National Antimicrobial Resistance Database: Building national response

Dr Kamini Walia
Indian Council of Medical Research
Indian Council of Medical Research (ICMR)

The apex body in India for the formulation, coordination and promotion of biomedical research under Department of Health Research, Ministry of Health and Family Welfare, Government of India.

To undertake and support basic, epidemiological, applied and operational research in the areas of national public health importance using tools including those of modern biology.

Intramural research is carried out through the Council's theme oriented 33 permanent research institutes/centers and including 6 regional centers addressing to regional health problems.

Extramural research is done through center for advanced research, task force projects, ad hoc research schemes and fellowships in different universities, medical colleges in the country.
Why are resistance rates so high in India?
Infectious Diseases in India

- Huge burden of infectious diseases
  - Malaria, TB, HIV/AIDS, vector borne diseases, Influenza, other outbreaks
    - Diarrhea, pneumonia
  - Sanitation conditions, malnutrition
  - Close animal human interface

WHO Workshop on AMR: Vellore July 28 - August 1, 2014
Management of infectious diseases is often mishandled

- India has one doctor per 1700 patients
- 70% of health care is dispensed through private sector
- Practitioners of alternate systems
- Wide urban-rural gap in the availability of medical services
- Infectious disease specialists/guidelines missing link
- Diagnostics under recognized underexploited tool for resistance containment
Resistance is accelerated through inappropriate use of antimicrobials

- Absence/ nonadherence to Standard treatment guidelines
- Drugs available without prescription
- Poor quality drugs
- Improper prescription
- Poor compliance
- Irrational self-administration

Antimicrobial resistance
Antibiotic overuse

- $12.4 billion pharmaceutical industry
- Regulations over sale of antibiotics
- Over the counter availability of antibiotics
- Use of antibiotics in livestock, poultry and agriculture

Evolution of antibiotic resistance is a consequence of selective pressure
ANTIMICROBIAL RESISTANCE
MDR-TB in new smear positive cases is ≤3 % and 12-17% in smear positive previously treated cases
- **Malaria**: Chloroquine failure rate 35%, Sulfa-pyramethamine 26%
- **Gonorrhoea** widely resistant to penicillin & fluoroquinolones, increasing against cephalosporins
- Prevalence of **MRSA** approx 20-40%
- **Enterobacteriaceae**: ESBLs - prevalence of 30-65%, 80% in ICUs
- Infections with drug resistant **Acinetobacter baumanii** and **Pseudomonas sps.** In ICUs, hospital settings

Multi-drug resistant and extensively drug resistant TB cases in India: ICMR consultation, 2012
*Sethi et al 2006 Deshpande et al 2011, Thoral et al 2011*
Role for antibiotics not limited to infectious diseases

- VAPs, CAIs, CLBSIs
- Knee and Hip replacements
- Transplants
- Cancer treatments
- Caesarean sections
Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study


Summary

Background Gram-negative Enterobacteriaceae with resistance to carbapenem conferred by New Delhi metallo-β-lactamase 1 (NDM-1) are potentially a major global health problem. We investigated the prevalence of NDM-1, in

Lancet Infect Dis 2010; 10: 597-602
Need for national response to Antimicrobial resistance

- Most of available data from small studies in labs or medical institutes
- Methodology, uniformity issues
- Not representative of trends and patterns in general population as data from hospital patients and very sick patients
- Need for nationwide surveillance system
**AMR activities in ICMR**

- Strengthening surveillance research in AMR
- Stewardship activities:
  - Treatment guidelines
  - Infection control guidelines
  - Understanding the Prescription practices
  - Addressing the missing infectious disease link
Antimicrobial Research and Surveillance Network at ICMR

- Nodal centres are focal points for six pathogenic groups:
  - *Enterobacteriaceae / sepsis* (PGIMER)
  - Gram negative non-fermenters (CMC)
  - Enteric fever organisms (AIIMS)
  - Diarrhoeagenic organisms (CMC)
  - MRSA, Enterococcus (JIPMER)
  - Fungal pathogens (PGIMER)
- Data management unit in Bioinformatics Center, ICMR Hqs
- 15 Regional Centres (RC) proposed
- Standardisation & Uniformity
  - Standard Operating Procedures (SOPs) Bacteriology, Mycology
- Training
- External Quality Assurance
AMR Surveillance Network
Roles and responsibilities

- Nodal Centres
  - Phenotypic tests
  - Genotypic tests for mechanism of resistance and clonality of isolates
  - Repository of relevant Isolates
  - Act as training hubs for other hospitals
  - Data validation
  - Communicate Nationally, Internationally
Regional centers: ROLE

- Defined geographical area of responsibility
- Receive training from NCs & become hub of training for its specified region
- Isolate, identify, AMST, store microbes
- Transport predefined representative DR, DS isolates to NCs
- Over time period, take over part or full responsibilities of NCs
- In tune with NCs, develop AMSP for region
**Salmonella typhi**

- *S. typhi* multidrug resistance (MDR): 100% sensitive to ampicillin, chloramphenicol and cotrimoxazole, cefixime
- High resistance to FQ, Ciprofloxacin in *S. typhi* is increasingly reported
Shigella spp

- High resistance to nalidixic acid
- 50% R to norfloxacin and ampicillin
- Association of ESBL genes with qnr genes – rare among Indian isolates
- \( \text{bla}_{\text{CTX-M-15}} \) occurrence in *Shigella spp* increases the threat for spread of cephalosporin resistance among Enterobacteriaceae

<table>
<thead>
<tr>
<th>Organism</th>
<th>Genes for sulfonamide resistance</th>
<th>Genes for β – lactam resistance</th>
<th>Genes for quinolone resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 31)</td>
<td>dhfr1a</td>
<td>Sul II</td>
<td>( \text{bla}_{\text{OXA}} )</td>
</tr>
<tr>
<td>S. flexneri (n = 22)</td>
<td>22</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>S. sonnei (n = 6)</td>
<td>6</td>
<td>5</td>
<td>-</td>
</tr>
</tbody>
</table>
Until 2005, resistance to carbapenem in Enterobacteriaceae had not been observed.

2012: it is estimated that 5% of *E. coli* and up to 40% of *Klebsiella spp* resistant to carbapenem.

A higher percent of susceptibility to colistin (>90%), tigecycline (up to 59%) followed by aztreonam and amikacin.

*Antimicrobial resistance global report on surveillance, WHO - 2014*
Klebsiella spp. and E. coli cause most of infections

- 100% sensitive to colistin followed by imipenem and meropenem (60%)
- Averages hide the variations
- Carbapenem resistance in E. coli NDM, Oxa-48, NDM+Oxa-48 at 58%, 18% and 14% respectively.
- Klebsiella Pneumoniae, Oxa-48 (55%), NDM producers (24%); co-producers of NDM+Oxa-48 (16%)
- Oxa-48 like genes positives from Klebsiella Pneumoniae were found to be Oxa-181 variant.
• Acinetobacter species 60% isolates, Pseudomonas species 24%, Strophomonas species 4%, Burkholderia species 4%.
• A baumanii isolates showed maximum susceptibility was to colistin (99%) followed by imipenem (53%) and meropenem (53%).
• Susceptibility for amikacin has increased by 23% from 2014-2015

• All isolates of P aeruginosa were susceptible to colistin, followed by imipenem (85%), amikacin (80%), ciprofloxacin (80%), piperacillin-tazobactam (58%) and meropenem (50%)
• Almost all antibiotics seems to have >70% susceptibility
### No. of genes identified in CRO multiplex PCR reaction

<table>
<thead>
<tr>
<th>ORGANISM</th>
<th>NC</th>
<th>‘n’</th>
<th>SPM</th>
<th>IMP</th>
<th>VIM</th>
<th>NDM</th>
<th>OXA-23</th>
<th>KPC</th>
<th>VEB</th>
<th>PER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P. aeruginosa</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>CMC</td>
<td>55</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIIMS</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>JIPMER</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>Acinetobacter sp.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMC</td>
<td>30</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>7</td>
<td>51</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>AIIMS</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>JIPMER</td>
<td>30</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>23</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>14</td>
</tr>
</tbody>
</table>

- **VEB** and **TEM** is prevalent in *Pseudomonas spp.*, whereas **PER**, **Oxa 23** is more prevalent in *Acinetobacter spp*
- **VIM** and **NDM** continue to be prevalent among CRO’s
### Molecular tests 2015

<table>
<thead>
<tr>
<th>Centre</th>
<th>Organism</th>
<th>ESBL &amp; CRO</th>
<th>CRO</th>
<th>OXA23,24 MULTIPLEX</th>
<th>OXA-51</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SHV</td>
<td>TEM</td>
<td>VEB</td>
<td>PER</td>
</tr>
<tr>
<td>CMC</td>
<td>Ps. aeruginosa (n = 30)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>JIPMER</td>
<td>Ps. aeruginosa (n = 30)</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>A</td>
<td>Acinetobacter (n = 20)</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>10</td>
</tr>
</tbody>
</table>

Multiple resistance coding gene presence *Pseudomonas aeruginosa* and *Acinetobacter baumannii*
- the reason for increased MIC
- resulting in requirement of combination therapy with high dose and extended duration.
Percentage resistance of *S. aureus* isolates for all centres

<table>
<thead>
<tr>
<th>Drug</th>
<th>Resistance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEN</td>
<td>89.2</td>
</tr>
<tr>
<td>CIP</td>
<td>63.3</td>
</tr>
<tr>
<td>TET</td>
<td>36.9</td>
</tr>
<tr>
<td>FOX</td>
<td>35.7</td>
</tr>
<tr>
<td>VAN</td>
<td>17.8</td>
</tr>
<tr>
<td>GEN</td>
<td>50.4</td>
</tr>
<tr>
<td>ERY</td>
<td>25</td>
</tr>
<tr>
<td>CLI</td>
<td>0.2</td>
</tr>
<tr>
<td>LNZ</td>
<td>0</td>
</tr>
<tr>
<td>TEC</td>
<td>1.9</td>
</tr>
<tr>
<td>MUP</td>
<td></td>
</tr>
<tr>
<td>SXT</td>
<td>45.7</td>
</tr>
</tbody>
</table>
Percentage resistance of CoNS isolates for all centres
Graph showing the resistance of all isolates of *Enterococcus faecium* for all centres (% Resistance)

Increasing glycopeptide resistance in *Enterococci* (e.g. VRE) and increasing mupirocin resistance *in S. aureus* is causing concern
### Antimicrobial Surveillance and Research network

<table>
<thead>
<tr>
<th></th>
<th>PGIMER</th>
<th>CMC Vellore</th>
<th>JIPMER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>% sensitivity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>&lt;10</td>
<td>30</td>
<td>19</td>
</tr>
<tr>
<td>Cef-sulbatam</td>
<td>50</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>Amikacin</td>
<td>78</td>
<td>&gt;90</td>
<td>83</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>8</td>
<td>25</td>
<td>30</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>PGIMER</th>
<th>CMC Vellore</th>
<th>JIPMER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>% sensitivity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>&lt;10</td>
<td>40</td>
<td>6</td>
</tr>
<tr>
<td>Cef-sulbatam</td>
<td>20</td>
<td>60</td>
<td>32</td>
</tr>
<tr>
<td>Amikacin</td>
<td>&lt;40</td>
<td>60</td>
<td>42</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>8</td>
<td>40</td>
<td>8</td>
</tr>
<tr>
<td>Pip-Tazo</td>
<td>30</td>
<td>45</td>
<td>****</td>
</tr>
</tbody>
</table>
Pseudomonas aeruginosa Susceptibility Pattern 2014

% susceptible

Antibiotics

CMC Susceptible (%)
AIIMS Susceptible (%)
JIPMER Susceptible (%)
PGIMER Susceptible (%)
#REF!
Antimicrobial Stewardship Program
Survey of AMSP Practices 2013

- Hospital or Lab accreditations
- AMSP, infection control and treatment guidelines
- AMSP team:ID physician, clinical pharmacist, IT specialist,
- Frequency of meetings, circulation of minutes
- Anti Microbial Resistance Data Analysis
- Anti Microbial Agents Usage Data Analysis
- AMSP Outcome analysis
Survey of AMSP Practices 2013

- 20 Hospitals: 13 public and 7 private
- Accreditations better in private hospitals
- AMSP documents in 4/20 hospitals
- Infection control document in 20/20
- Most hospitals did not have infectious disease physicians and clinical pharmacists
- Anti Microbial Resistance Data Analysis 20/20
- Anti Microbial Agents Usage Data Analysis 5/20
- AMA Prescription Audit & Feedback practised by 2/20
- Comprehensive treatment guidelines missing in most hospitals
  - Syndrome specific guidelines frequently available
- AMSP not linked with IT system in most hospitals
Special Report

Indian J Med Res 142, August 2015, pp 30-38

Antimicrobial stewardship programme (AMSP) practices in India

Kamini Walia, V.C. Ohri & Dilip Mathai* for Antimicrobial Stewardship Programme of ICMR

Division of Epidemiology & Communicable Diseases, Indian Council of Medical Research, New Delhi & *Apollo Institute of Medical Sciences & Research, Hyderabad, India
Building collaborations

- **Center for Disease Control, USA**
  - Strengthening infection control

- **National Institute of Allergy and Infectious Diseases, NIH, USA**
  - Systems biology of AMR
  - Epidemiology of neonatal sepsis
  - Clinical trials for new entities

- **Research Council Norway, Norway**
  - Methods for assessment of the burden of resistance
  - Integrated project surveillance systems for AMR and antibiotic use in humans and/or animals.
  - Ecological, evolutionary and molecular studies of AMR in clinical and non-clinical environments.
Way forward....

- Sustain and strengthen quality data collection
- Real time collection and dynamic analysis
- Enough evidence that stewardship practices are effective
- Improving quality of antimicrobial prescribing
- Strengthen infection control
- Innovative ideas to address infection control in nosocomial settings
Way forward....

• Work with the agriculture and poultry industry regarding antibiotic usage in veterinary and meat industry
• Address the diagnostics gap
• Role for industry to identify potential new drug targets and new drug molecules
Thank you...

- Questions??