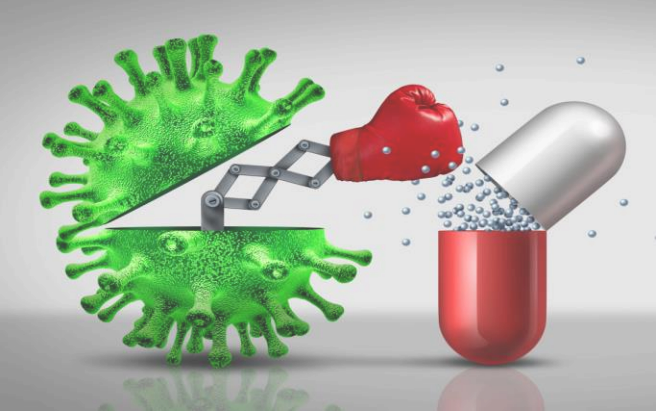


Antimicrobial Resistance (AMR): Challenges & Approaches

Professor Y. K. Gupta

Principal Advisor (Projects), THSTI - DBT

Former Dean (Academics), and Head, Department of Pharmacology,

All India Institute of Medical Sciences, New Delhi 110029

President, Indian Society of Nanomedicine
National Scientific Co-ordinator, Pharmacovigilance Program of India

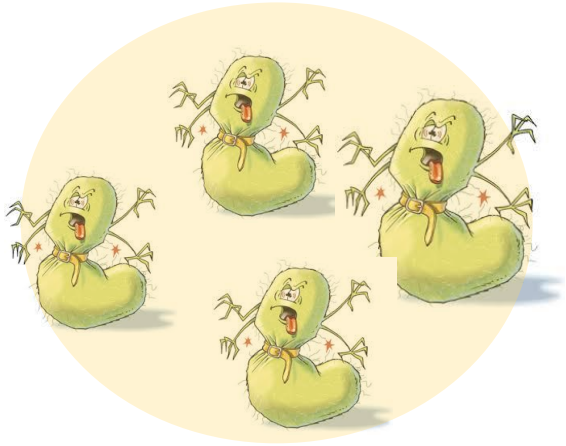
Chairman, National GLP Technical committee, DST, Govt of India

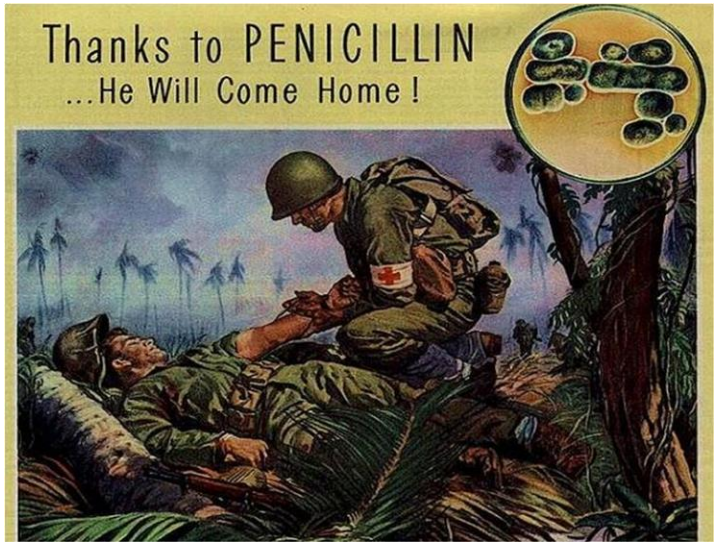
The evolution..

Pre-antibiotic era
(Before 1930)

Infections caused epidemic and pandemics leading to huge morbidity and mortality

Antibiotic era
(1930- early 2000)





Post-antibiotic era???
(Present)

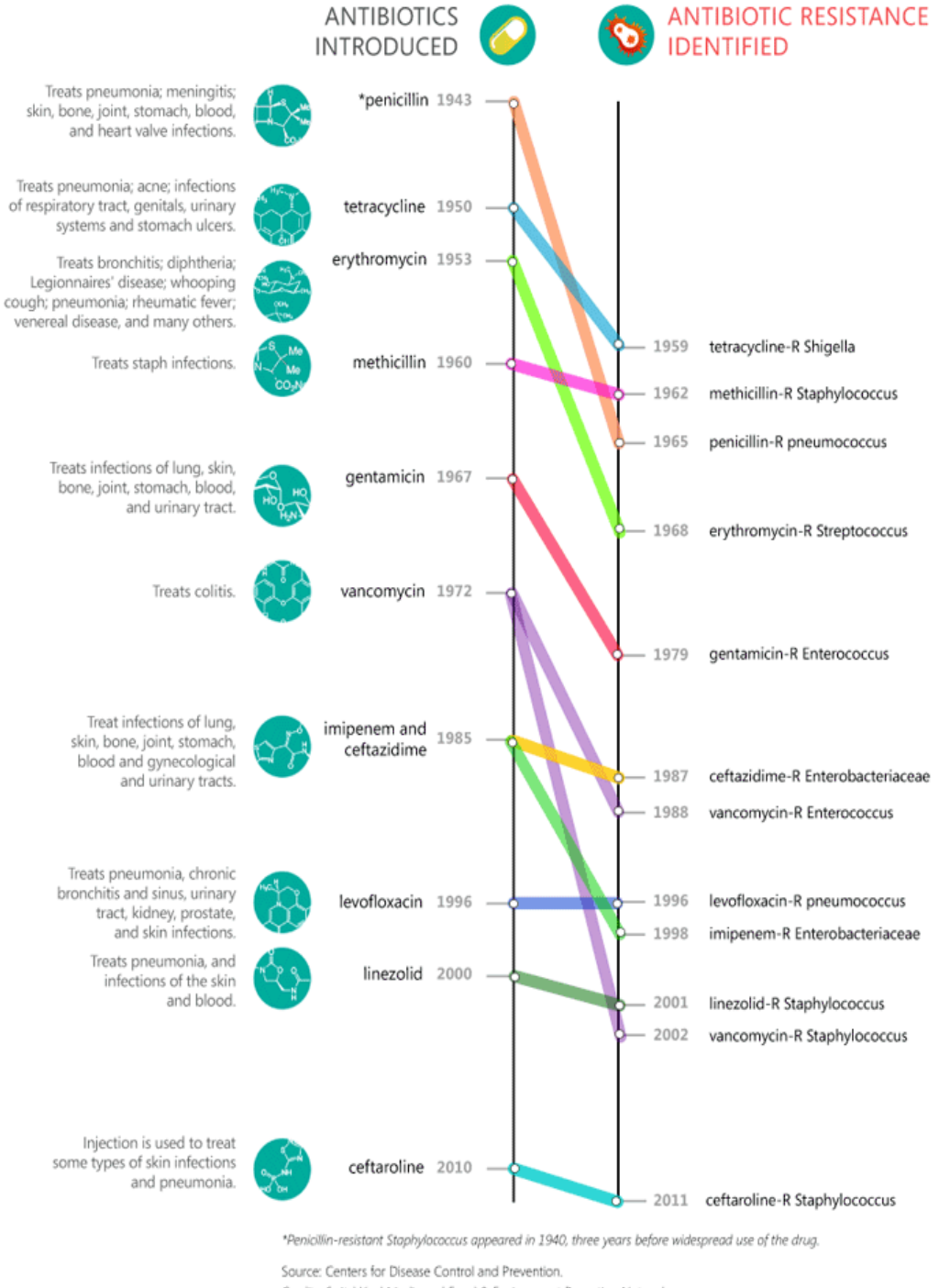
Emergence of Antibiotic resistance to even high-end antibiotics

Ten threats to global health in 2019 - WHO

- Air pollution and climate change
- Antimicrobial resistance
- Threat of a global influenza pandemic
- HIV
- Noncommunicable diseases
- Ebola and high-threat pathogens
- Vaccine hesitancy
- Dengue
- Weak primary care
- Fragile & vulnerable settings (drought and conflict)

Resistance developed faster for recently introduced antibiotics

Strains acquire resistance even before discovery



Antibiotic resistance

Vs

Antimicrobial resistance

Resistance to

- bacteria only

Resistance to

- bacteria
- parasites (e.g. protozoa or helminths)
- viruses (e.g. HIV)
- fungi (e.g. Candida)

Global Scenario of Antimicrobial Resistance

Resistance in ***Klebsiella pneumoniae*** to carbapenem antibiotics

Rising incidence of MDR and XDR tuberculosis

Resistance in ***E. coli*** to fluoro- quinolone a

laria (Cambodia, lic, Myanmar,

Resistance reported in almost all bacterial, viral, protozoal & fungal infections

Treatment failure in **gonorrhea** to third generation cephalosporins

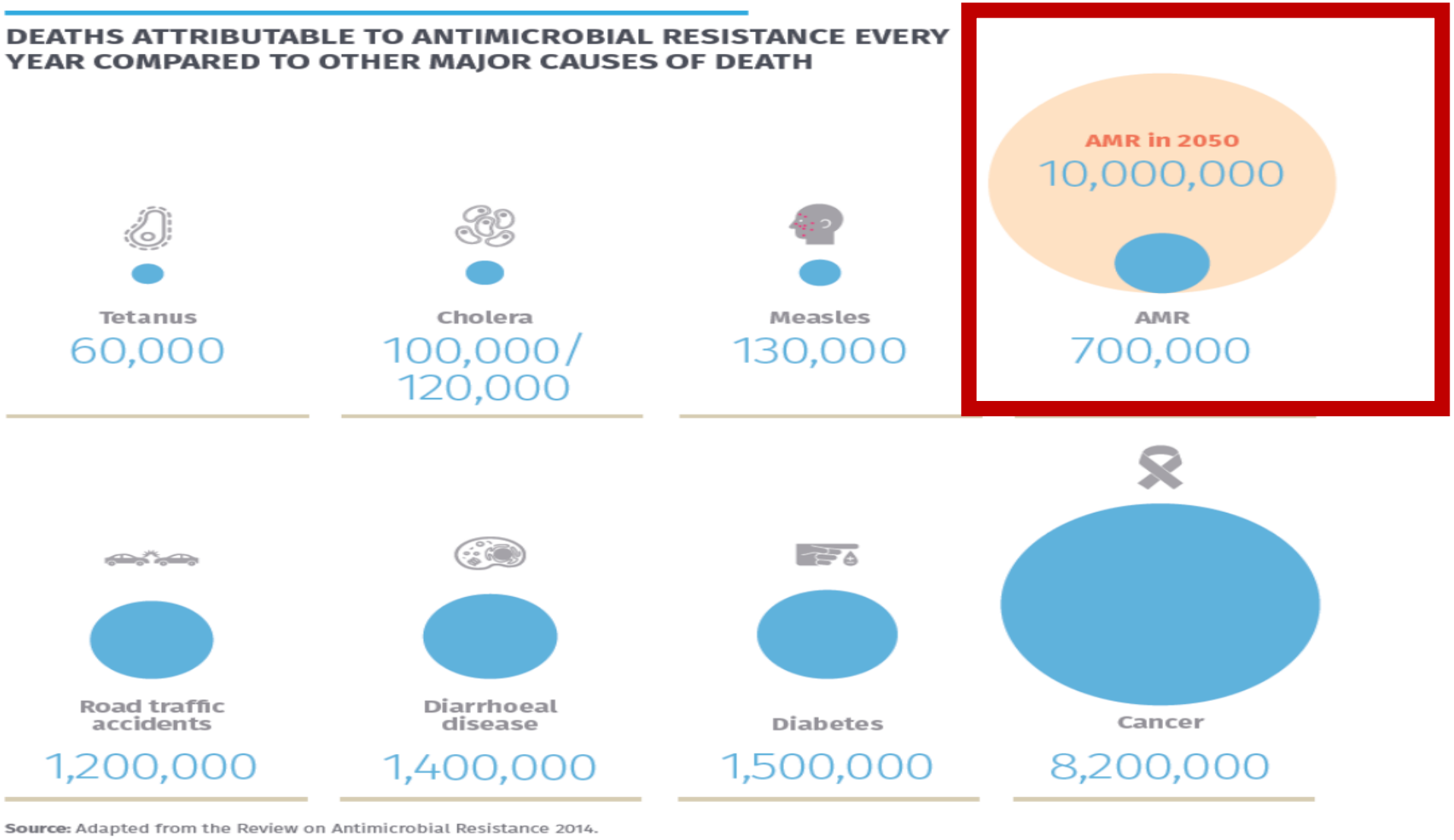
Resistance to ART:
>15% new HIV cases, and up to **40%** in re-starting treatment

Resistance to colistin in *Enterobacteriaceae* has recently been detected

Virtually all influenza A viruses are resistant to M2 Inhibitors and **1-2%** resistant to neuraminidase inhibitor oseltamivir

MRSA: methicillin resistant *S. aureus*; MDR: multidrug resistance; XDR: extensive drug resistance; ACT: Artemisinin-based combination therapies;
ART: Antiretroviral therapy; HIV: human immunodeficiency virus. WHO 2016. Antimicrobial resistance. Available from: http://www.who.int/mediacentre/factsheets/fs194/en/

Mortality due to AMR



Mortality due to AMR - Indian scenario

- Mortality rate – MDR Gram Positive Infections in India is -~**10.8%** (In ICU settings ~**16%**)

- Over 58,000 children died in 2013 due to antimicrobial resistance (may rise to **two million by 2050** if no action is taken)[3]

MRSA: methicillin resistant *S. aureus;* ESBL: extended spectrum beta lactamase. Interdisciplinary Perspectives on Infectious Diseases, 2019

1. Kulkarni et al. Current Perspectives on Treatment of Gram-Positive Infections in India: What Is the Way Forward?
2.Laxminarayan R and Chaudhary RR. Antibiotic Resistance in India: Drivers and Opportunities for Action. *Plos Med.* 2016;13; 2.Laxminarayan R, *et al.* Antibiotic resistance-the need for global solu
Infect Dis. 2013;13:1057–98; 3. Laxminarayan R, *et al.* Access to effective antimicrobials: a worldwide challenge. *Lancet*. 2016;387:168-75;
3.4. Damle SG. The good, the bad and
the ugly!! - Antibiotics. *Contemp Clin Dent*. 2015;6:S139-40.

Geographical Variation in Antibiotic-Resistance

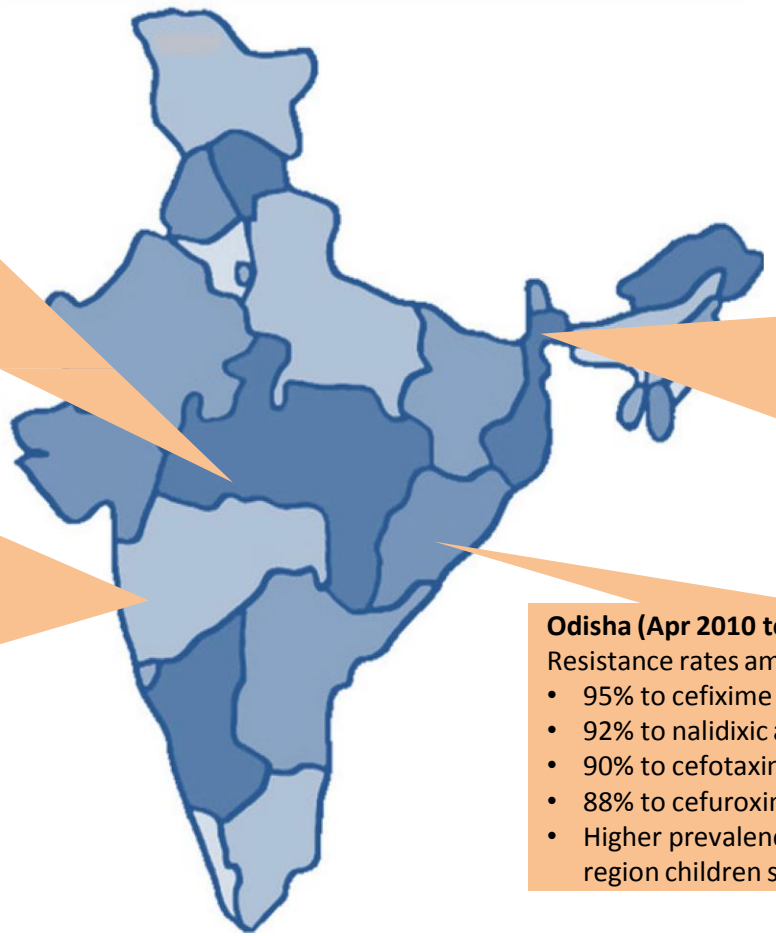
Ujjain, Madhya Pradesh (Jan to Mar 2011):[1]

- Resistance rates among 529 *E. coli* isolates:
- 33% MDR
- 9% ESBL-producers
- 45% to nalidixic acid
- 37% to tetracycline and ampicillin
- 33% to piperacillin
- 13-14% to 2nd and 3rd generation cephalosporins

Tata Memorial Hospital, Mumbai (Jan-Dec 2014):[2]

Among 573 isolates:

- 42% *E. coli* and 35% K. pneumoniae were ESBL producers
- 34% *E. coli* and 48% *K. pneumoniae* were carbapenem-resistant
- 60% of all carbapenem-resistant Enterobacteriaceae colonizers were East Indian children



A referral tertiary care hospital, Sikkim (Jan-Dec 2016):[3]

Among 291 isolates 111 (38.14%) were MRSA:

- Higher among males than females
- Extremely significant higher MRSA positivity among:
  - Age <30 years
  - In-patients
  - Hospitalization >15 days
  - Previous intake of broad spectrum antibiotics

Odisha (Apr 2010 to May 2011):[4]

Resistance rates among among 277 *E. coli* isolates:

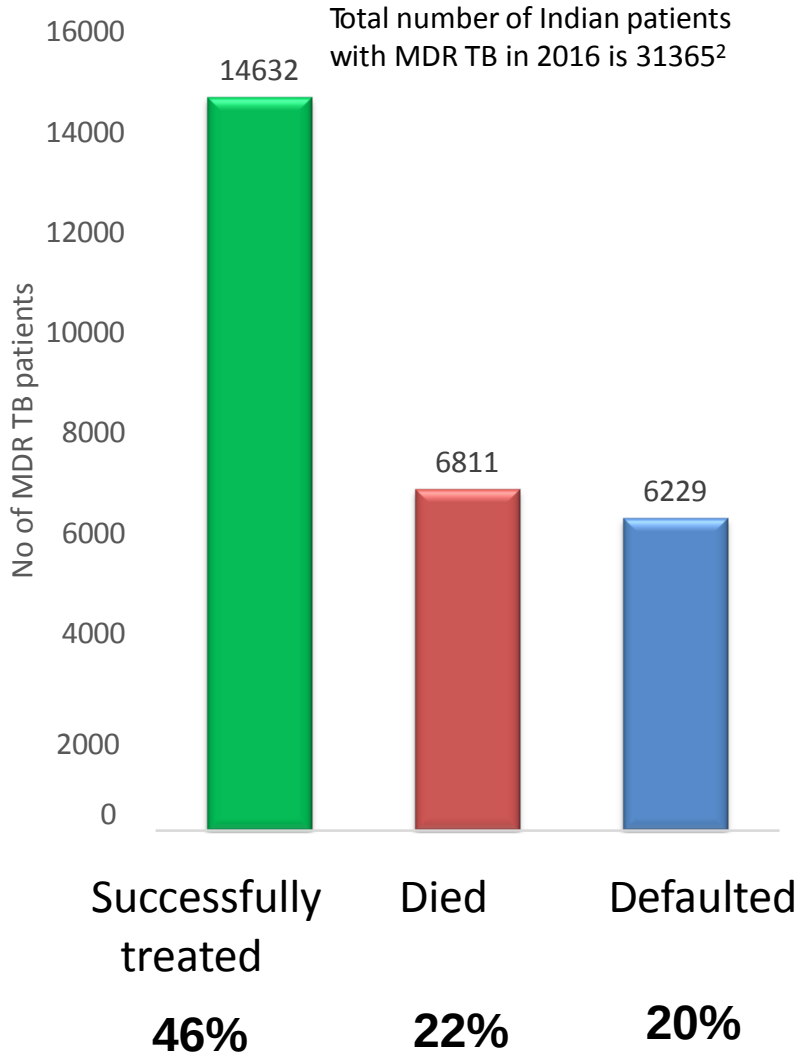
- 95% to cefixime
- 92% to nalidixic acid
- 90% to cefotaxime
- 88% to cefuroxime
- Higher prevalence in the non-coastal than coastal region children stool sample (OR = 3.1, P = 0.021)

ESBL: Extended-spectrum beta-lactamases; OR: Odd ratio; MDR: Multi drug resistance; OR: odd ratio.

1. Shakya P, et al. Antibiotic Resistance among E. coli Isolates from Stool Samples of Children Aged 3 to 14 Years from Ujjain, India. BMC Infect Dis. 2013;13:477. 2. Thacker N, et al. "Alarming prevalence of community-acquired multidrug-resistant organisms colonization in children with cancer and implications for therapy: A prospective study." Indian J Cancer. 2014;51(4):442-6. 3. Tsering DC, et al. Methicillin-Resistant Staphylococcus Aureus: Prevalence and Current Susceptibility Pattern in Sikkim. J Glob Infect Dis. 2011;3(1):9–13. 4. Sahoo, KC, et al. Geographical Variation in Antibiotic-Resistant Escherichia Coli Isolates from Stool, Cow-Dung and Drinking Water. Int J Environ Res Public Health. 2012;9(3):746-59.

Burden of MDR and XDR-TB in India

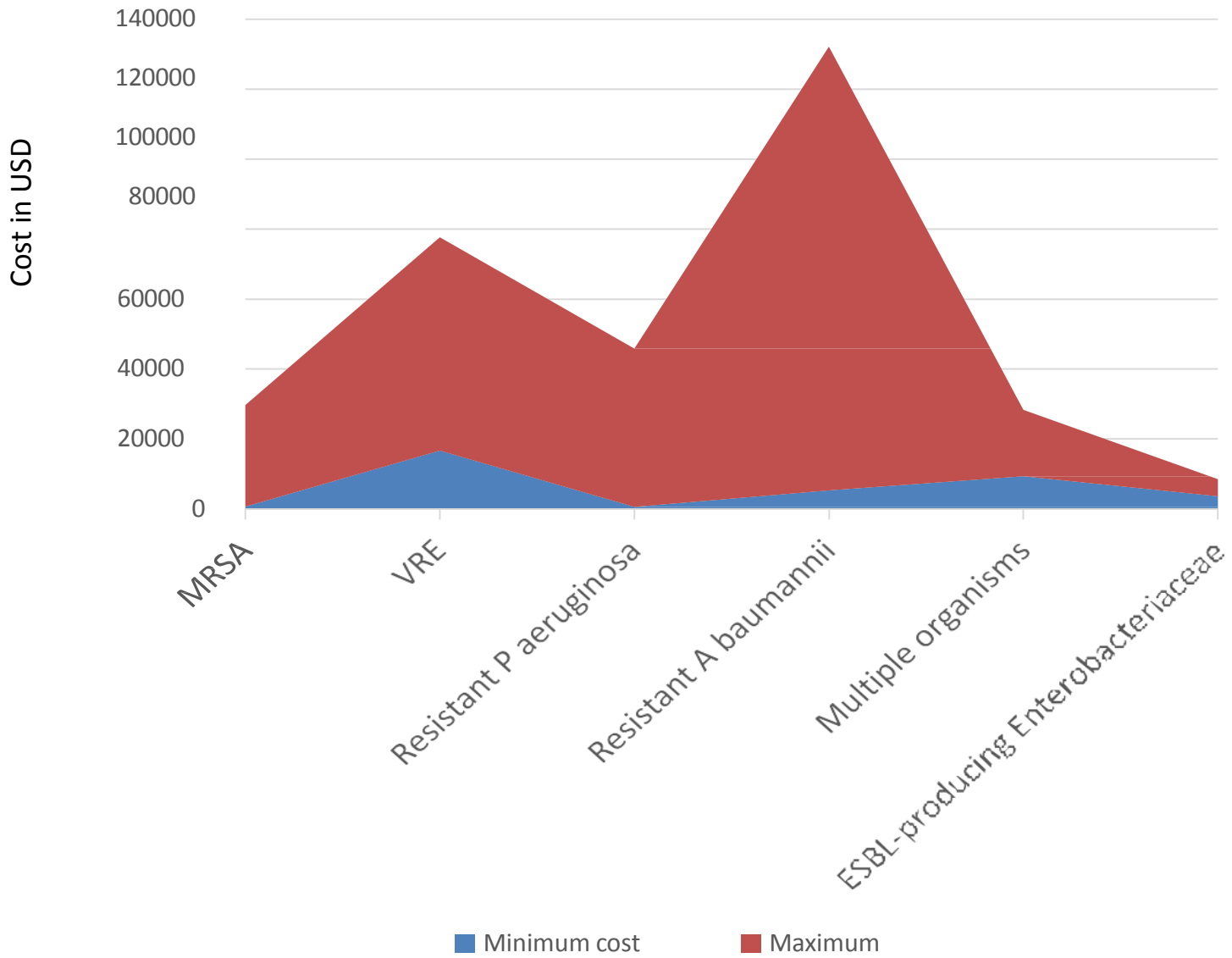
- Between 2013-15 a **34% increase** in number of new and relapse TB cases notifications in India[1]
- 30% of **XDR –TB** were notified in India (2015)[1]



MDR: multi drug resistance; XDR: extensive drug resistance; TB: tuberculosis.

1. WHO 2016. Available from: http://www.who.int/mediacentre/factsheets/fs104/en/. 2. TB India 2016. Available from: http://www.tbcindia.nic.in/showfile.php?lid=3180.

Economic burden due to AMR



Cost of treatment of resistant infections was higher by minimum ~500 USD to a maximum ~1,20,000 USD when compared to susceptible infections

Gandra S, *et al.* Economic burden of antibiotic resistance: how much do we really know? *Clin Microbiol Infect*. 2014;20:973-80.

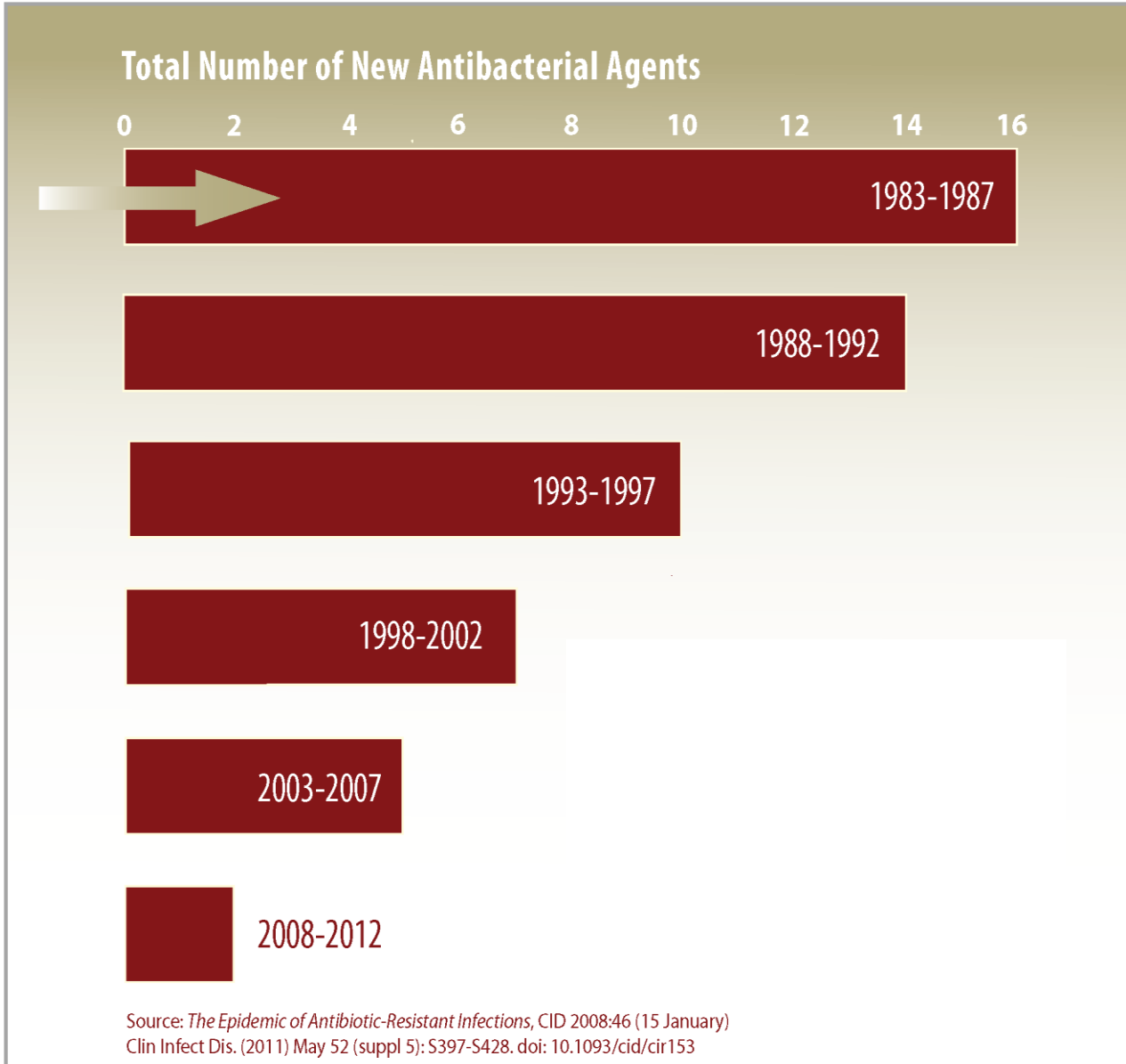
Rising AMR

Shrinking Antibiotic pipeline

Dwindling antibiotic development

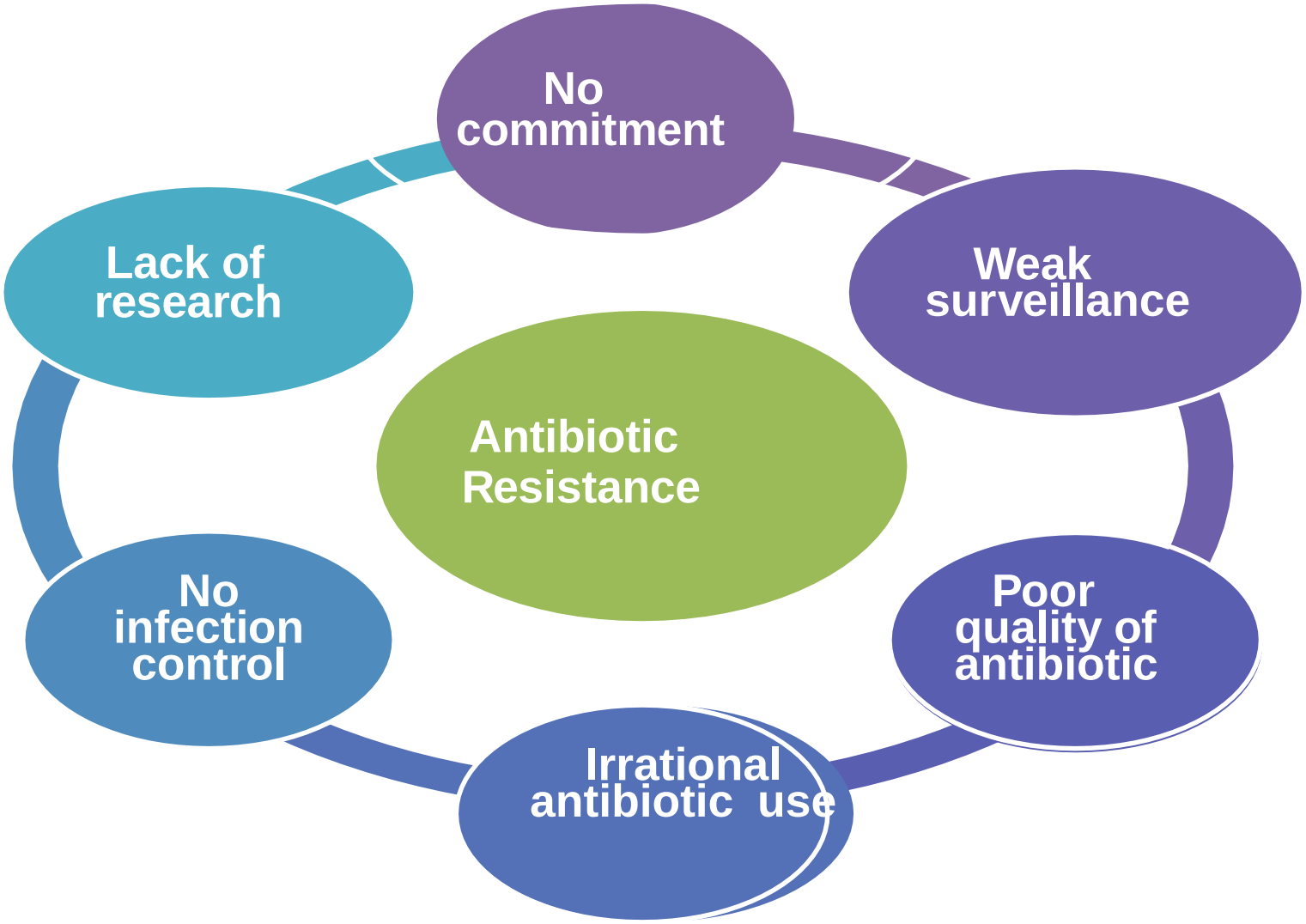
Reasons

- Not economically viable
- Antibiotics used only for short periods
- Benefit expected for a new antibiotic $50 million when compared to $1billion for non-communicable diseases
- Restriction to the use of new antibiotic



Ventola. The antibiotic resistance crisis.P T. 2015 Apr; 40(4): 277–283.

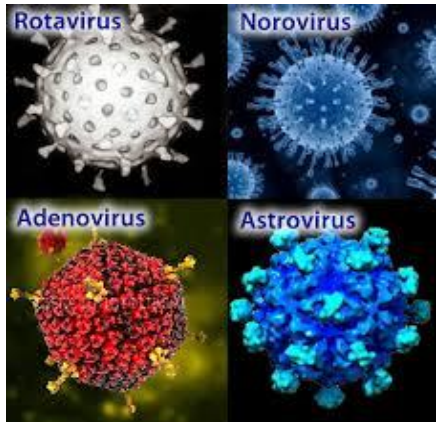
Factors contributing to AMR



Overprescribing of antibiotics

60- 75% of the antibiotic prescriptions each year for ARI

Common cold, flu, bronchitis



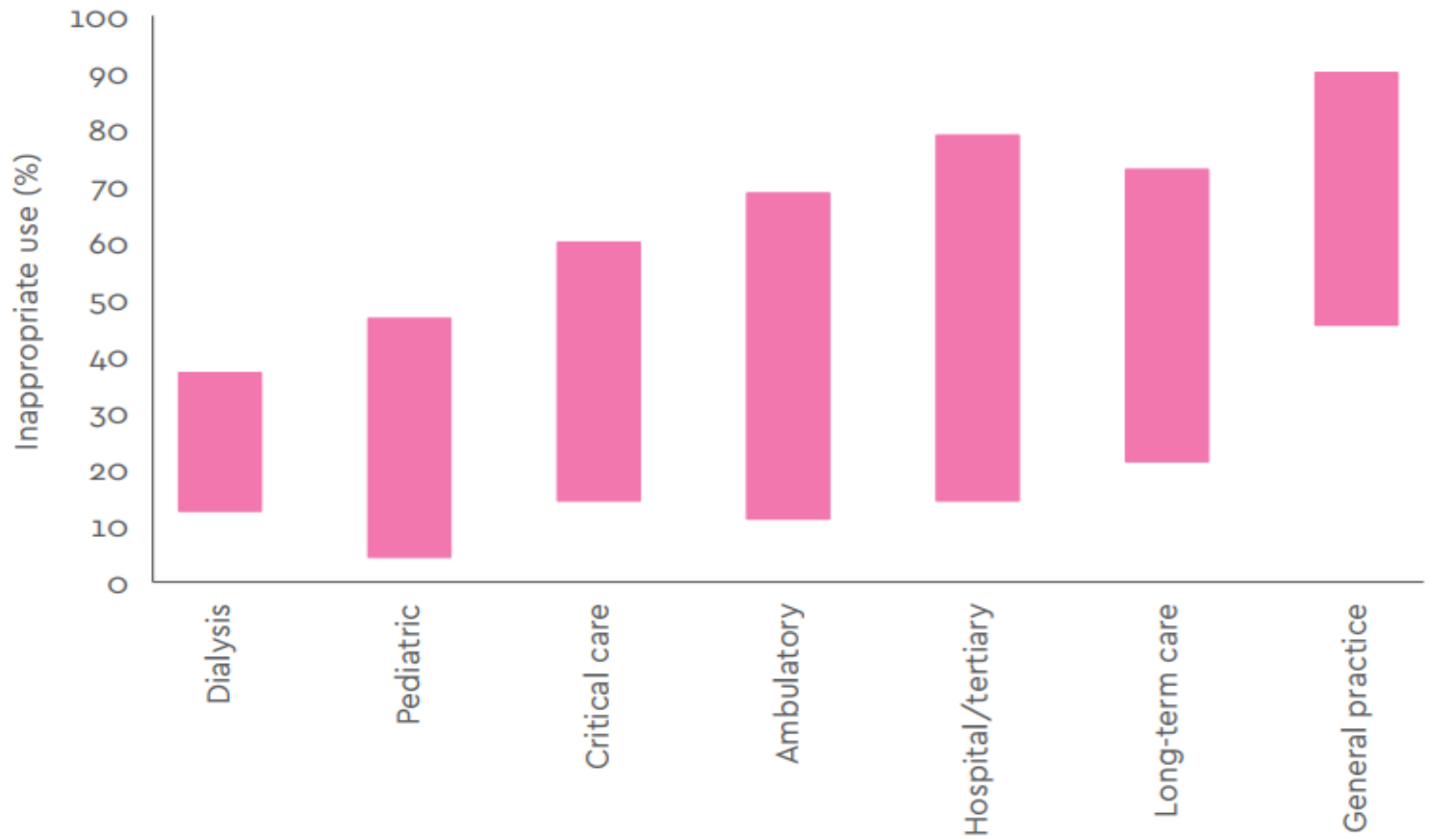
Mostly Viral etiology

30-45 % of the antibiotic prescriptions each year for Acute gastroenenteritis

Acute gastroenteritis

Antibiotics offer no benefit

Estimated proportion of inappropriate antimicrobial use



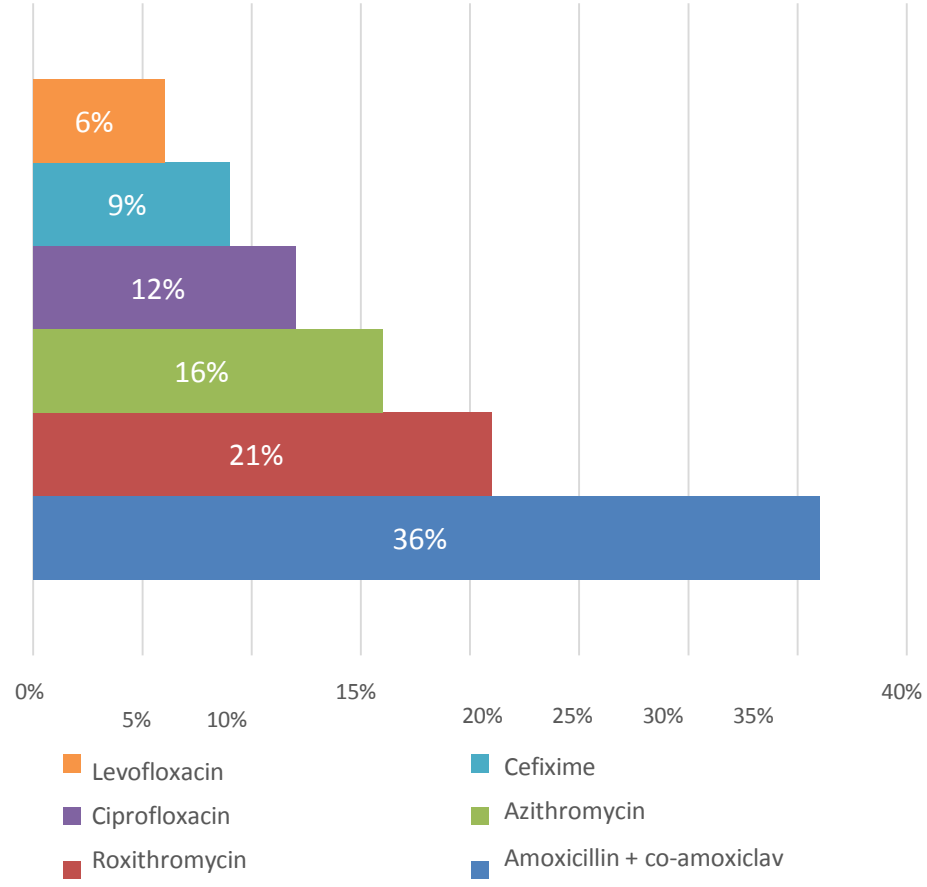
Source: OECD (2017)

Over-the-counter use & poor medication adherence

A retrospective study of 200 patients visiting a dental clinic in a north Indian city showcased

- Only 21% completed the full course
- 18% stopped on getting symptomatic relief
- Rest stopped on experiencing a side effect

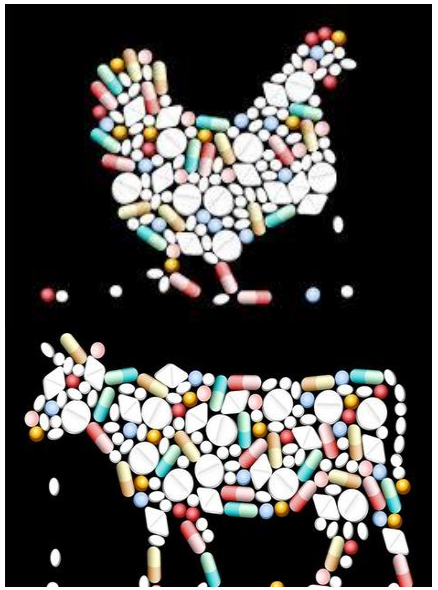
Most Common Antibiotics used OTC in India



OTC: over the counter; URTI: upper respiratory tract infections. Bhanwra S. A study of non-prescription usage of antibiotics in the upper respiratory tract infections in the urban population. *J Pharmacol Pharmacother*. 2013;4:62–4.

Unregulated antibiotic use in livestock and poultry

- India - largest antimicrobial consumption in food animals
- Residues of multiple antibiotics such as fluoroquinolones and tetracyclines in chicken meat samples from Delhi NCR (CSE report 2014)
- Industry growth expected to increase by 80% by 2030



CSE: Centre for Science and Environment.

1. Antibiotics in food. Available at: http://www.cseindia.org/userfiles/02%20Honey.pdf; 2. Boeckel TPV, *et al.* Global trends in antimicrobial use in food animals. *PNAS*. 2015;12:5649-54; 3. Laxminarayan R, Chaudhury RR. Antibiotic Resistance in India:Drivers and Opportunities for Action. *PLoS Med.* 2016;13:e1001974.

Antibiotics found in many honey brands

ScientificWorldJournal. 2012; 2012: 930849.
Published online 2012 Oct 14. doi: 10.1100/2012/930849
PMCID: PMC3477659
PMID: 23097637

Antibiotic, Pesticide, and Microbial Contaminants of Honey: Human Health Hazards

Noori Al-Waili, [1,*] Khelod Salom, [1] Ahmed Al-Ghamdi, [2] and Mohammad Javed Ansari [2]

Oxytetracycline and chloramphenicol residues have been found above the regulatory standards in hone

Antibiotics in environment –

Improper disposal

Industry effluent

Hospital waste

Household leftover medicines

Antibiotics in river

HEALTH

Rivers across the world have high levels of antibiotics

Researchers estimate presence of 14 antibiotics in rivers of 72 countries across six continents

NEXT NEWS >

By Vibha Varshney
Last Updated: Tuesday 28 May 2019

Antibiotics in river contd..

Environ Pollut. 2019 Mar;246:443-451. doi: 10.1016/j.envpol.2018.12.022. Epub 2018 Dec 11.

River Ganges water as reservoir of microbes with antibiotic and metal ion resistance genes: High throughput metagenomic approach.

Reddy B[1], Dubey SK[2].

Author information

1 Molecular Ecology Laboratory, Centre of Advanced Study in Botany, Institute of Science, Banaras Hindu University, Varanasi, 221005, India.

2 Molecular Ecology Laboratory, Centre of Advanced Study in Botany, Institute of Science, Banaras Hindu University, Varanasi, 221005, India. Electronic address: skdubey@bhu.ac.in.

Strategies to control and prevent AMR

Antimicrobial stewardship

Alternatives to antibiotics

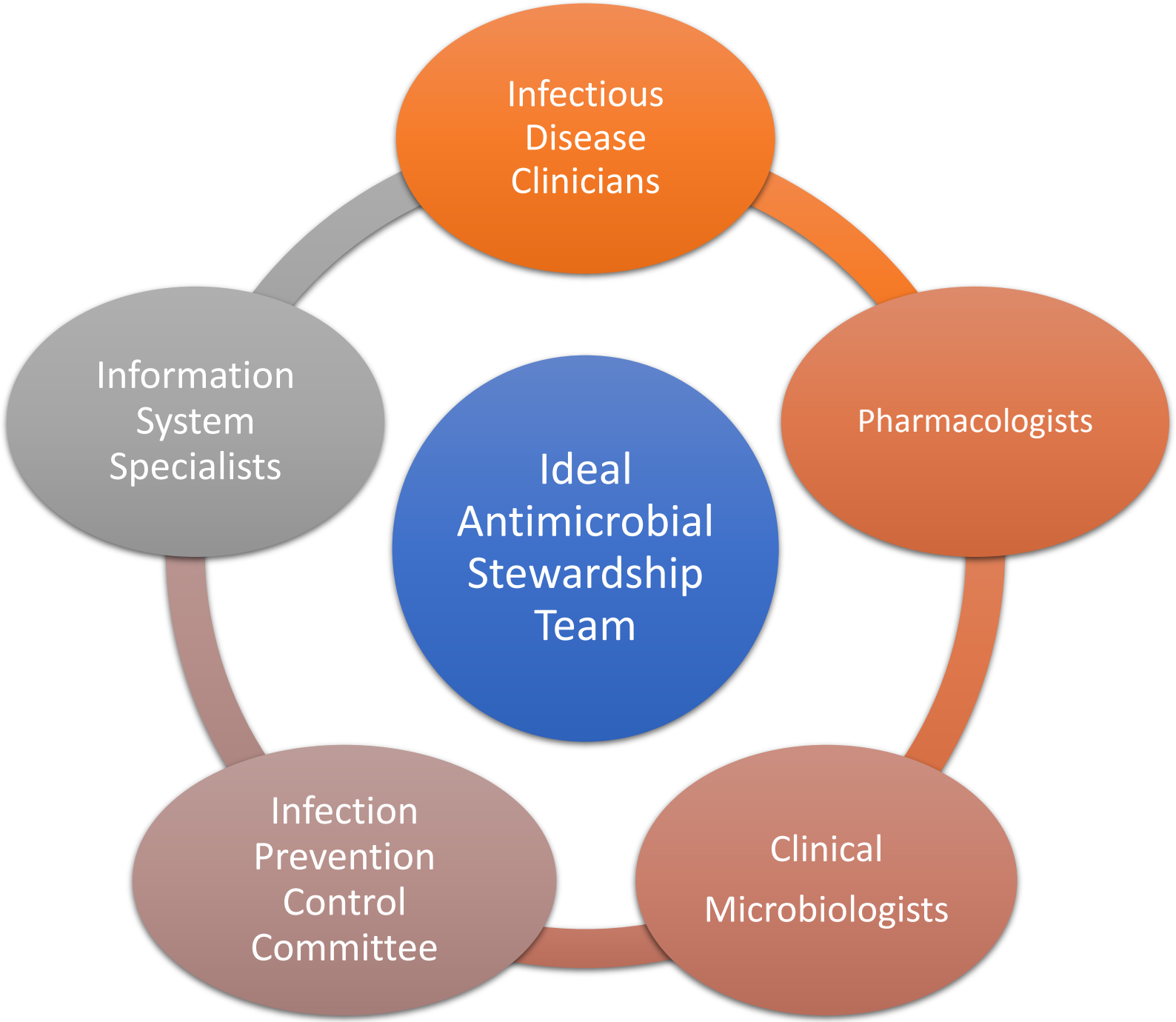
Antimicrobial Stewardship Program (ASP)

Purpose of stewardship program

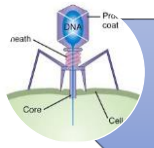
1. **optimize safe and appropriate use of antibiotics** to improve clinical outcomes and minimize adverse effects of antibiotics
2. **reduce health care costs** without adversely impacting quality of patient care **reduce the incidence of** antibiotic induced **collateral damage**

Essential components of ASP

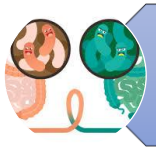
- Appropriate antimicrobial therapy (4Rs)
- Prospective audit with feedback and timely intervention
- Formulary restriction/ preauthorisation
- 
  Switch from parental to oral
- Streamlining/
  De-escalation
- Appropriate use of microbiology lab
- Education and administrative action


Infectious Disease Clinicians
Pharmacologists
Clinical Microbiologists
Infection Prevention Control Committee
Information System Specialists
Ideal Antimicrobial Stewardship Team

Alternatives to antibiotics

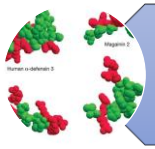


Bacteriophage therapy

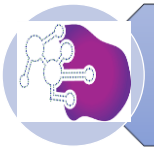


Fecal microbiota transplantation

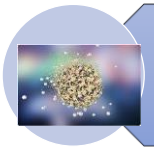
Antimicrobial adjuvants



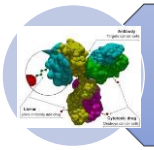
Antimicrobial peptides



Nucleic acid-based aptamers



Novel delivery platform using nanocarriers



Antibiotic-antibody conjugates

Initiatives undertaken..

WHO Essential Medicine List

Classifies antibiotics into

Access

Which indicates the antibiotic of choice for each of the 25 most common infections. These antibiotics should be available at all times, affordable and quality-assured.

Watch

Which includes most of the "highest-priority critically important antimicrobials" for human medicine and veterinary use. These antibiotics are recommended only for specific, limited indications

Reserve

Antibiotics that should only be used as a last resort when all other antibiotics have failed.

AWaRe Classification of antimicrobials – WHO EML

Access

Amoxicillin
Amoxicillin and clavulanic acid
Ampicillin
Benzathine benzylpenicillin
Benzylpenicillin
Cefalexin or cefazolin
Chloramphenicol
Clindamycin
Cloxacillin
Doxycyline
Gentamicin or amikacin
Metronidazole
Nitrofurantoin
Phenoxymethylpenicillin
Procaine benzylpenicillin
Spectinomycin
Sulfamethoxazole and trimethoprim

Core access antibiotics

Azithromycin
Cefixime
Cefotaxime
Ceftriaxone
Ciprofloxacin
Clarithromycin
Piperacillin and tazobactam
Meropenem
Vancomycin

* Antibiotics that are also in the Watch group

Watch

Anti-pseudomonal penicillins with beta-lactamase inhibitor (eg, piperacillin and tazobactam)
Carbapenems or penems (eg, faropenem, imipenem and cilastatin, meropenem)
Cephalosporins, third generation (with or without beta-lactamase inhibitor; eg, cefixime, cefotaxime, ceftazidime, ceftriaxone)
Glycopeptides (eg, teicoplanin, vancomycin)
Macrolides (eg, azithromycin, clarithromycin, erythromycin)
Quinolones and fluoroquinolones (eg, ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin)

Reserve

Aztreonam
Cephalosporins, fourth generation (eg, cefepime)
Cephalosporins, fifth generation (eg, ceftaroline)
Daptomycin
Fosfomycin (intravenous)
Oxazolidinones (eg, linezolid)
Polymyxins (eg, colistin, polymyxin B)
Tigecycline

Revision of NLEM- 2015

To align with AMR initiatives

National Consultation Meeting to be held on

4th November 2019

D&C Rule,1945 amended to include **Schedule H1** in 2013

'35' *out of 46 listed drugs are antibiotics*

- Recorded in a **separate register** at the time of the supply
  - **Name and address of the prescriber**
  - **Name of the patient**
  - **Name of the drug**
  - **Quantity supplied and such records**

- Records shall be maintained for **three years** and be open for inspection

- **Drug Label contain:**

Schedule H1 Drug-Warning:
-It is dangerous to take this preparation except in accordance with the medical advice
-Not to be sold by retail without the prescription of a Registered Medical Practitioner

What next??

Schedule H2 !!

Vancomycin
Daptomycin
Linezolid
Tigecycline
Colistin
5th generation cephalosporine

Schedule H3 !!

Bedaquiline
Delomanid
Pretomanid
Sutezolid

Colistin ban in live stock industry

MINISTRY OF HEALTH AND FAMILY WELFARE

(Department of Health and Family Welfare)

NOTIFICATION

New Delhi, the 19th July, 2019

S.O. 2607(E).—Whereas, it is brought to the notice of the Central Government that the use of the drug Colistin and its formulations for food producing animals, poultry, aqua farming and animal feed supplements is likely to involve risk to human beings;

And whereas, the Drugs Technical Advisory Board has considered the said matter and recommended for prohibiting the said drug and its formulations for food producing animals, poultry, aqua farming and animal feed supplements;

And whereas, the Central Government is satisfied that it is necessary and expedient in the public interest to prohibit the manufacture, sale and distribution of the drug Colistin and its formulations for food producing animals, poultry, aqua farming and animal feed supplements;

Now, therefore, in exercise of powers conferred by section 26A of the Drugs and Cosmetics Act, 1940 (23 of 1940), the Central Government hereby—

(a) prohibits the manufacture, sale and distribution of the following drug with immediate effect, namely:—

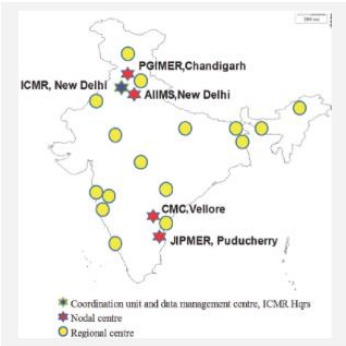
"Colistin and its formulations for food producing animals, poultry, aqua farming and animal feed supplements"; and

(b) directs that the manufacturer of Colistin and its formulations shall label the container of the drug and mention the words "NOT TO BE USED IN FOOD PRODUCING ANIMALS, POULTRY, AQUA FARMING AND ANIMAL FEED SUPPLEMENTS" in conspicuous manner on the package insert and promotional literature of the said drug and its formulations.

[F. No. X. 11014/8/2019-DR]

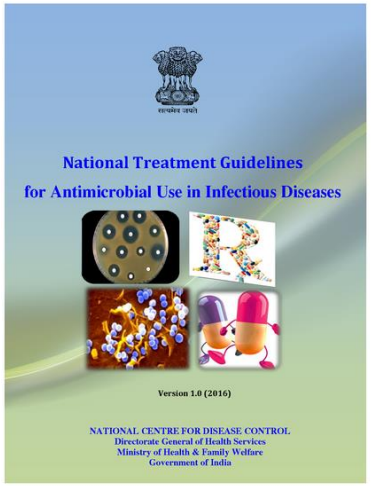
Dr. MANDEEP K. BHANDARI, Jt. Secy.

ICMR initiatives



2013

Antimicrobial Resistance Surveillance & Research Network (AMRSN)

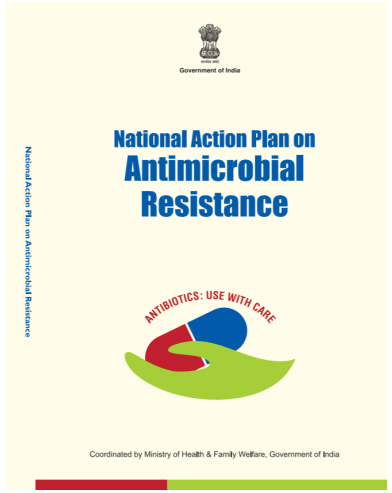


2016

National treatment Guidelines for antimicrobial use in infectious diseases

Antimicrobial stewardship guidelines

2017



National Antimicrobial Resistance Surveillance System

ICMR has established a National Program on Antimicrobial Surveillance in ten laboratories which will focus on:

Diarrhea (e.g., *Shigella*, *Vibrio cholerae*)

Enteric fever (e.g., *S. typhi, S. paratyphi*)

Sepsis caused by Enterobacteriaceae (e.g., *E. coli*, *K. pneumoniae*), Other **Gram-negative organisms** (e.g., *Pseudomonas aeruginosa*, *A. baumannii*) Gram-positive bacteria (e.g., **MRSA** and **VRE**)

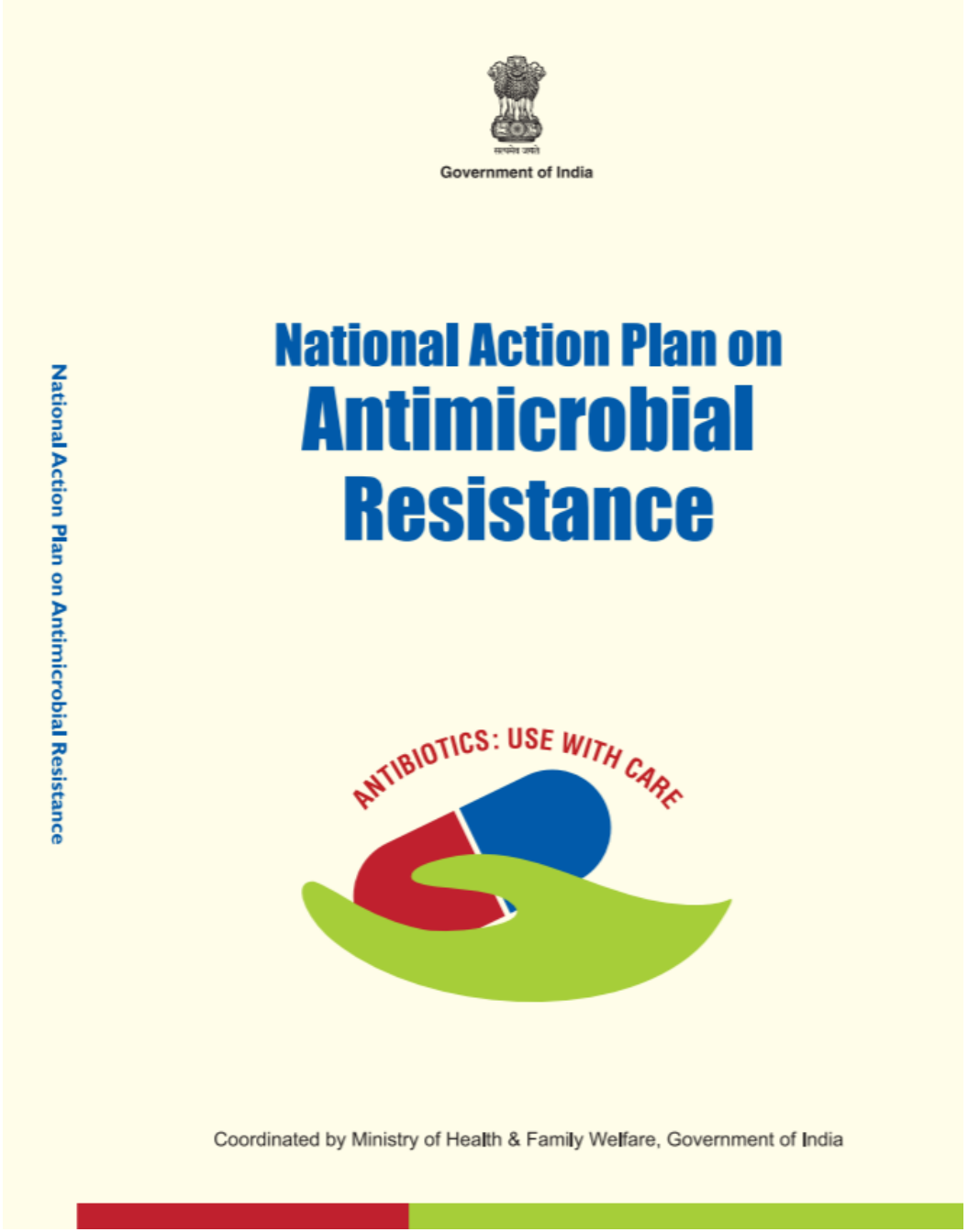
Fungal infections (e.g., *Candida* spp.)

Respiratory pathogens (e.g., *Streptococcus pneumoniae*)

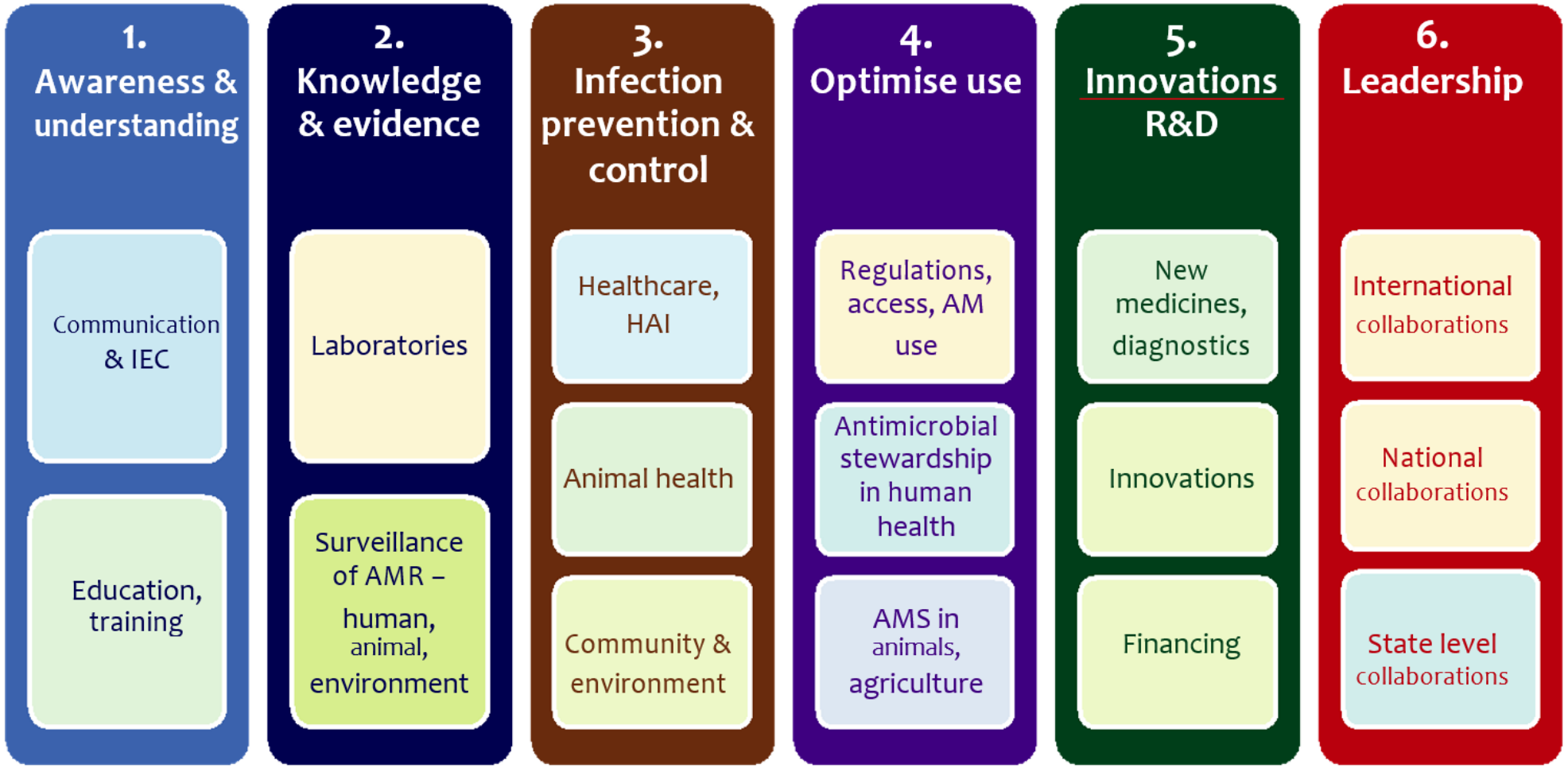
ICMR: Indian Council of Medical Research; VRE: vancomycin-resistant enterococci; MRSA: Methicillin resistant *S. aureus*

Laxminarayan R, Chaudhury RR. Antibiotic Resistance in India: Drivers and Opportunities for Action. *PLoS Med.* 2016;13:e1001974.

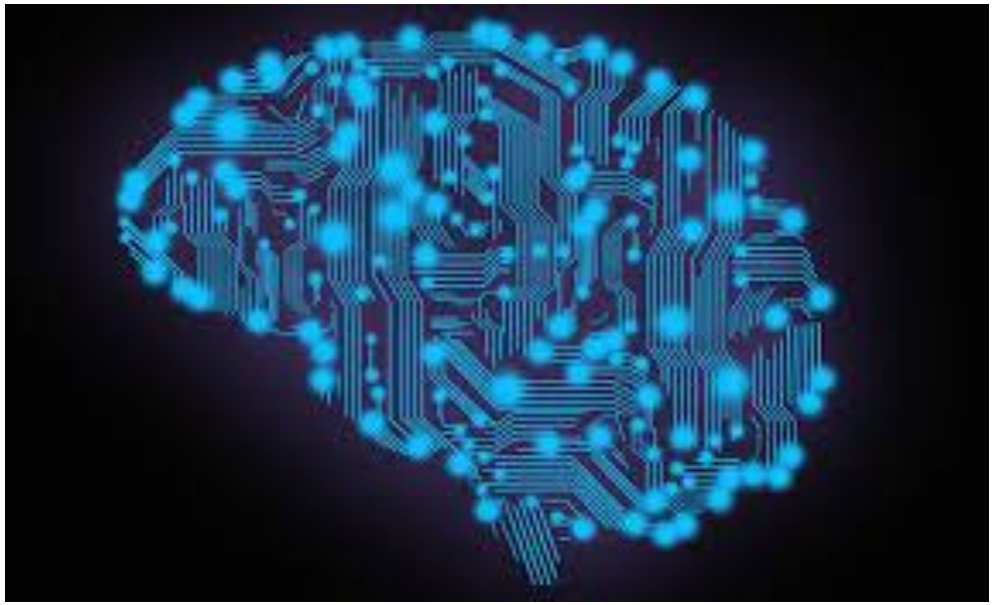
National Action Plan on Antimicrobial Resistance (NAP-AMR) 2017 – 2021



Focus areas of NAP-AMR strategic priorities



Artificial intelligence & AMR



Shared responsibility of all stakeholders to combat AMR

Thank you..