Overview of Needs on the Ground and Surveillance Issues

The Case of India

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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.
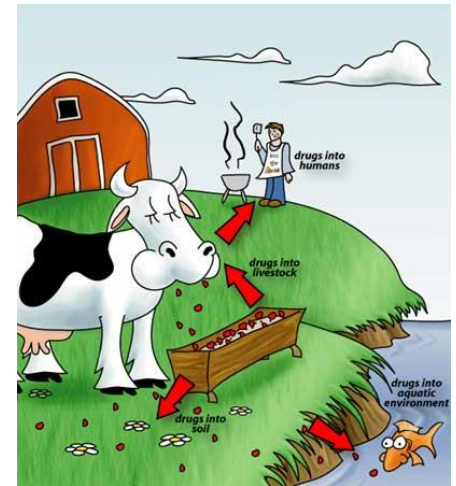
Why are resistance rates so high in India?

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

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

'OVERUSE OF ANTIBIOTICS IS LEADING TO RESISTANCE'
THE PILL POPPING SYNDROME

COMMONLY USED ANTIBIOTICS
- Erythromycin
- Azithromycin
- Amoxicillin
- Ciprofloxacin
- Ofloxacin

COMMON CONDITIONS THEY ARE TAKEN FOR
- Fever
- Common cold
- Cough
- Sore throat
- Diarrhoea

- Antibiotics should be prescribed in optimal doses/regimens and stopped when infection is treated

- Clinicians should be familiar with local antibiotic sensitivity profiles
- Hospital antibiotic policy should be formulated based on local antibiotic resistance data

Source: Central Drugs Standard Organisation

www.mayaclinic.in

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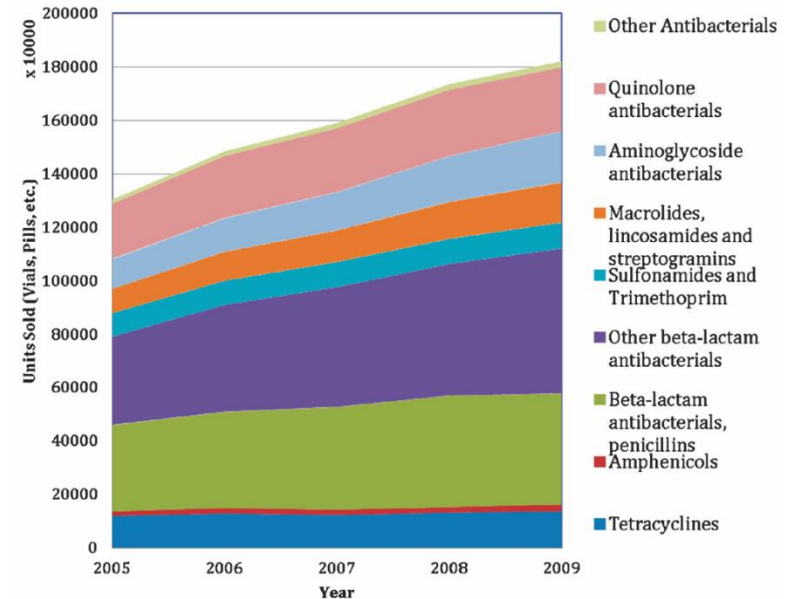- Irrational self-administration
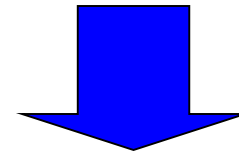
Antimicrobial resistance

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

Trends in recent past

- 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

- **Compromising the gains made in control of infectious disease through national programs**

Multi-drug resistant and extensively drug resistnat TB cases in India:ICMR consultation, 2012
Sethi et al 2006 Deshpande etal 2011, Thoral et al 2011

Role for antibiotics not limited to infectious diseases

- 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 setting

- VAPs, CAIs, CLBSIs

- Knee and Hip repla

- Transplants

- Cancer treatments

- Caesarean section

Invisible threats, invisible victims

ANTIMICROBIAL RESISTANCE RESEARCH INITIATIVE

ICMR's Antimicrobial Resistance Surveillance and Research Initiative

Surveillance and Stewardship

- **Strengthening surveillance research in AMR**
- **Stewardship activities:**
  - **Treatment guidelines**
  - **Infection control guidelines**
  - **Understanding the Prescription practices**
  - **Addressing the missing infectious disease link**

Research

- **Epidemiology**
- **Prescription practices, cycling and combinations**
- **New approaches for drug delivery**
- **New drug targets**
- **New antimicrobial candidates**
- **Vaccine candidates**

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 understanding drug resistance mechanisms, patterns, clonality
- To guide treatment and prevention interventions based on country specific scientific evidence

AMR activities in ICMR

- Strengthening surveillance research in AMR through network of labs
  - Mechanisms of resistance
  - Systems biology: new drug targets, POC diagnostics
- Stewardship activities:
  - Understanding current AMSP practices: underlying factors
    - Understanding the Prescription practices
    - Treatment guidelines
   - Infection control guidelines
    - 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

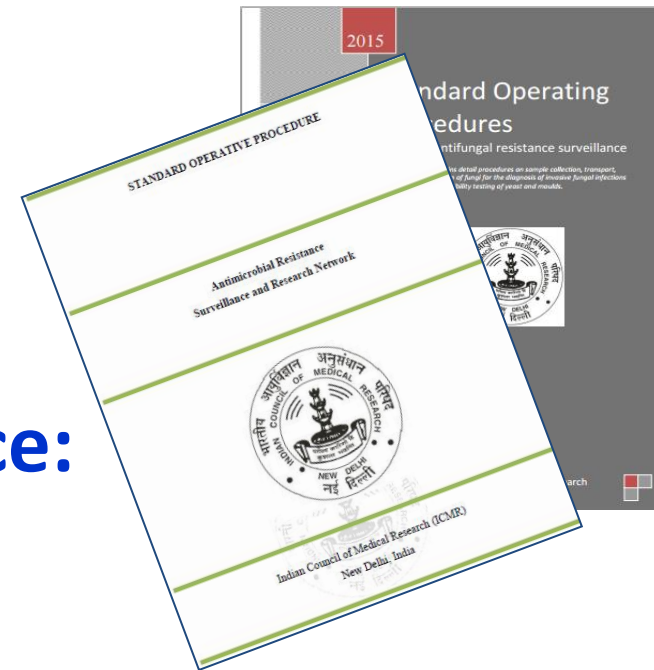- **15 Regional Centres (RC) proposed**

Nodal Centres

PGIMER Chandigarh

AIIMS New Delhi

ICMR, New Delhi

CMC Vellore

JIPMER Puducherry
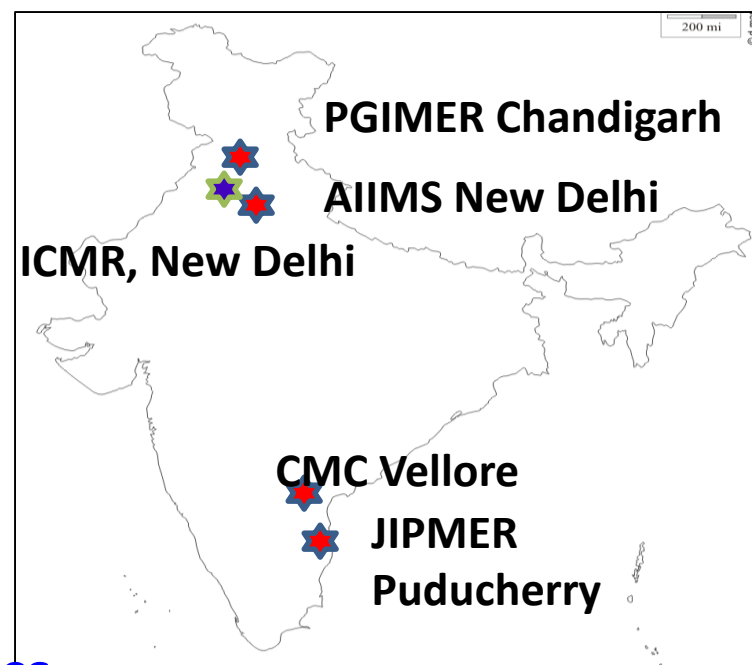
IMPERATIVES

- ➤ Standardisation & Uniformity
- ■ Standard Operating Procedures
  (SOPs Bacteriology, Mycology)
- ■ Training
- ➤ External Quality Assurance
- ➤ **Going beyond simplistic science:**
  - ➤ **Next generations sequencing**

AMR 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

AMR Network
Roles and responsibilities

- **Regional Centers**
- 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
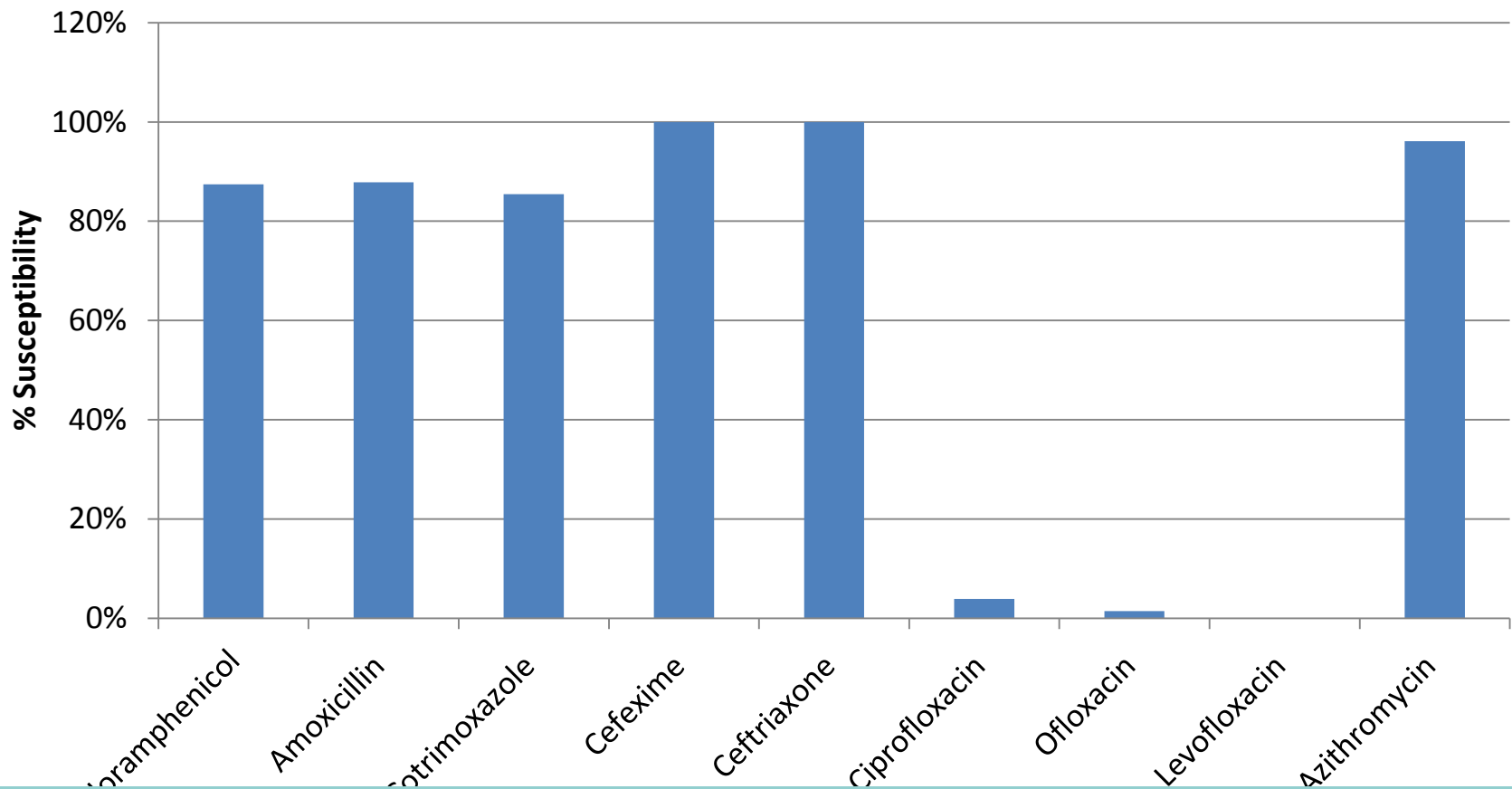- In tune with NCs, develop AMSP for region
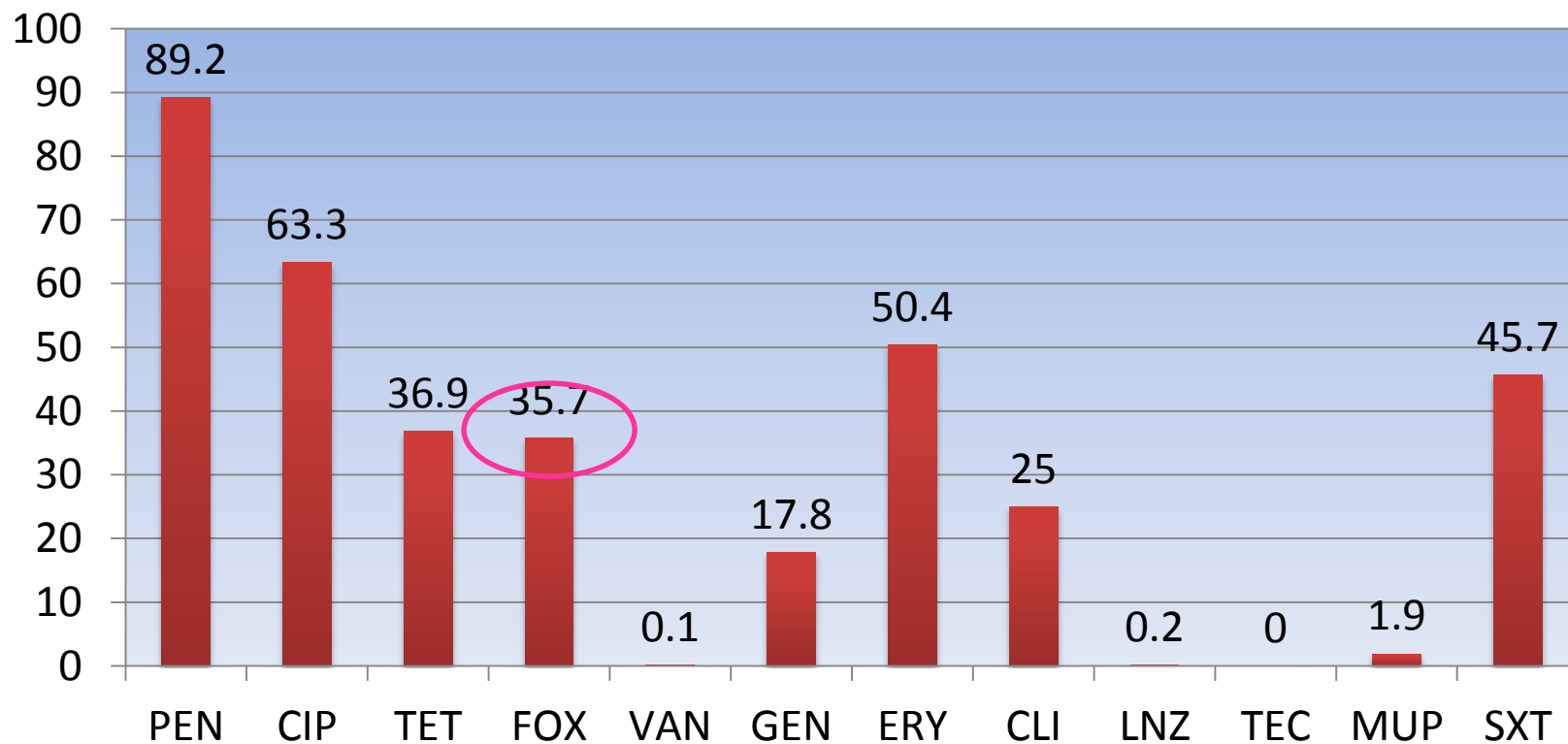
EMERGING PICTURE OF AMR IN HOSPITALS

Present Cumulative Antibiogram Of Typhoidal Salmonellae

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

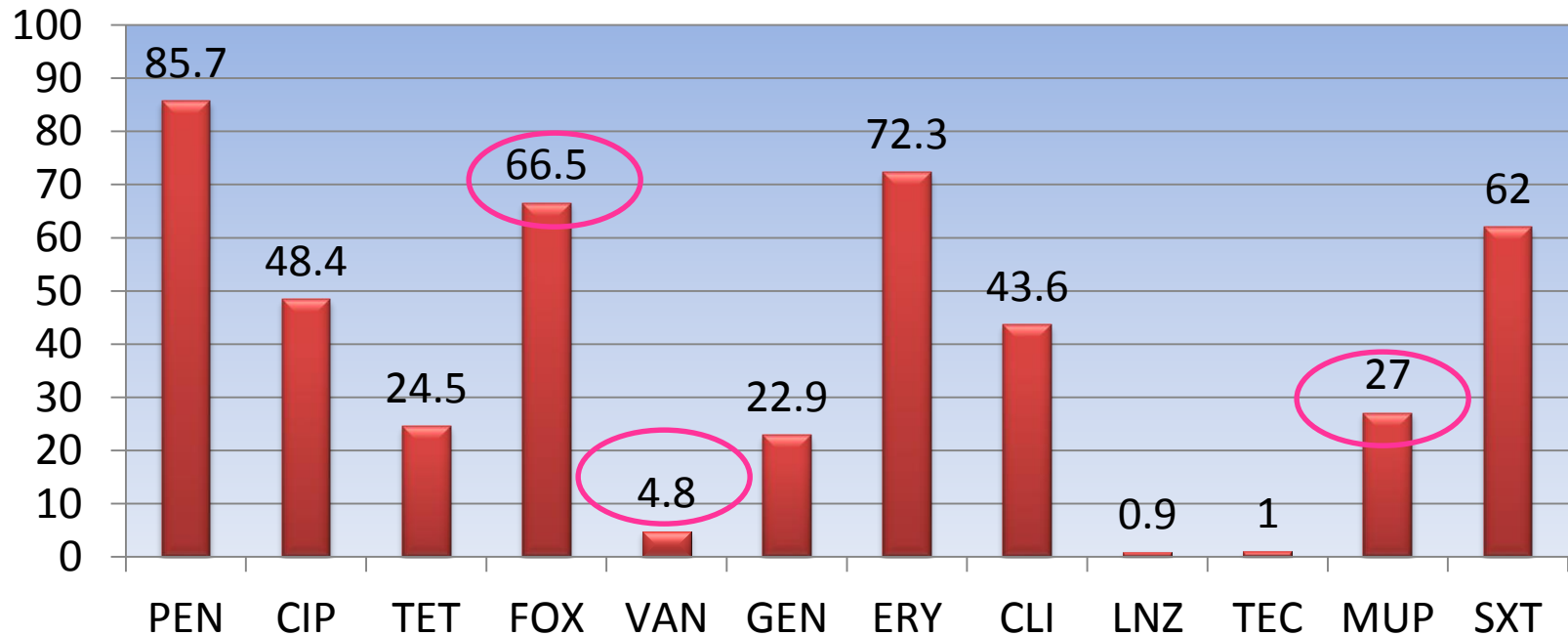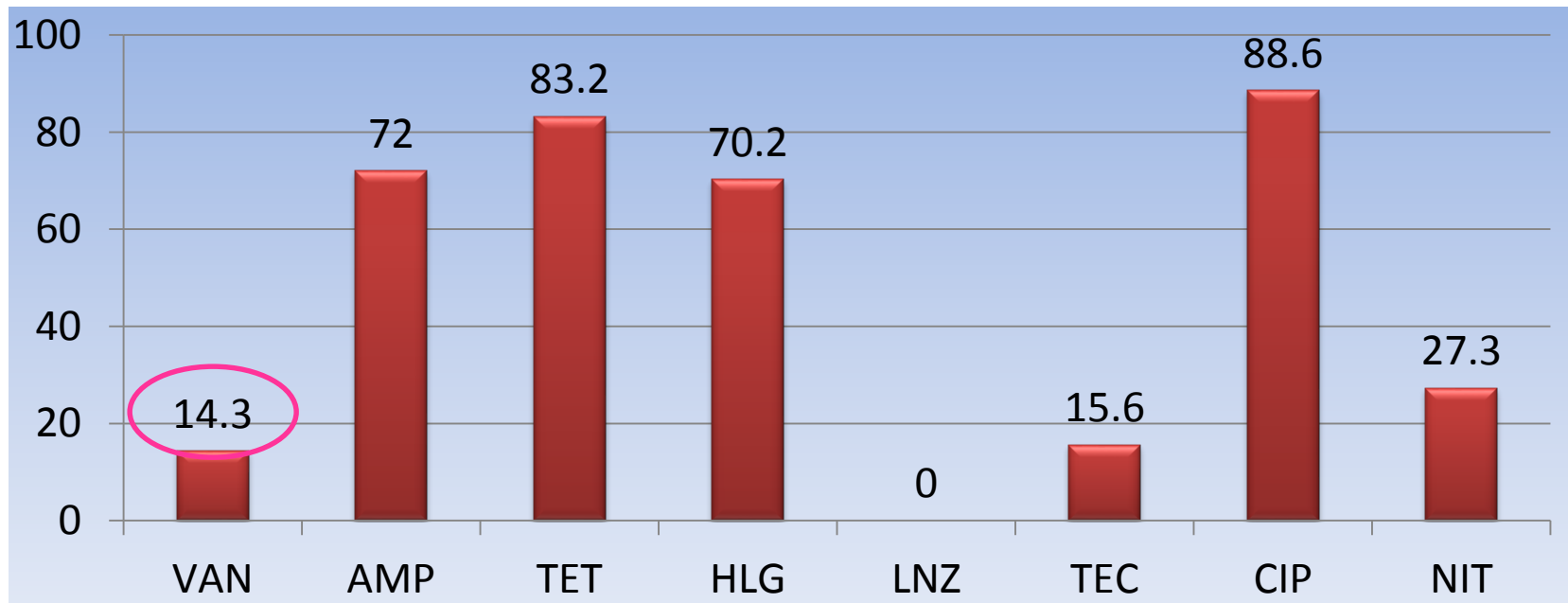# Percentage resistance of *S. aureus* isolates for all centres

# Percentage resistance of CoNS isolates for all centres

# Graph showing the resistance of all isolates of *Enterococcus faecium* for all centres (% Resistance)
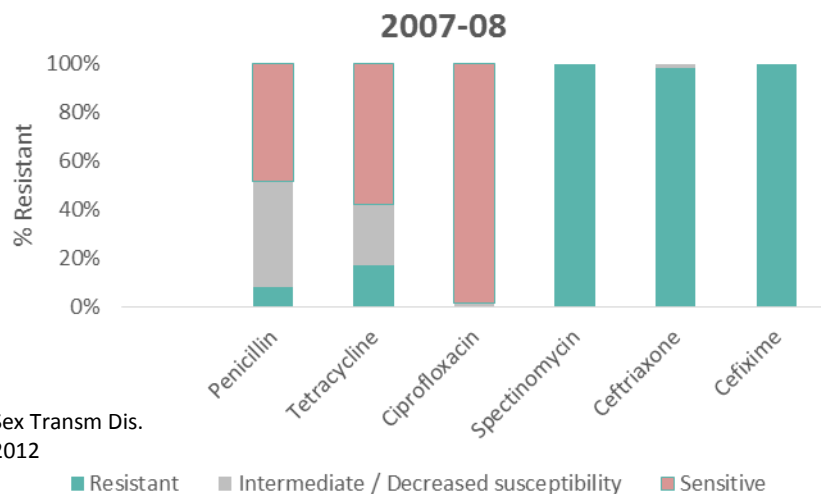

Increasing glycopeptide resistance in *Enterococci* (e.g. VRE) and increasing mupirocin resistance *in S. aureus* is causing concern

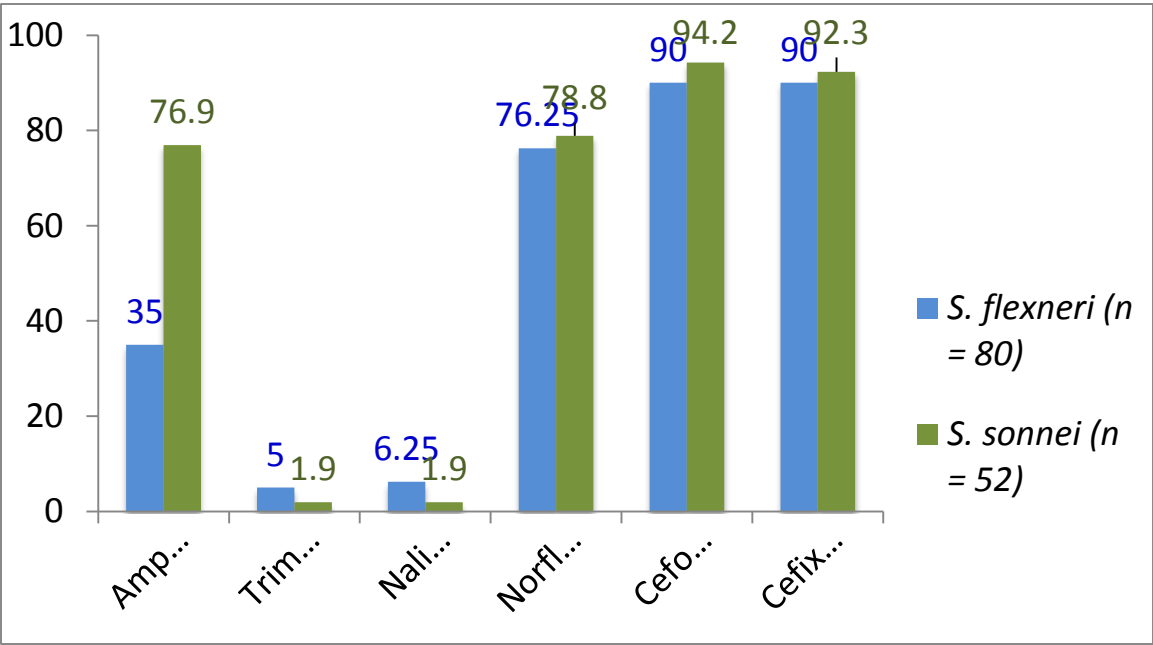**Antimicrobial susceptibility of *N.gonorrhoeae* in Pune from 1996 to 2007**

Indian J Sex Transm Dis. 2011
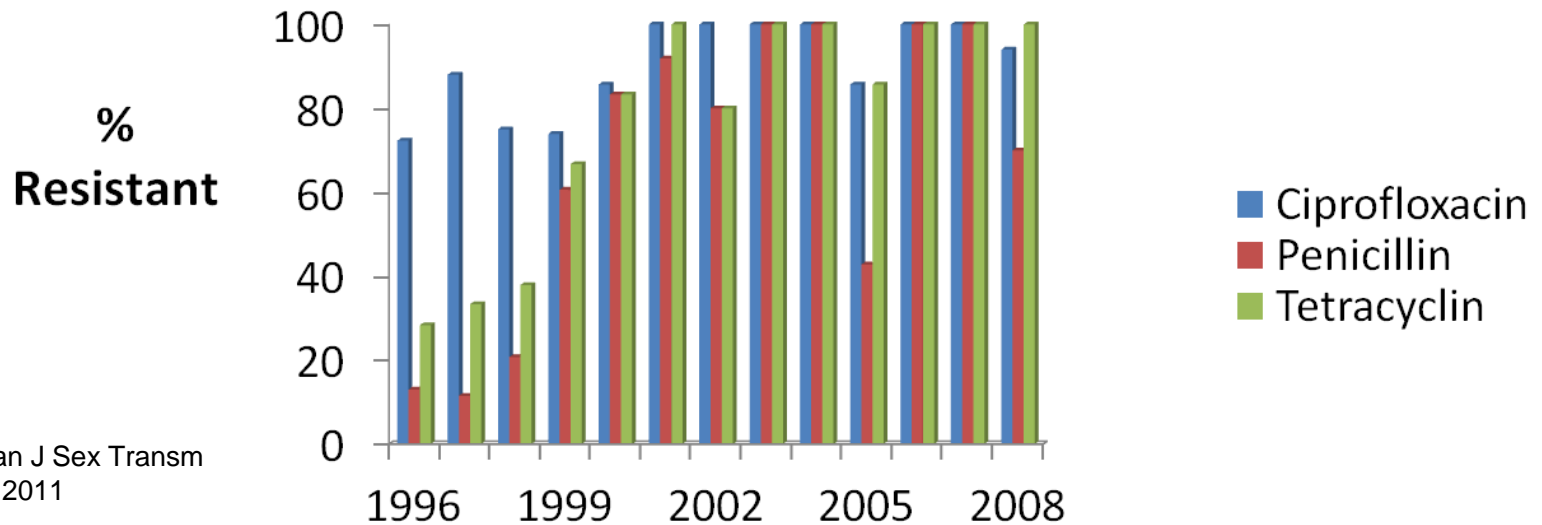
Antimicrobial susceptibility of *N.gonorrhoeae identified as part of genetic studies in 2007-8 & 14-15*

Sex Transm Dis. 2012
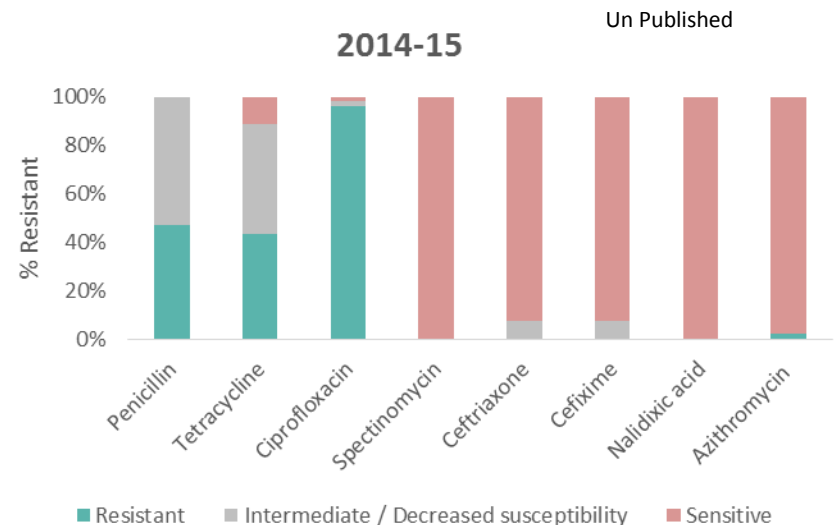
Shigella spp.

High resistance to nalidixic acid

50 % R to norfloxacin and ampicillin

Association of ESBL genes with *qnr* genes – rare among Indian isolates

***bla*CTX-M-15 occurrence in *Shigella spp* increases the threat for spread of cephalosporin resistance among Enterobacteriaceae**

Organism (n = 31)	Genes for sulfonamide resistance		Genes for β – lactam resistance				Genes for quinolone resistance
	dhfr1a	Sul II	bla_{OXA}	bla_{TEM}	$bla_{CTX-M-1}$	AmpC	qnr A, B, S
S. flexneri (n = 22)	22	15	12	4	2	2	6
S. sonnei (n = 6)	6	5	-	-	1	-	1

Carbapenem resistance rates in *Enterobacteriaceae*

- **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

58%

Upto 11%

Upto 54%

44 %

55%

Antimicrobial resistance global report on surveillance, WHO - 2014

Pie chart legend:
- Klebsiella — 46%
- Escherichia coli — 38%
- Enterobacter — 10%
- Proteus sps — 2%
- Morganella morganii — 1%
- Citrobacter — 1%
- Serratia — 1%
- Pantoea — 0%
- Providencia Stuartii — 0%
- Others species — 1%
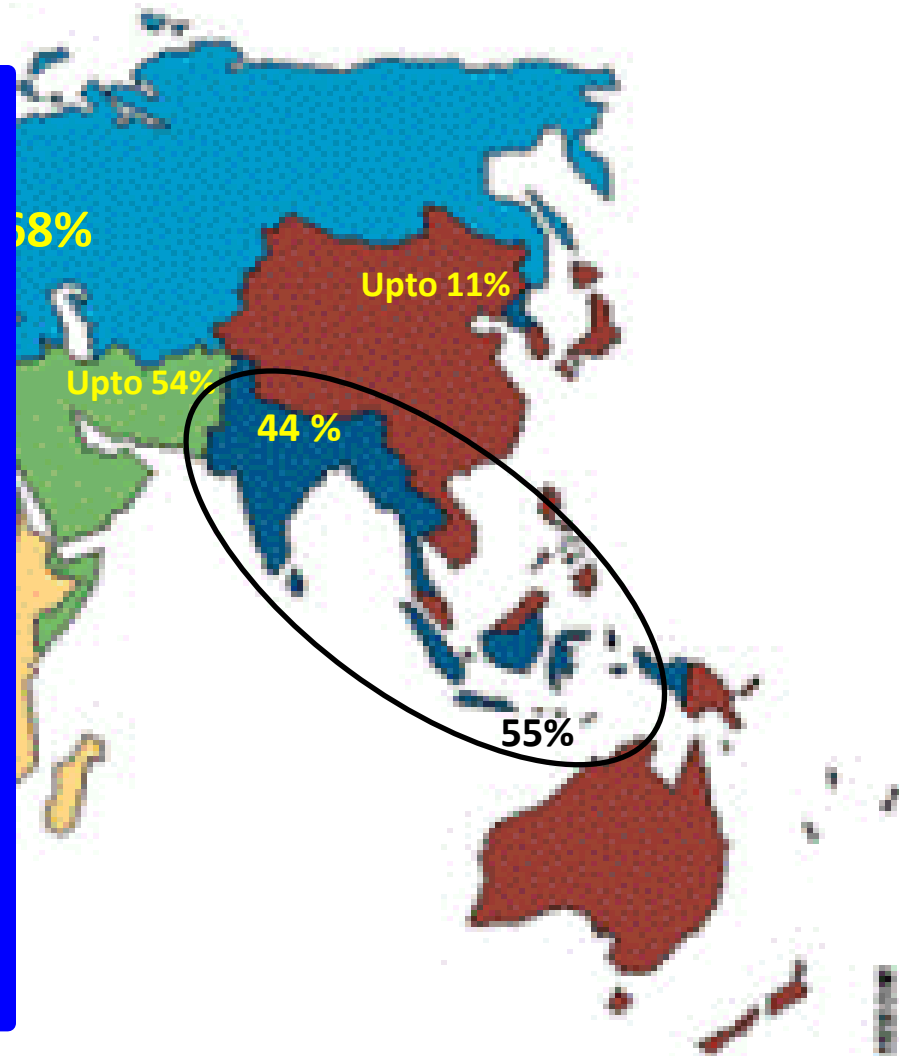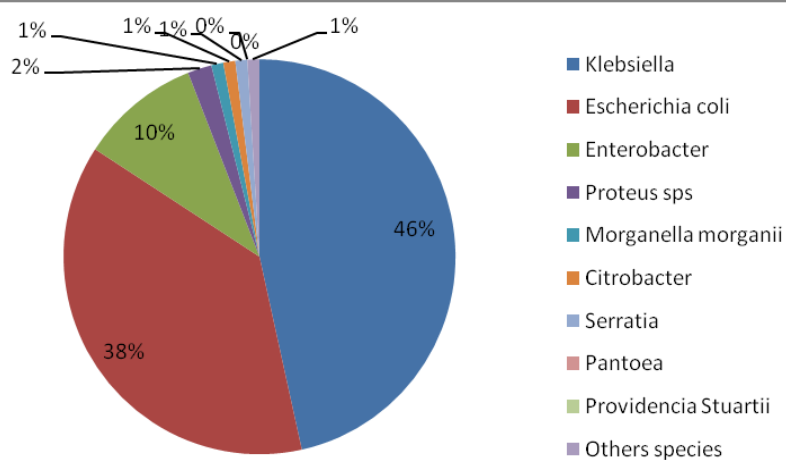
Enterobacteriaceae
Klebsiella spp. and E. coli cause most of infections
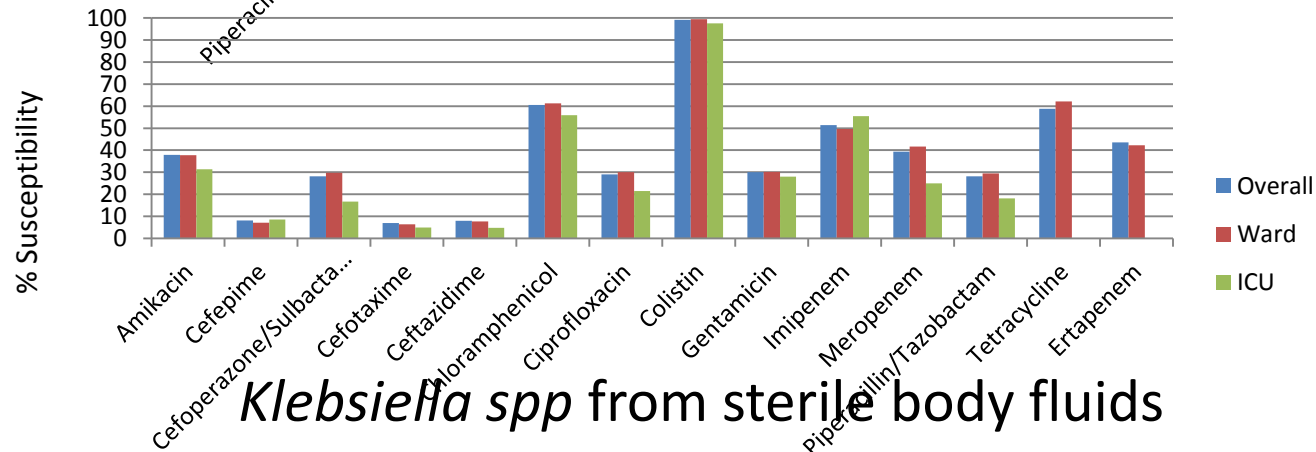
100% sensitive to colistin followed by imipenem and meropenem(60%)
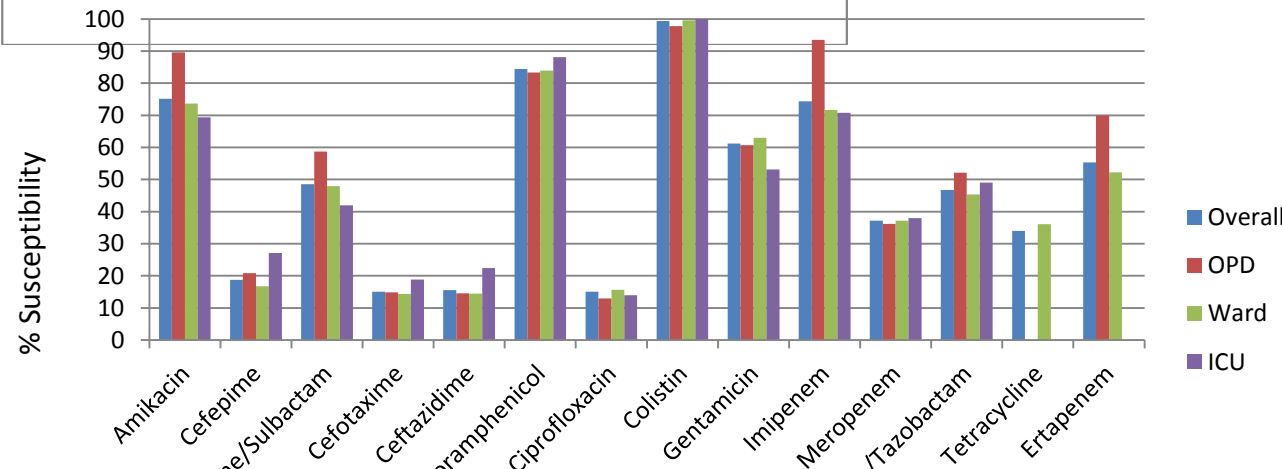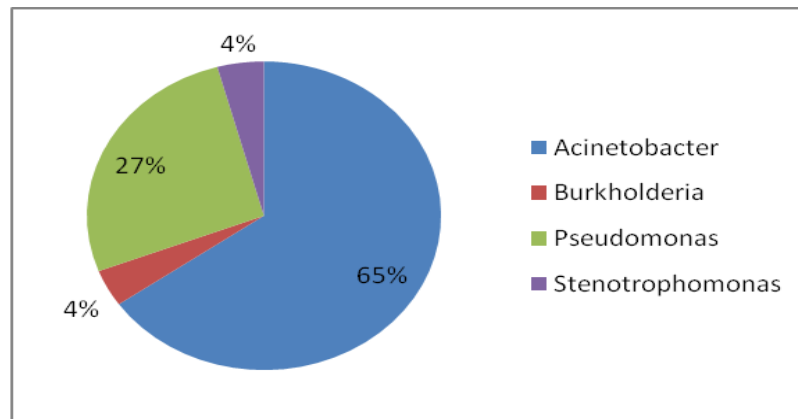
E. Coli from sterile body fluids

Klebsiella spp from sterile body fluids

Non-fermenting gram negative bacilli (NFGNB)
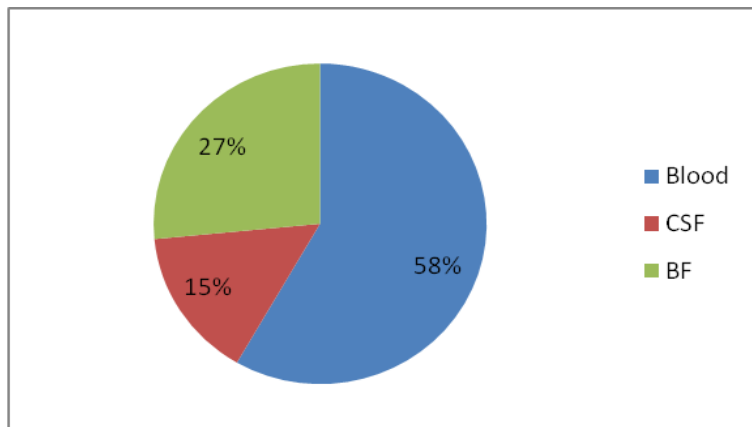
- *Acinetobacter species* 60% isolates, *Pseudomonas species* 24%, *Strophomonas species* 4% , *Burkholderia species* 4%.
- *A baumanii* isolates showed maximum susceptibility was to colistin (99%) followed by imipenem (53%) and meropenem (53%).
- Susceptibility for amikacin has increased by 23% from 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 2015

ORGANISM	NC	'n'	SPM	IMP	VIM	NDM	OXA-48	KPC	Oxa 23	24	58	51
P. aeruginosa	CMC	30	0	0	5	2	0	0				
	AIIMS	30	0	0	2	1	0	0				
												29
Acineto er sp.												26
	JIPMER	30	0	0	0	0	0	0	19	0	1	20

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.

- *Oxa 23* is mo, Oxa 51 re prevalent in *Acinetobacter spp*
- *VIM* and *NDM* continue to be prevalent among CRO's

# Using WGS to understand partial susceptibility to carabapenems

13 carbapenem resistant *P. aeruginosa* isolates of imipenem resitant/meropenem susceptible and/or meropenem resistant/imipenem susceptible.

- Negative for AMR genes were selected for efflux and porin mechanism analysis

- *oprD* gene sequencing- down regulated, which was the reason for this isolate to be resistant to imipenem but not to meropenem

Pseudomonas aeruginosa Susceptibility Pattern 2014
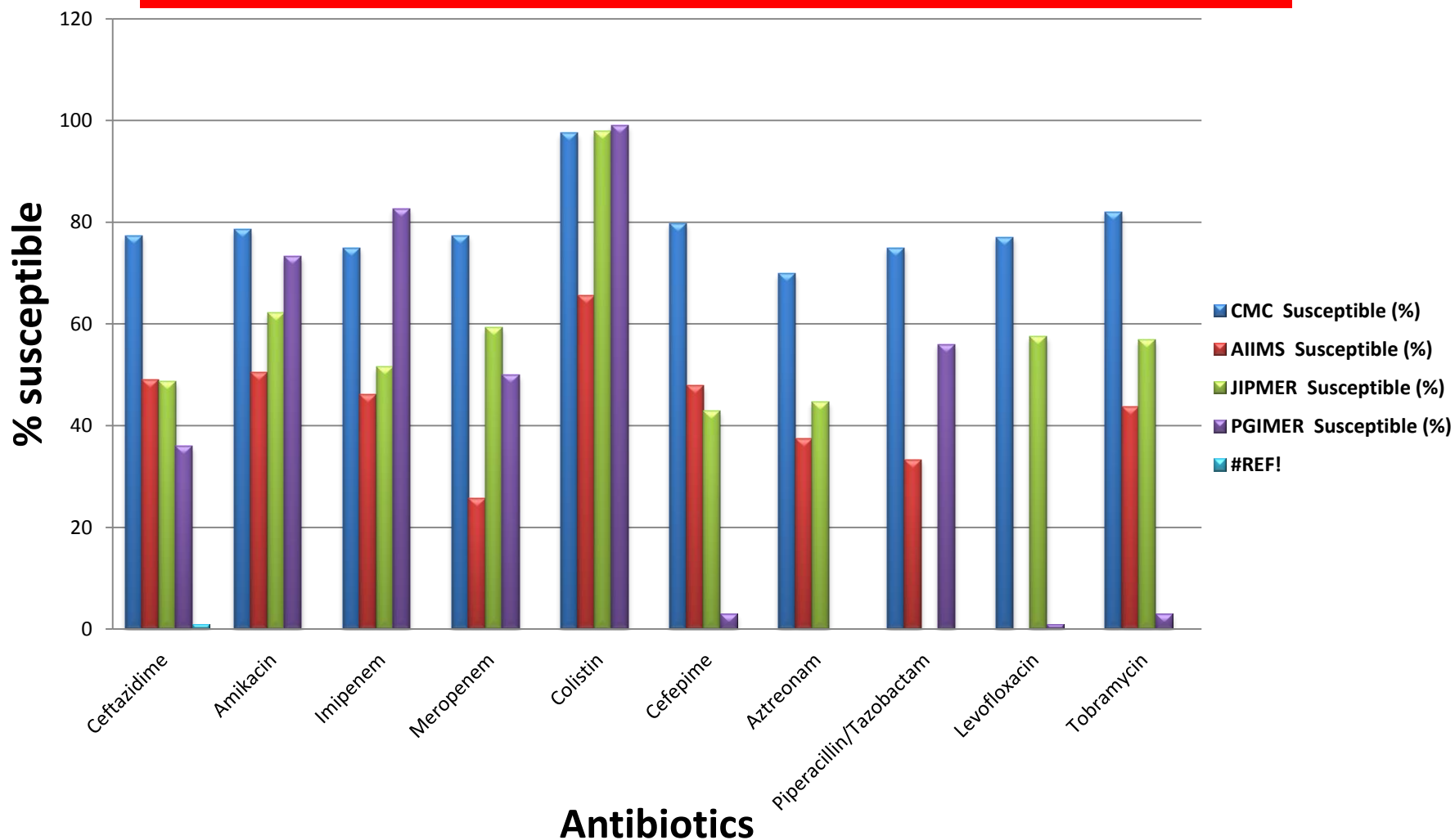
# Antimicrobial Stewardship Program

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

- **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**
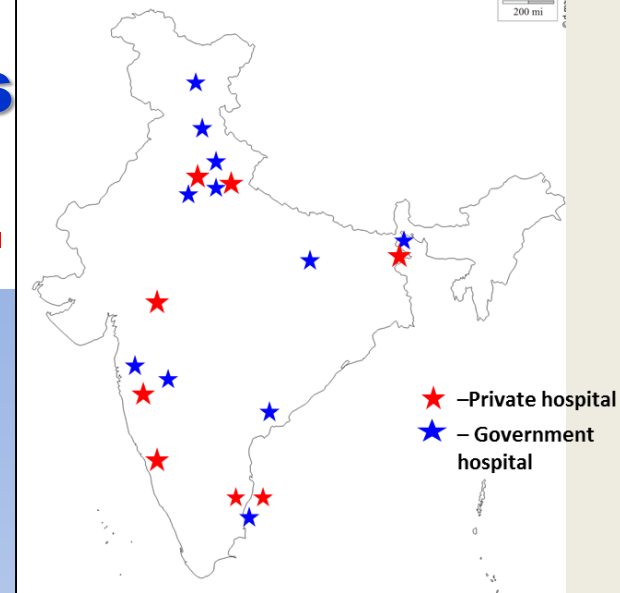
- **Anti Microbial Resistance Data Analysis** 20/20
- **Anti Microbial Agents Usage Data Analysis** 5/20
- **AMA Prescription Audit & Feedback practised by 2/20**
- **Comprehensive treatment guidelines missing in most hospitals**
  - **Syndrome specific guidelines frequently available**
- **AMSP not linked with IT system in most hospitals**

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

- Antibiotic resistance data from the livestock and poultry

- Evidence that stewardship practices are effective

  - Improving quality of antimicrobial prescribing

  - Strengthen infection control

Way forward....

- Expand understanding of antimicrobial resistance: horizontal and vertical
- Wok with industry
  - to identify potential new drug targets and new drug molecules
  - address the diagnostics gap
  - address infection control in nosocomial settings

Priority areas for future

Diagnostics

- A point of care test to rapidly and accurately differentiate between viral and bacterial infections is needed. For example, a much improved version of serum procalcitonin or molecular signature patterns.

Priority areas for Clinical Research

- One or more effective oral options for the treatment of ESBL Enterobacteriaceae

- Effective parenteral options for the treatment of carbapenemase (esp NDM-1) producing Enterobacteriaceae

- Randomised controlled trials to decide the role of monotherapy versus combination therapy for carbapenem resistant gram negative bacteria

- *In-vitro* culture susceptibilities of resistant bugs to forgotten or re-purposed

- Trials on PK/PD to optimise administration of antibiotics in Indian patients

- Role of EDTA adjuvants in clinical practice, to overcome resistance may be elucidated.

Industry

- Good surveillance data on key HAI pathogens and current AMR profiles pan-India – urban, rural, tier 1-2 cities, public aided hospitals, private hospitals etc.

- Conducive investment climate to enable discovery of next generation novel antibiotics

- Sharing of the research cost for the development of new drugs among governments, pharmaceutical industry, health systems, development agencies and large charitable foundations.

Industry

- Antibiotic research fund to fund Biotechs/Pharma companies that work in the new-mechanism area.

- Simplified regulations to allow for faster approvals for trials and extended patent rights

WHAT DOES NOT
KILLS YOU
MAKES STRONGER