AMR Containment: Country Response

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“Drug resistance follows the drug like a faithful shadow.”

- Paul Erhlich 1854-1915
What is Antimicrobial resistance (AMR)

- **Suspicion**: A microorganism usually responsive to an antimicrobial becomes nonresponsive to that drug

- **Confirmed AMR**: Always by Lab AST result
Antibiotic Selection for Resistant Bacteria

- **Antibiotic present**
  - 2 generations later
  - Spontaneous AB-resistant bacterial mutant
  - AB-sensitive bacteria die, AB-resistant bacterium survives

- **Antibiotic absent**
  - 2 generations later
  - 1 generation later
  - Spontaneous AB-sensitive bacterial mutant
Antibiotic deployment

Antibiotic resistance observed
## Drug Dev Process

<table>
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<tr>
<th>Phase of Dev</th>
<th>Timeline</th>
<th>Probability of Success</th>
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<tbody>
<tr>
<td>Preclinical</td>
<td>1-6 Yrs</td>
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<tr>
<td>Clinical</td>
<td>6-11 Yrs</td>
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<tr>
<td>Phase 1</td>
<td>2-2.5 Yrs</td>
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<td>Phase 2</td>
<td>2.2-3 Yrs</td>
<td>14%</td>
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<td>Phase 3</td>
<td>2.6 yrs</td>
<td>9%</td>
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<tr>
<td>Approval New Drug Application</td>
<td>1-2 yrs</td>
<td>8%</td>
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<tr>
<td>Phase 4(Post Marketing Surv)</td>
<td>10-14 yrs</td>
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AMR Contributory Factors

- Inappropriate use (overuse, underuse and misuse) of antimicrobials in
  - Clinical medicine
  - Veterinary medicine
  - Agronomic and industrial practices.

- Poor infection prevention and control in hospitals.

- Use /availability of poor quality drugs.
Sources and pathways for antibiotic contamination of water and soil

Antibiotics for human use
- excreta (hospital effluents)
- excreta (private households)
- waste disposal (unused medicine)

Antibiotics for animal use
- excreta
- manure

- municipal waste water
- sewage farm
- sewage sludge

- sewage treatment plant
- surface water
- aquaculture
- pharmaceutical production plant

- domestic waste
- waste disposal site
- soil
- groundwater
- drinking water
Consequences of Antimicrobial Resistance

- Infections resistant to available antibiotics
- Increased cost of treatment
- Increase morbidity and mortality

Global Trends AMR
Percentage of MRSA, by country (most recent year, 2011–14)
Percentage of ESBL producing Escherichia coli (2011–2014)
Percentage of carbapenem-resistant Klebsiella pneumoniae, by country (most recent year, 2011–2014)
Six strategies needed for AMR containment

1. **Reduce** the need for antibiotics through improved water, sanitation, and immunization

2. **Improve** hospital infection control and antibiotic stewardship

3. **Change** incentives that encourage antibiotic overuse and misuse to incentives that encourage antibiotic stewardship

4. **Reduce** and eventually phase out subtherapeutic antibiotic use in agriculture

5. **Educate** health professionals, policy makers, and the public on sustainable antibiotic use

6. **Ensure** political commitment to meet the threat of antibiotic resistance
AMR Issues: Indian Scenario

- India has a high burden of bacterial infections, an estimated 410,000 children aged under five years die from pneumonia in India annually,
- The crude mortality from infectious diseases in India today is estimated to be 417 per 100,000 persons.
- At 12.9x10^9 units of antibiotics consumed in 2010, India was the largest consumer of antibiotics for human health, although the per capita consumption of antibiotics in India (10.7 units/capita) was lower than that seen in many other developed countries eg (USA 22 units/capita).
Units of antibiotics sold in India, by type.
AMR Issues: Indian Scenario...2

- **Uncontrolled** use of antibiotics in human as well as veterinary sector

- Availability of **Substandard** Antibiotics

- Inadequate **Regulations** (Schedule H for human use, Limited regulations for food animals, however, No regulations in Non food animals)

- Inadequate **technical** infrastructure to generate usable AMR data

- Very little national data of **antimicrobial use**

- Inadequate **interaction** among clinicians and Laboratory experts
Regulations for Antibiotics in Food Animals

India:

- FSSAI has set the tolerance limit for antibiotics and other pharmacologically active substances only for sea foods including shrimps, prawns or any other variety of fish and fishery products under the Food Safety and Standards (Contaminants, Toxins and Residues) Regulations, 2011.23

- No tolerance limit has been set for antibiotics and other pharmacologically active substances in poultry meat and meat products.
Studies on use of antimicrobials in the country

• Very limited studies

• No National data

• Few studies at CMC Vellore in South

• Sir Ganga Ram Hospital, VPCI New Delhi

• Hinduja hospital, Mumbai

• VPCCI Delhi Dr Anita Kotwani
## Percentage of patients prescribed single, two, and three ABs at the two hospitals 2007-12: New Delhi

<table>
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<tr>
<th>Study Period</th>
<th>Single antimicrobial [N (%)]</th>
<th>Two antimicrobials [N (%)]</th>
<th>Three antimicrobials [N (%)]</th>
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<tr>
<td>Period 1</td>
<td>[8 (16.0%)]</td>
<td>[41 (82.0%)]</td>
<td>[1 (2.0 %)]</td>
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<td>Period 2</td>
<td>[7 (16.7 %)]</td>
<td>[33 (78.6%)]</td>
<td>[2 (4.8%)]</td>
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<td>Period 3</td>
<td>[10(23.8%)]</td>
<td>[25(59.5%)]</td>
<td>[7 (16.7 %)]</td>
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<tr>
<td>Period 4</td>
<td>[6(8.8 %)]</td>
<td>[44(64.7 %)]</td>
<td>[18(26.5%)]</td>
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<td>Period 5</td>
<td>[2(3.4 %)]</td>
<td>[40(67.8 %)]</td>
<td>[17(28.8%)]</td>
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</table>

Monthly use of Cephalosporins: Delhi

Cephalosporins

% Prescriptions with Antibiotic

Private Clinics
Private Pharmacy
Public Sector
Average
CSE Study 2014: Antibiotics in Chicken Meat: Percentage of Samples Positive for Antibiotics Residues

# Neomycin was not detected in any sample
AMR Surveillance: Country Scenario
AMR Surveillance : India

- Data available from some public health programmes eg RNTCP, NVBDCP, NLEP, NACO for specific diseases/pathogens
- GASP for Gonococcus (network of 15 labs)
- However, No national AMR surveillance for other pathogens eg Salmonella, Shigella, Staph, Klebsiella, Acinetobacter etc
- Indiaclen : Data generated by (India clinical epidemiology network) through IBIS and CAMR surveillance for Pneumococcus, H.inf
- INSAR: Network of 20 labs with WHO support not existent anymore
- ICMR Recently initiated AMR surveillance with Network of 4 Institutions
- MOHFW/NCDC initiated AMR surveillance with network of 10 labs
AMR trends: India

- **Enteric Fever:** Chloramphenicol, Ampicillin, Co-trimoxazole (10-20%), Fluoroquinolones (up to 30%), recently reversal seen to Chloro, Cotrimoxazole

- **Meningococcal Infections:** Co-trimoxazole, Ciprofloxacin and Tetracycline (50-100%)

- **Gonococcal Infections:** Penicillin (50-80%), Ciprofloxacin (20-80%), Ceftriaxone

- **Malaria:** Chloroquine Res in *Falciparum* Malaria

- **TB:** MDR: 3-5% in new cases, 10-15% In treated cases, XDR: 4-7% of MDR Cases, High MDR in Sikkim, Mumbai

- **HIV:** Primary and secondary low level resistance reported.
AMR trends: India....

• An indicator of the rising tide of AMR in India is the rapidly increasing proportion of isolates of methicillin resistant *Staphylococcus aureus* (MRSA) – from 29% in 2008 to 47% in 2015

• Carbapenem Resistant *Enterobacteriaceae* (CRE), has been a major concern

• Increase in Carbapenem resistant isolates of *Klebsiella pneumoniae* (from 29% in 2008 to 57% in 2014)
Antimicrobial resistance: N. gonorrhoeae 2007 to 2012
Chloroquine Resistance in Pf in India

- Change in policy in areas with CQ failures
- RI, RII, RIII categories formed basis of policy change

Districts with CQ treatment failure ≥10% (red) in any trial between 1978 and 2007 and Pf endemic areas (pink)

Lancet Infectious Diseases 2011, 11, 54-67
MRSA resistance rates from various Indian studies vary but appear to increase over time.
Prevalence of ESBL, Carbapenem resistance in E.coli in Environment & Community

NCDC Study (2011-2014)

1. Community: 763 E.Coli isolates obtained from stool samples (Healthy children).
   - ESBL production: 13% - 15%, Carbapenem Res: 6-10% 
   - NDM-1 production: 3.2% - 4.5%

2. Sewage: Seven collection sites selected in Delhi for study from October 2011 to Dec 2014, total of 976 E. coli isolates obtained from sewage samples
   - ESBL: 20-60%, Carbapenem Res: 12-20%, NDM-1: 5-7.2%
Country Response
The National Policy for Containment of Antimicrobial Resistance

• A National task force was set up in 2010 under the chairpersonship of the DGHS to review AMR situation in the country and formulate a strategy for containment.

• The National Policy for AMR containment were formulated in 2011 with following objectives.
JAIPUR DECLARATION ON AMR BY HEALTH MINISTERS OF THE SOUTH-EAST ASIA REGION

Sept 2011

Strong commitment to tackle AMR in the Region
As per National Policy, National Programme on AMR was developed and approved for implementation during 12th Five Year Plan.

National Centre for Disease Control, Delhi identified as the nodal institution for this activity.
Activities Envisaged Under AMR containment

- Establishment of Quality Assured AST Lab Network for AMR surveillance.
- Surveillance of antibiotic usage & operational research.
- Strengthening Regulations for use of antimicrobials.
- Strengthening Hospital Infection Control in Health care facilities.
Activities Envisaged Under AMR containment...

- IEC /BCC about Rational use of antibiotics.
- Interface with Animal Husbandry/Agriculture etc. to rationalize use of antibiotics.
- Strengthening diagnostic tools to prevent misuse of antimicrobials.
Activities Undertaken:

• Promote rationale use of antibiotics. (National guidelines for use of antimicrobials to treat infectious diseases have been developed and displayed on website of NCDC for use by different stakeholders

• Lots of ASP activities carried by NCDC other institutes

• AMR surveillance established with a network of 10 labs in the country (Another network of 4 institutions by ICMR)

• Hospital Infection control: To strengthen hospital infection control guidelines and practices, guidelines developed
Activities Undertaken…..2

• **Schedule H1** enacted to regulate sale of antibiotics (March 2014)

• Banning of 354 FDC (fixed dose combinations) also those containing antimicrobials

• **International AMR conference** Organised in Feb 2016: Participation of 350 delegates from 16 countries including Policy makers, Clinicians Lab experts others
Treatment Guidelines: The Highlights

Therapy of Common Infections: Syndrome vise

- Gastro-intestinal system
- Central Nervous System
- Cardio-vascular system
- Skin and Soft tissue
- Respiratory tract
- Genitourinary tract
- Pediatric and Neonatal infections
- Obstetrics & Gynecological infections
- Ophthalmic Infections
- Infections of Ear, Nose & Throat
Schedule H-1

- Since March 2014 a separate schedule H-1 incorporated in Drug and Cosmetic rules
- Contains 46 drugs including
  - 24 antimicrobials belonging to 3rd, 4th Generation Cephalosporins and Carbapenems
  - 11 Anti TB drugs and
  - 11 Habit forming drugs

The drugs required to be labelled with the following with red border

- ‘SCHEDULE H1 DRUG – WARNING’
- It is dangerous to take the drug except in accordance with medical advice
- Not to be sold by retail without the prescription of a Registered medical practitioner
- A separate register has to be maintained giving details of prescriber, patient drug
Regulatory mechanism is being strengthened by adding Schedule H1 for use of antibiotics as well as starting Pharmaco-vigilance activity under DCGI.
AMR Surveillance

- A total of 30 labs in state medical colleges will be strengthened in a phased manner to carry out surveillance.

- Ten labs selected in the first phase in different geographical regions

- Pathogens identified for AMR Surveilance

- Panel of antibiotics for different identified pathogens finalised

- AST (disc Diffusion) methodology finalised based on CLSI guidelines

- Data analysis tools identified

- Data Flow started
Pathogen selection for AMR surveillance

- To begin with the following bacteria included for the AMR surveillance: (Initially four pathogens out of WHO priority list)
  - Klebsiella pneumonia
  - Escherichia coli
  - Staphylococcus aureus
  - Enterococci
- Isolates both from community acquired infections and hospital acquired infections included.
## Resistance (%) Staph. Aureus

<table>
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<tr>
<th></th>
<th>PEN</th>
<th>CEFOX</th>
<th>CHL</th>
<th>CIP</th>
<th>CLIN</th>
<th>ERY</th>
<th>GEN</th>
<th>SXT</th>
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<th>LNZ</th>
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<tbody>
<tr>
<td>DL RML</td>
<td>84%</td>
<td>21%</td>
<td>9%</td>
<td>58%</td>
<td>14%</td>
<td>64%</td>
<td>22%</td>
<td>66%</td>
<td>0%</td>
<td>0%</td>
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<tr>
<td>DL SJH</td>
<td>88%</td>
<td>34%</td>
<td>10%</td>
<td>72%</td>
<td>33%</td>
<td>62%</td>
<td>52%</td>
<td>55%</td>
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<tr>
<td>DL LHMC</td>
<td>90%</td>
<td>20%</td>
<td>6%</td>
<td>75%</td>
<td>11%</td>
<td>73%</td>
<td>30%</td>
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<td>AHM</td>
<td>92%</td>
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<td>68%</td>
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<td>57%</td>
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The bar chart above illustrates the percentage of resistance to various antibiotics for Staph. Aureus. Each bar represents the percentage of resistance for a different hospital or location, with the y-axis showing the resistance percentage ranging from 0% to 100%.
### RESISTANCE (%) E.COLI

<table>
<thead>
<tr>
<th></th>
<th>AMK</th>
<th>CEFO</th>
<th>ESBL</th>
<th>CIP</th>
<th>COL</th>
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<th>MEM</th>
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<tr>
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<td>21%</td>
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<td>54%</td>
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# RESISTANCE (%) KLEBSIELLA.SP

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Dev of National action plan

- Three committees proposed to oversee various activities including development and Implementation of national action Plan

1. Core Working Group (CWG) under Director NCDC

2. Technical advisory group (TAG) under the Joint Chairmanship of Secretary Deptt of Health Research / Director General ICMR and Director General of Health Services

3. Inter-sectoral coordination committee (ISCC) chaired by Secretary Min of Health and family Welfare

- The first core working group meeting organized at NCDC Delhi dated 6th Oct 2016 and members given overview of the activities done so far, There were deliberations on how to take forward various activities under the national AMR containment programme including the steps forward, various subcomitees constituted
CWG Sub Groups

1. CWG sub-group on training and communication

2. CWG sub-group on strengthening AMR Surveillance

3. CWG sub-group on Infection Prevention and Control

4A. CWG group on Strengthening regulations for sale of antibiotics/surveillance of antibiotic use

4B. CWG group on optimising antibiotic use (human health)

4C. CWG group on optimising antibiotic use (animal/food/environment)

5. CWG group on Innovations and Research & Development

6. CWG group on Financing for AMR
AREAS OF CONCERN/CHALLENGES

• Increasing drug resistance trends in the country based on available data

• Uncontrolled use of antibiotics

• Inadequate Infection Control Practices in Health Care facilities

• Inadequate Microbiological Diagnostic facilities specially in the veterinary sector

• Sustainability of Funds release and political commitment
**Way Forward**

• Promote Rational **Antibiotic Use**

• Reduce **Self Medication Practices**

• Restrict sale of spurious antimicrobials

• Regular surveillance of antibiotic use in healthcare/other settings

• Expand **AMR surveillance to District level** to get more community data also AMR surveillance in Vety sector

• Strengthen **infection Control** in Health care settings

• Restrict use of antibiotics in **veterinary/Agri** sector

• Need for **Newer Vaccines** for infectious diseases

• Need To Develop new Simple, Cost effective and accurate **Diagnostic tools**

• Constant Roll out of **Newer antimicrobials**
The Road Continues.....

THANK YOU