

# Tackling AMR crisis in India: Changing paradigm



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## ABSTRACT

Antimicrobial resistance (AMR) is an important public health concern globally. For India, undoubtedly, AMR has had profound impact on its health & socioeconomic parameters. Several hospital and community-based surveys have indicated alarming rise in incidence of multidrug resistant microbes, especially 'superbugs', having direct links with antibiotic use/misuse. Additionally, paucity in data with regards to quantification of AMR crisis & its determinants has been concerning. However, the national commitment to address AMR has steadily increased of late, with an oft-repeated realization – *it is time to act*. Recent initiatives like *National Policy for Containment of AMR (2011)*, *Chennai Declaration (2012)*, *Anti-microbial Resistance Surveillance and Research Network (2013)*, *The Red Line Campaign (2016)*, *National Action Plan (NAP) for AMR (2017)*, *ICMR Treatment Guidelines for Antimicrobial Use in Common Syndromes (2019)* are promising measures expected to have positive impact on both clinical and economic outcome in India. This paper provides a snapshot of major strategies proposed in recent years, including educational and awareness initiatives, infection control guidelines, audit and feedback, antimicrobial stewardship, surveillance projects etc. It also identifies technical challenges & opportunities for improved AMR mitigation in India.

**Key words:** Antibiotics; Antibiotic resistance; Knowledge; Rational use; Challenges; India

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## INTRODUCTION

Infectious disease burden in India is among the highest in the world, including those caused by multi-drug resistant (MDR) pathogens. The crude mortality rate from infectious disease in India today is nearly 417 per 100,000 persons.<sup>1</sup> Antibiotic-resistant strains have emerged among both Gram-positive and Gram-negative pathogens. Meta-analysis of drug susceptibility data from several Indian laboratories show increasing antimicrobial resistance (AMR) against pathogens like *Staphylococcus*, *Vibrio*, *Salmonella*, *Shigella*, *Neisseria*, *Mycobacterium tuberculosis* and HIV.<sup>1</sup> Of late, MDR 'superbugs' showing resistance against high-end antibiotics like carbapenems and colistin (last resort antibiotics) have been also identified.<sup>1</sup>

There are several determinants to the burgeoning AMR epidemic. One of the main compounders include public lack of knowledge regarding appropriate use of antibiotics. Self-medication and poor compliance are additional concerns. Inadequate infection control practices in hospitals also increases the risk of transmission of MDR pathogens to vulnerable subjects. Paucity in local susceptibility data makes it difficult to identify factors responsible for emergence of MDR pathogens. Besides the healthcare sector, antibiotic use in livestock such as in animal husbandry, fisheries and agricultural sectors for non-therapeutic purposes is also an unmeasured burden in India.

However, in the past few years, India has recognized AMR mitigation as a national priority. It has introduced

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catalogue of strategies, ranging from educational and awareness initiatives, infection control guidelines, audit and feedback, antimicrobial stewardship (AMS) and surveillance programmes to control the AMR crisis, **Table 1**.

Studies show that such resources have a positive impact on both clinical and economic outcomes.<sup>1</sup> Experts are also mulling if antibiotics can be grouped into categories with recommendations when each category should be used, in line with the recent 2019 WHO AWaRe Classification<sup>2</sup> (**Figure 1**) to ensure appropriate antibiotic usage in the country.

As India continues to formulate innovative action plans, this review highlights major policies introduced in recent years, expected to mitigate AMR trends significantly.

### Jaipur Declaration (2011)

Acknowledging the growing global importance of AMR, the Health Ministers of all Member States of the WHO South-East Asia Region, including India, adopted the “Jaipur Declaration on Antimicrobial Resistance”.<sup>3</sup> The Declaration recognizes that it is imperative that the national

governments accord utmost priority to this problem to preserve the efficacy of antibiotics in the fight against microbial diseases. India along with other nation signatories pledged to form multi-sectoral steering committees and formulate national antibiotic policies, laboratory-based antimicrobial surveillance programmes, hospital infection-control policies and evidence-based national antimicrobial prescribing guidelines.

### National Policy for Containment of AMR (2011)

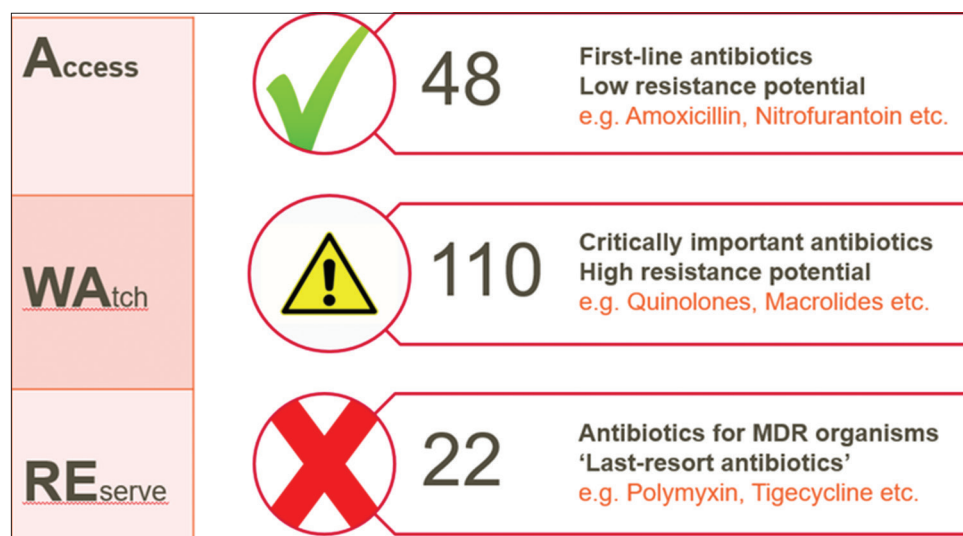
A substantial step toward tackling AMR was taken in the form of a National Task Force on AMR Containment in 2010. Subsequently, the National Policy for Containment of Antimicrobial Resistance<sup>4</sup> was included in the 12<sup>th</sup> 5-year plan (2012 – 2017). Major recommendations within the policy include launch of *Schedule H1* (March 1, 2014) for prescription antibiotics and hospital-based sentinel surveillance system for monitoring AMR.<sup>5,6</sup>

The notification on Schedule H1 (Aug 30, 2013) is particularly important. In India, currently 46 drugs (35 antimicrobials) have been placed under this category, mostly consisting cephalosporins, carbapenems, fluoroquinolones and

**Table 1: Key initiatives by India to contain antimicrobial resistance**

Timeline	Description
2007	Bureau of Indian Standards – Specifications on Poultry feeds banning use of antibiotic growth promoters with systemic action (such as chloramphenicol, doxycycline, tetracycline etc.)
2009	Establishment of the Global Antibiotic Resistance Partnership (GARP)-India
2011	Food Safety and Standards Authority of India (FSSAI) released standards tolerance limit for antibiotics in veterinary use India along with member states of WHO South-East Asia Region becomes signatory to the “Jaipur Declaration on Antimicrobial Resistance” The “National Programme on Containment of Antimicrobial Resistance” launched under the 12th five-year plan (2012-2017), which included <i>Schedule H1</i>
2012	Launch of ICMR-ASPIC (Antibiotic Stewardship, Prevention of Infection & Control) programme
2013	National Livestock Policy released that encouraged rational antibiotic prescribing by the states ICMR initiated Antimicrobial Resistance Surveillance and Research Network (AMRSN)
2015	Strengthening AMR surveillance network for key pathogens and enrolment in WHO Global Antimicrobial Resistance Surveillance System (GLASS) ICMR releases Standard Operating Procedures for Mycology & Bacteriology (laboratory testing)
2016	National Centre for Disease Control (NCDC) published the National Treatment Guidelines for Antimicrobial Use in infectious diseases & hospital-infection control guidelines An international conference on AMR - “Combating Antimicrobial Resistance: A Public Health Challenge and Priority” jointly organized by the Government of India and the WHO. “Medicines with the Red Line” media campaign launched
2017	ICMR published its guidelines (first edition) on antimicrobial use in common syndromes. The Indian Network for Fisheries and Animals Antimicrobial Resistance established with Food and Agriculture Organization’s (FAO’s) assistance The National Action Plan on AMR adopted Delhi declaration – an inter-ministerial consensus on AMR by Government of India (INDIA) “National Consultation to Operationalize Action Plan for AMR Containment” was jointly organized by the Ministry of Health and Family Welfare-INDIA, National Centre for Disease Control (NCDC)-INDIA, and WHO Country Office for India, State health ministries and other relevant stakeholders, to initiate NAP-AMR implementation Updated draft standards for antibiotic residues in pharmaceutical industrial effluent and common effluent treatment plants released by the Central Pollution Control Board (CPCB).
2018	NCDC released ‘Guidance for developing State Action Plans for Containment of Antimicrobial Resistance’ (SAPCAR) Kerala became the first state to adopt the sub national SAPCAR ICMR releases the Antimicrobial Stewardship Guidelines
2019	ICMR releases second edition of guidelines on antimicrobial use in common syndromes; includes updated information on guidelines for treatment of <i>bone and joint infections, skin &amp; soft tissue and central nervous system infections</i> .

\*The above list is not exhaustive. The list is created independently by GSK for description purposes



**Figure 1: WHO AWaRe Classification of Antibiotics 2019**

\*This figure has been independently created by GSK for illustration purposes.

The 2019 WHO AWaRe Classification Database includes details of 180 antibiotics classified as Access, Watch or Reserve, their pharmacological classes, Anatomical Therapeutic Chemical (ATC) codes and WHO Essential Medicines List status.

**ACCESS GROUP ANTIBIOTICS:** Includes 48 antibiotics, 19 of which are included individually on the WHO Model List of Essential Medicines as first- or second -choice empiric treatment options for specified infectious syndromes. **WATCH GROUP ANTIBIOTICS:** This group includes antibiotics that have higher resistance potential and includes most of the highest priority agents among the Critically Important Antimicrobials for Human Medicine and/or antibiotics that are at relatively high risk of selection of bacterial resistance. The Watch group includes 110 antibiotics, 11 of which are included individually on the WHO Model List of Essential Medicines as first- or second -choice empiric treatment options for specified infectious syndromes. **RESERVE GROUP ANTIBIOTICS:** This group includes antibiotics and antibiotic classes that should be reserved for treatment of confirmed or suspected infections due to multi-drug-resistant organisms. Antibiotics in Reserve group should be treated as "last resort" options. 22 antibiotics have been classified as Reserve group. Seven Reserve group antibiotics are listed individually on the WHO Model List of Essential Medicines.

Source: AWaRe Classification Database <https://apps.who.int/iris/bitstream/handle/10665/327957/WHO-EMP-IAU-2019.11-eng.xlsx?ua=1>

anti-tubercular drugs. The packaging of these drugs will have a mandatory 'Schedule H1' warning with 'Rx' symbol in red. The drugs within the list can be sold by pharmaceutical chemist only against a valid prescription. The chemist will maintain a separate register where prescription data will be recorded. The register must be retained for at-least 3-years, subject to inspection by drug regulatory agencies.

Additionally, the policy introduces a system of colour-coding of third generation antibiotics and all newer molecules like carbapenems, tigecycline, daptomycin etc. for restricting their access to only tertiary hospitals. Other interventions such as recent ban on 343 irrational fixed dose combinations (FDC) were aimed to limit antibiotic abuse.<sup>7</sup>

### Chennai Declaration (2012)

"A Roadmap to Tackle the Challenge of Antimicrobial Resistance - A Joint meeting of Medical Societies in India" was organized as a pre-conference symposium of the 2nd annual conference of the Clinical Infectious Disease Society (CIDSCON) at Chennai on August 24, 2012.<sup>8,9</sup> This was the first ever meeting of medical societies in India on issue of tackling AMR, with a plan to formulate a road map to tackle the global challenge of AMR from the Indian perspective.

The meeting had representatives from most medical societies in India and eminent policy makers. A consensus, what came to be known as *Chennai Declaration*<sup>10</sup> was adopted that essentially proposed a 5-year strategy to control AMR. This was a major landmark in India's fight against AMR. Major strategies proposed under the declaration include complete ban on OTC sale of antibiotics without prescription, in-hospital antibiotic usage monitoring, step up microbiology laboratory facilities, establishment of National AMR surveillance system etc.

### ICMR - Antibiotic Stewardship, Prevention of Infection & Control Programme (2012)

The need for AMS practices in hospitals across the country has been evident since many years. In several cases, hospitals do not maintain records of antibiograms or do not have an antibiotic policy altogether. In this regard, ICMR launched the programme on Antimicrobial Stewardship, Prevention of Infection and Control (ASPIC) in 2012 through collaboration between the office of the National Chair of Clinical Pharmacology, ICMR and the Christian Medical College, Vellore.<sup>11</sup> A national workshop was hosted as a part of a 1-year programme to develop capacity of key stakeholders in AMS.

### Anti-microbial Resistance Surveillance and Research Network (2013)

Previously, India did not have a national surveillance system to monitor AMR and this gap was evident when the NDM-1, story was published in 2010.<sup>12</sup> To streamline data collection and have nation-wide picture, the ICMR in 2013 set up an Anti-microbial Resistance Surveillance and Research Network (AMRSN),<sup>13</sup> which is currently networking the tertiary care hospitals in the country. The National Centre for Disease Control (NCDC) is the focal point for implementation of the programme. The overarching aim of this network is to understand the extent and pattern of AMR and use this evidence to guide strategies to control the spread of AMR.

Currently the AMRSN labs includes 20 state medical colleges from 18 states. The focus indication (pathogens) include (i) diarrhea (e.g., *Shigella*, *Vibrio cholerae*), (ii) enteric fever (e.g., *S. Typhi*, *S. Paratyphi*), (iii) sepsis caused by Enterobacteriaceae (e.g., *E. coli*, *K. pneumoniae*), (iv) other Gram-negative organisms (e.g., *Pseudomonas aeruginosa*, *A. baumannii*), (v) Gram-positive bacteria (e.g., MRSA and vancomycin-resistant enterococci [VRE]), (vi) fungal infections (e.g., *Candida* spp.), and (vii) respiratory pathogens (e.g., *Streptococcus pneumoniae*). These labs are required to submit specific AMR surveillance data on a quarterly basis and feedback is provided to the labs by NCDC regarding completeness of data etc. The data is then analyzed at NCDC on an annual basis. The AMRSN 2018 annual report was recently published, along with the AMR data emanating between January 2018 to December 2018.<sup>14</sup>

### The Red Line Campaign (2016)

In 2016, the Ministry of Health & Family Welfare (MoH&FW) launched the 'Red Line Campaign' at the 3-day International Conference on Combating Antimicrobial Resistance, held during February 2016.<sup>15,16</sup> It was a much-needed AMR awareness campaign, that directs patients not to use medicines marked with a red vertical line, comprising of antibiotics, without the prescription of a doctor. These medicines are called as the 'Medicines with the Red Line'. This campaign was intended at discouraging needless prescription and OTC sale of antibiotics. Additionally, a logo 'Use with Care' for antibiotics was launched.<sup>16</sup> Some medicines, such as antibiotics already have the red line, but patients are often unaware of its meaning.

### Antimicrobial Stewardship Guidelines (2017)

In November 2017, ICMR released the Antimicrobial Stewardship Guidelines,<sup>17</sup> to mark the World Antibiotic Awareness Week (12<sup>th</sup> to 17<sup>th</sup> November). It entails developing AMSP curriculum, conducting workshops

and developing AMSP research projects. The aim of the guideline is to provide guidance to Indian hospitals to set up structure and process of AMSP. The audience for this document is hospital administrators and clinicians. Moreover, recognizing the need to create AMSP structures in hospitals across the country,<sup>18</sup> the ICMR also carried out four workshops on AMSP capacity building across the country in the second quarter of 2017 (<http://iamrsn.icmr.org.in/index.php/events/amsp>). More than 30 hospitals across the country participated in the workshop. Several deliverables were identified which could be initiated at the earliest, **Table 2**.

### National Action Plan (2017-2021)

In May 2015, the 68<sup>th</sup> World Health Assembly (WHA) endorsed the *Global Action Plan on Antimicrobial Resistance* (GAP-AMR) – including AMR.<sup>19</sup> The WHA resolution urged Member States to align their National Action Plan on AMR (NAP-AMR) with GAP-AMR by May 2017. To this effect, after consultation with various stakeholders, India released its final draft on NAP-AMR in April 2017,<sup>20</sup> which was then submitted at the 70<sup>th</sup> WHA in Geneva in May 2017. The 5-year NAP on AMR (2017–2021) outlines the priorities and implementation strategies for curbing AMR in India, **Table 3**.

In 2018, India released a guidance document<sup>21</sup> for states to formulate region-specific AMR containing policies or State Action Plans for Containment of Antimicrobial Resistance (SAPCAR). Kerala became the first state to adopt the sub-national SAPCAR.

### ICMR Treatment Guidelines for Antimicrobial use in Common Syndromes (2019)

The Treatment Guidelines for Antimicrobial Use in Common Syndromes aims to rationalize the usage of antibiotics on National List of Essential Medicines (NLEM) and to establish consistency in the treatment of various infectious conditions. The first edition of evidence-based treatment guidelines for treatment of common syndromes was developed by ICMR in 2017. A comprehensive second edition<sup>22</sup> was released on September 12, 2019 and includes updated information on guidelines for treatment of bone and joint infections, skin & soft tissue and central nervous system infections with their dosing, route of administration and duration of therapy. **Table 4** summarizes the steps of rational antimicrobial use in accordance with the 2019 guidelines.

### Technical challenges & opportunities

The increasing national focus on AMR underlines that the issue is cross-sectoral, affecting all strata of society. Apart from rational antibiotic prescribing, a proactive approach towards following issues can further mitigate the AMR crisis:

**Table 2: Recommendations for Indian hospital settings based on the ICMR-AMSP guideline**

Guidelines features	Description
Specific deliverables	1. Hospital antibiogram 2. Hospital antibiotic policy including surgical prophylaxis based on antibiograms 3. Culture of cultures: Point prevalence study 4. Measurement of antibiotic consumption rate (DDD/DOT) 5. Consider introducing audit and formulary restrictions 6. Staff education: CME for hospital staff and for hospitals in surrounding areas
Structure	Antibiotic stewardship team formed in hospitals will be responsible for implementing and monitoring AMSP. The team will coordinate the activities in connection with the hospital and pharmacy, governance, infection control and drug committees. The team must include, but not limited to physician or surgeon trained in infectious disease, a pharmacist, a clinical microbiologist, and infection control personnel.
Antibiogram & antibiotic policy	Hospital-specific antibiograms to be generated periodically; guidelines for antibiotic to be based on antibiograms. Policy must consider site of infection (e.g., skin or soft-tissue infection, intra-abdominal etc.) and mention alternate treatment regimens.
Formularies & guidelines	Approvals for prescribing and dispensing specific drugs and for sale of certain non-prescription drugs to be made mandatory. Guidelines for antimicrobial treatment and prophylaxis need to be available in all healthcare systems.
Training	Periodical training and certification of hospital staff on AMSP is mandatory, and prescribers must have training on "Therapeutic guidelines for antimicrobial use".
Monitoring	Background information on current antibiotic use and prescription rates to be collected. Use of electronic patient records to track prescription and antibiotic usage trends to be devised. Expenditure on antibiotics over time must be monitored.
Goals & measurable outcome	1. The process measures include compliance with surgical prophylaxis prescribing, and 'care bundles' [three-day antibiotic review bundle, VAP bundle]. 2. The outcome measures include antimicrobial usage rates, bacterial culture rate, resistance rates, <i>Clostridium difficile</i> rates, and length of hospital stay etc. 3. The balancing measures are mortality rates, treatment-related toxicity, rates of complications and surgical site infections, admissions in ICU and readmission within 30 days of discharge.
Audit & feedback	Review of prescriptions, laboratory results, clinical notes etc. and most importantly audit of carbapenem and polymyxin use in intensive-care settings.
Interventions	Therapy based on standard guidelines and patients' clinical status to control use of restricted antimicrobials for empirical treatment. Other interventions include directed therapy based on early microscopy tests, antibiotic "time outs", de-escalation of therapy, dose optimization, change of broad-spectrum antibiotics after culture results are available and shortening treatment duration in prophylactic use.
Education & awareness	Medical education curriculum should include AMSP as part of the main course for HCPs. It is also important to create awareness among patients, healthcare workers, administrators and governing authorities through advertising, media and messages.
Research on AMR	AMS research focused on novel strategies of stewardship, implementation and impact of AMSP, point prevalent studies, effective interventions, surveillance and management of antimicrobial usage data, needs be devised for Indian settings

The table has been adapted from ICMR-AMSP guidelines.

AMR, Antimicrobial resistance; DDD, defined daily dose; DOT, days of therapy; VAP; Ventilator-associated pneumonia; CME, continuing medical education; AMS, Antimicrobial stewardship; AMSP, Antimicrobial stewardship programme; HCP, Health-care professionals.

Source: ICMR-AMSP guideline [http://iamrsn.icmr.org.in/images/pdf/AMSP\\_Guidelines\\_final.pdf](http://iamrsn.icmr.org.in/images/pdf/AMSP_Guidelines_final.pdf)

**Table 3: India's National Action Plan on Antimicrobial Resistance (2017-2021)**

Strategic priorities	Main objective
Strategic priority #1	Improve awareness and understanding of AMR through effective communication, education, and training
Strategic priority #2	Strengthen knowledge and evidence through surveillance
Strategic priority #3	Reduce the incidence of infection through effective infection, prevention, and control
Strategic priority #4	Optimize the use of antimicrobial agents in all sectors
Strategic priority #5	Promote investments for AMR activities, research, and innovations
Strategic priority #6	Strengthen India's leadership on AMR by means of collaborations on AMR at international, national, and sub-national levels

Within each strategic priority and focus area, strategic interventions, key activities and outputs have been defined with tentative responsibility and timelines – short (within 1 year), medium (between 1 and 3 years) and long-term (between 3 and 5 years).

Source: National Action Plan on Antimicrobial Resistance (2017-2021) <https://ncdc.gov.in/WriteReadData/linkimages/AMR/File645.pdf>

### Improvement in perception of AMR

The GAP-AMR highlighted important deficits in the understanding of what antibiotics are, how they should be used and when to take them. Instances across the world indicate that integrating concepts of AMR in public-health education can have a beneficial impact.<sup>23</sup> India has started focusing on the component of training in infectious diseases (apart from tuberculosis) through various programmes, e.g. ASPIC, ICMR-AMRSN etc. Providing similar but expanded training in the society can empower people to understand the appropriateness of treatment. India has already shown remarkable reductions in smoking in buildings and workplaces through regulation and behavior change communication. In this regard, successful media campaigns harnessing celebrity power championing for AMR could add benefit, as with campaigns on polio vaccination and tuberculosis screening.

**Table 4: Steps of rational antibiotic use (2019 ICMR guidelines on antimicrobial use)**

Steps	Description
Step #1	<p><b>Making a clinical diagnosis</b></p> <p>An accurate clinical diagnosis is more helpful rather than blindly relying on tests (procalcitonin levels, WBC counts, cultures or radiology) to make a diagnosis of infection. Thought process must include following questions:</p> <ol style="list-style-type: none"> <li>I. Is it an infection?</li> <li>II. Risk assessment of how likely is it that the patient has an infection?</li> <li>III. What are the possible non-infectious mimics?</li> <li>IV. Have we taken the appropriate cultures to confirm the final diagnosis?</li> </ol>
Step #2	<p><b>Limiting empiric antibiotic therapy to genuine seriously ill patients</b></p> <p>Empiric antibiotic therapy is ONLY recommended for a select group of patients after taking appropriate cultures (in cases like febrile neutropenia, severe sepsis and septic shock, necrotizing fasciitis, community acquired pneumonia, ventilator associated pneumonia). It is important to <i>start smart and then focus</i>, i.e., evaluate if empiric therapy can be justified or de-escalated and then plan about the duration of therapy.</p>
Step #3	<p><b>Know your bugs</b></p> <ol style="list-style-type: none"> <li>I. Identify the clinical syndrome</li> <li>II. Elucidate possible sources of infection</li> <li>III. Predict possible microbial pathogens</li> <li>IV. Predict the local resistance pattern based on institutional antibiogram</li> </ol>
Step #4	<p><b>Choose the appropriate antibiotic</b></p> <ol style="list-style-type: none"> <li>I. Based on the spectrum of the antibiotic considering possible resistant patterns</li> <li>II. Use the correct dose, route and duration</li> <li>III. Ensure chosen antibiotic has adequate tissue penetration at the site of infection</li> <li>IV. Optimize PK-PD parameters according to co-morbidities</li> </ol>
Step #5	<p><b>De-escalation/modification</b></p> <ol style="list-style-type: none"> <li>I. Modify empiric broad spectrum antibiotics depending on culture and antimicrobial susceptibility reports and patient status</li> <li>II. Stop polymyxins and glycopeptides, if no carbapenem resistant organisms (CRO) or methicillin resistant <i>Staphylococcus aureus</i> (MRSA) identified on cultures</li> <li>III. Avoid double or redundant gram negative or anaerobic coverage</li> <li>IV. Discontinue antibiotics if a non-infectious mimic identified</li> <li>V. De-escalate combination therapy to a single agent</li> <li>VI. Change a broad-spectrum antibiotic to a narrow spectrum one</li> <li>VII. Change intravenous to oral antibiotics</li> </ol>
Step #6	<p><b>Stop antibiotics in the following clinical situations</b></p> <ol style="list-style-type: none"> <li>I. Respiratory tract syndromes (e.g. viral pharyngitis - viral rhinosinusitis - viral bronchitis - non-infectious cardio-pulmonary syndromes misdiagnosed as pneumonia)</li> <li>II. Skin and Soft Tissue Infections (e.g. subcutaneous abscesses, lower extremity stasis dermatitis)</li> <li>III. Asymptomatic bacteriuria and pyuria including in catheterized patients</li> <li>IV. Microbial colonization and culture contamination</li> <li>V. Low grade fever</li> </ol>
Step #7	<p><b>Reduce the duration of therapy</b></p> <p>Duration of therapy should be optimized to minimum possible to reduce selection pressure. Practice guidelines and recommendations for optimum duration of therapy for various infectious disease syndromes suggest the following durations:</p> <ol style="list-style-type: none"> <li>1. Community acquired pneumonia: 5 days</li> <li>2. Hospital acquired pneumonia: 8 days</li> <li>3. Skin and Soft tissue infections: 5 days</li> <li>4. Urinary tract infections <ol style="list-style-type: none"> <li>a. Cystitis: 3-5 days</li> <li>b. Pyelonephritis: 5-14 days</li> <li>c. Catheter associated: 7 days</li> </ol> </li> <li>5. <i>Staphylococcal aureus</i> bacteremia <ol style="list-style-type: none"> <li>a. low risk of complications = 2 weeks; high risk of complications = 4-6 weeks</li> <li>b. Intra-abdominal infection: 4-7 days</li> <li>c. Surgical antibiotic prophylaxis: 1 dose</li> </ol> </li> </ol> <p>A stop date should be planned and recorded in advance to ensure antibiotic is not given beyond the recommended duration.</p>
Step #8	<p><b>Optimize PK-PD parameters</b></p> <p>Exposure of the infective agent to the unbound antibiotic drug fraction at the relevant effect site seems to be the most important factor. Optimizing PK/PD parameters include loading doses when needed, therapeutic drug monitoring for toxicity and efficacy and optimization of drug infusion or administration. For e.g.,</p> <p>Loading dose of Colistin 9 million units stat and then followed by 3 million units Q8H or 4.5 million units Q12H [to target Colistin Average Steady State Plasma Concentration (C<sub>ss</sub>, avg = 2-2.5 mg/L)</p> <p>Inj. vancomycin 1g IV Q12H and dose to be adjusted to maintain a trough level between 15-20 µg/ml [however there are increasing recent data that suggests that AUC/MIC may be a better indicator of clinical efficacy than a trough level]</p> <p>Extended infusion of β lactams</p>

The table has been adapted from ICMR Treatment Guidelines for Antimicrobial Use in Common Syndromes (2019)

Source: ICMR Treatment Guidelines for Antimicrobial Use in Common Syndromes (2019) [https://www.icmr.nic.in/sites/default/files/guidelines/Treatment\\_Guidelines\\_2019\\_Final.pdf](https://www.icmr.nic.in/sites/default/files/guidelines/Treatment_Guidelines_2019_Final.pdf)

### Scaling up AMS strategy

The WHO recently published AMR surveillance data from 169-member countries, mentioning the lack of national surveillance data on MDR pathogens 14 other member countries, including India.<sup>24</sup> The ICMR-AMRSN partly addresses this unmet need with a structured nationwide surveillance of high-priority pathogens in clinical settings & animal husbandry, which was previously inadequate in most cases. Expansion of AMRSN to include all health-care set-ups, including primary and secondary care, would help build a comprehensive database.

Consequently, a systematic reporting system for hospital-acquired infection can be immensely helpful in India. While recent studies have indicated that hospitals in India have initiated written infection control policy,<sup>11,25</sup> studies looking at implementation are still needed. In this regard, a strategy for rapid scale-up of AMSP and strengthening of resource training becomes a priority, since successful stewardship models in India are currently limited.<sup>26</sup>

### Restricting antibiotic misuse

To restrict antibiotic misuse in India, first step includes interventions like antibiotic surveillance studies,<sup>26</sup> periodic prescription audits, drug utilization studies and monitored generic drug that quantify the AMR crisis. They can also aid in assessment of antibiotic consumption trends helping policy makers immensely.

Next step includes reducing self-medication among consumers, partly encouraged by easy OTC access to prescription antibiotic. Equally important will be restricting the use of substandard antimicrobials. While stricter oversight is necessary in this regard, provisions also need to be balanced against the need to maintain access for the significant proportion of the population that lacks access to quality healthcare. Data shows that surveillance and monitoring of usage/sale of antibiotics can be effective, as was seen with the government's restriction on *bedaquiline*.<sup>27</sup>

### Addressing environmental issues contributing to AMR

Public-health education must include environmental issues contributing to AMR, including knowledge of soil related factors, animal husbandry, waste management, potable and wastewater, and food safety. Healthcare education must also address the need to understand biological plausibility of environmental determinants playing role in the propagation of AMR.<sup>28,29</sup> For instance, preliminary studies indicated continued use of pre-mixed feeds with antibiotics (often high-end antibiotics like colistin).<sup>30,31</sup> With the likelihood of increased demand for meat and poultry globally (expected to grow 312% by 2030), emphasis on continued scrutiny of implementation measures by broad-based surveillance systems will be crucial.

### Newer antibiotics: Addressing the innovation crisis

Despite increased research and development expenditure, novel anti-infectives have been hard to develop. Most of the research (70%) has concentrated on newer congener formulations with characterization of antimicrobial properties of known synthetic or natural products or chemical modification of existing compounds rather than on attempting to discover new antimicrobial agents.<sup>32</sup> In fact, most studies have been limited to in vitro experiments or small-scale animal studies, limiting clinical evaluation of any first-in-class antimicrobial agent.<sup>33,34</sup> Currently, only few organizations are focusing on development of 'superbug antibiotics'.<sup>35</sup>

### Fostering AMR research through greater investments

Traditionally, research in the anti-infective arena has largely been focused on the disease epidemiology. However, there is insufficient research into the mechanisms of AMR, including use of rapid antimicrobial susceptibility diagnostics, which could provide a better guide to antimicrobial prescribing. Data sharing mechanism are needed to ensure that these results are available to guide policy makers and clinicians in a timely manner.<sup>36</sup> Incentivized preclinical research or early clinical development could also help in this regard. WHO already advocates institutions allocating at least 2% of the total healthcare budget towards research.<sup>37</sup> A similar allocation would help donor agencies to mobilize their resources and plan an effective research programme.

### Galvanizing public-private partnerships to increase outreach

Sustainable solutions to curb AMR can be achieved by creating a broad industry momentum and facilitating collaboration between the public and private sectors. The AMR Industry Alliance<sup>38</sup> is a welcome step in this regard, being one of the largest coalitions set up to provide solutions to curb AMR, with over 100 biotech, diagnostics, generics and research-based pharmaceutical companies and associations joining forces. Partnering with bio/pharmaceutical organizations in their AMR campaigns<sup>39</sup> could also help increase physician outreach in a vast country like India.

## CONCLUSION

India has introduced promising measures for tackling AMR, that requires significant efforts from all stakeholders involved. The issue AMR awareness although slow to gain momentum but is now dominating the national conscience. Robust increased intersectoral co-ordination and public-private partnerships will likely strengthen country's fight against AMR.

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