
<td>15 (1)</td>
<td>6 (3)</td>
<td>22 (0.5)*</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>2 (0.012)</td>
<td>4 (0.25)</td>
<td>1 (0.012)</td>
<td>8 (0.5)*</td>
</tr>
</tbody>
</table>

** High percentage of resistance to quinolones in ETEC and EAEC isolated from travelers to North Africa and India


Emergence of Resistance to Quinolones and β-Lactam Antibiotics in Enterotoaggregative and Enterotoxigenic Escherichia coli Causing Traveler’s Diarrhea

- Rifaximin is still active against EAEC and ETEC strains (no strains had MIC > 32 g/ml

Guiral E et al. AAC 2019 Volume 63 Issue 2
**Diarrheagenic Escherichia coli (ETEC, EAEC) – selected references**

- Enterotoxigenic E. coli (ETEC)
  - ETEC resistance to nalidixic acid (NA) reported from Indian subcontinent (Vila J, 2000)
  - Quinolone Resistance in Enterotoxigenic Escherichia coli Causing Diarrhea in Travelers to India in Comparison with Other Geographical Areas
- Enteraggregative E. coli (EAEC)
  - Hebbelstrup Jensen B et al. Clin Microbiol Rev 2014. EAEC - increasing rates of MDR (defined as the ‘older’ agents) reported in the range of 75%; cipro resistance reported as high as 65% in surveys in India and Iran (in children under 5 y/olds)

**Continued emergence of resistant Shigella**

- Case series and regional reports
  - Rise in clinical resistance, other MDR, to third-line antibiotics (e.g., fluoroquinolones and sulphonamides) and alternative agents (e.g., third-generation cephalosporins) as well as ESBL production has been reported in Shigella spp. and Salmonella spp. diphtheriae patients
  - Goel N et al. Indian J Pediatr 2013 – Emergence of Ceftriaxone resistant S. flexneri – life-threatening infection in child with a MDR isolate (resistant to Amp, CIP, TMY/SMX, TCM; Ceftriaxone; sensitive to carbapenem)
  - Documented Shigella resistance rates in India as high as 75% nalidixic acid; 69% AMP; 72% TMY/SMX; 48% CIP; 19% ceftriaxone/sulphonamide, and also increase in AZM resistance

**Proportion of FoodNet Campylobacter Cases and Antimicrobial Resistant Isolates by Region: 2005–2011**

<table>
<thead>
<tr>
<th>Region</th>
<th>Total Isolates</th>
<th>Quinolone-Resistant Isolates</th>
<th>Macrolide-Resistant Isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia</td>
<td>206 (7.2%)</td>
<td>14 (20.2%)</td>
<td>9 (1.9%)</td>
</tr>
<tr>
<td>Australia/New Zealand</td>
<td>88 (31.2%)</td>
<td>50 (68.0%)</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>South America</td>
<td>80 (12.5%)</td>
<td>15 (18.8%)</td>
<td>2 (2.5%)</td>
</tr>
<tr>
<td>Mexico</td>
<td>50 (12.5%)</td>
<td>14 (28.0%)</td>
<td>1 (2.0%)</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>69 (1.0%)</td>
<td>5 (7.3%)</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td>Western Europe</td>
<td>60 (1.0%)</td>
<td>20 (33.3%)</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>North America</td>
<td>87 (1.0%)</td>
<td>7 (8.1%)</td>
<td>2 (2.3%)</td>
</tr>
<tr>
<td>Total</td>
<td>3234</td>
<td>198 (6.1%)</td>
<td>39 (1.2%)</td>
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*Of 841 cases with known international travel destination, 277 reported multiple destinations.
*Numbers for Asia exclude Ohio. Numbers for Central America exclude Mexico.
*There were 135 isolates from cases reporting Central America as their destination and 138 isolates from cases reporting Western Europe submitted for sulphonamide resistance testing.

**Proposed Strategies to Address One Health Challenges Related to Antibiotic Misuse in Lower- and Middle-Income Countries**

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<td>Target antibacterial therapy</td>
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<td>93 (levofloxacin 50%)</td>
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**Emerging and well established antibiotic resistance among Campylobacter jejuni/coli**

- Since late 1980’s an increasing trend in the proportion of FQ-resistant strains of members of the genus Campylobacter isolated from both clinical samples and livestock, where FQs (particularly enrofloxacin) are frequently used to treat animals in intensive production
- C. coli resistance to FQs as well as AZM more common compared with C. jejuni
- AMR trend is also observed in isolates from livestock, especially chickens, which are a major source of human disease
- Foreign travel, particularly to SE Asia, major risk factor for infection with FQ-resistant Campylobacter

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May 2015 World Health Assembly adopted a WHO global action plan on AMR

Global Action Plan on AMR - Objectives

- to improve awareness and understanding of antimicrobial resistance;
- to strengthen knowledge through surveillance and research;
- to reduce the incidence of infection;
- to optimize the use of antimicrobial agents; and
- develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines diagnostic tools, vaccines and other interventions.