India is among the world’s largest consumers of antibiotics. The efficacy of several antibiotics is threatened by the emergence of resistant microbial pathogens. Multiple factors, such as a high burden of disease, poor public health infrastructure, rising incomes, and unregulated sales of cheap antibiotics, have amplified the crisis of antimicrobial resistance (AMR) in India. The Global Action Plan on AMR emphasises the need to increase knowledge through surveillance and research. Box 1 provides examples of global research into AMR and its impact. Most research into AMR is carried out in developed countries. This includes research into the biology of resistant pathogens, mechanisms of AMR, natural sources of AMR, development of new antimicrobials from uncultered bacteria, expanding the chemical diversity of existing antimicrobials, re-sensitising resistant pathogens against available antibiotics, and development of non-antibiotic agents as substitutes.

Table 1 outlines the scope of research into AMR and the importance of the different areas of research. Little such research is being conducted in India, reflecting the situation of AMR research in South East Asia in general. A key strategy of the National Action Plan on AMR (NAP-AMR), launched by the government of India in 2017, is to promote investment for research. We provide an overview of research into AMR in India, describing gaps and possible obstacles. We propose strategies to advance research and to convert research evidence into policies and actions at a local and national level.

### Methods

We searched PubMed for studies, reports, and policy documents on AMR in India using the search terms “antimicrobial resistance, India,” “Antibiotics, India,” and “Antibiotic resistant pathogens, India.” We identified 5530 publications up to August 2016. Articles referring to helminths, mosquitoes, scorpion, steroids, and other unrelated topics were excluded. AMR research in animals, agriculture, and aquaculture were also not considered. A total of 4872 articles, including original research, review articles, case reports, comments, and editorials, on AMR in India were considered for this analysis.

We also reviewed patents filed in India for antimicrobial drug discovery, herbal antimicrobial preparations, diagnostic tools for antimicrobial susceptibility, and alternatives to antimicrobials. We relied on information from the United States Patent and Trademark Office; the Office of the Controller General of Patents, Designs, and Trademarks; the Indian Patents and Trademarks Office; and the public database “lens.org.” Two authors (BD and SC) extracted information from relevant publications and all authors analysed the findings according to the type of research domain. We modified and adopted the Parasuraman gap model of service quality to assess our knowledge of AMR. We developed this article based on these findings and our experience. We did not evaluate the quality and robustness of identified publications.

### Insufficient research to guide action

AMR research in India has largely focused on the epidemiology—that is, understanding the incidence and burden of resistant pathogens in clinical and community settings. Research into the mechanism of AMR is the second most common type. This includes the effectiveness of routinely used antimicrobials, genesis of resistant pathogens, and acquisition of AMR traits. The remaining publications focused on the development of interventions to tackle AMR. Over 170 different organisations across India have contributed to AMR research.

Indian investigators have filed a total of 93 relevant patents. Most were filed by private pharmaceutical or biopharmaceutical companies, followed by academic research organisations and individual inventors. Most patents are for new formulations and new antibiotic compounds from natural sources. The...
Overall, we note that insufficient research has been carried out into new interventions and alternatives to antimicrobial treatment. Most research (70% of 1744 studies) has concentrated on new antimicrobial formulations, characterisation of antimicrobial properties of known synthetic or natural products, and development of nanoparticle based antimicrobial agents. Most studies are

**Table 1 | Potential effect of research into antimicrobial resistance (AMR)**

<table>
<thead>
<tr>
<th>Category of research</th>
<th>Types of studies included</th>
<th>Role of this research</th>
<th>Potential effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology</td>
<td>Disease burden studies for various microorganisms in the community or hospitals incidence studies, reports of new resistance strains</td>
<td>To understand the trend in emergence of AMR</td>
<td>To guide actions locally, regionally, and nationally</td>
</tr>
<tr>
<td>Clinical</td>
<td>AMR related to healthcare set-up, treatment regimen, drug evaluation, evaluation of diagnostics</td>
<td>To understand the effectiveness of interventions and trends of AMR in health</td>
<td>To help to develop strategies to combat AMR</td>
</tr>
<tr>
<td>Mechanistic</td>
<td>Mechanism of emergence of resistance and spread across species and from environment, characterisation of resistance traits/strains</td>
<td>To understand factors contributing to emergence and transmission of resistance</td>
<td>To provide knowledge of the mechanism of emergence to enhance readiness for emergence of new resistance traits</td>
</tr>
<tr>
<td>Intervention</td>
<td>New drug development, diagnostics, alternative antimicrobial treatment, assay development, evaluation of antibiotic properties of herbal preparations</td>
<td>To rapidly and efficiently diagnose resistant traits and pathogens, and develop medications to treat infections</td>
<td>To provide a rapid diagnostic assay to guide clinical decision making to develop alternative treatment and drugs to deal with the emergence of multidrug resistance</td>
</tr>
<tr>
<td>Policy</td>
<td>Policies and priorities and opinion articles, health systems research to improve effectiveness of stewardship programmes, regulatory research</td>
<td>To monitor impact of policies and programmes and guide further interventions</td>
<td>To devise health systems improvisations, set up governance arrangements, develop target product profile for new interventions, recommend modification of the regulatory process for drugs, diagnostics, and devices for AMR</td>
</tr>
<tr>
<td>Review</td>
<td>Review of literature on AMR</td>
<td>To provide update of knowledge and comparison of research into AMR</td>
<td>-</td>
</tr>
</tbody>
</table>

**Fig 1 | Introduction of antibiotics in clinical practice and emergence of antimicrobial resistance.** The timeline shows that most new antibiotics (scaffolds) were discovered up to the 1970s. In subsequent years, these scaffolds were expanded chemically by introducing new functional groups. Few clinically used antibiotics with new scaffolds (≤5) were discovered in the past 50 years. Resistance to almost all antibiotics (scaffolds) were discovered up to the 1970s. In subsequent years, these scaffolds were expanded chemically by introducing new functional groups.

**Discovery and deployment of antibiotics**

- **1940-50**
  - Tetracycline (tetracycline)
  - Chloramphenicol (phenylpropanoid)
  - Polymyxin (lipopeptide)
  - Chlorotetracycline (tetracycline)
  - Cephalosporin (β-lactam)
  - Penicillin (β-lactam)
  - Neomycin (aminoglycoside)
  - Streptomycin (aminoglycoside)
  - Bacitracin (cyclic peptide)
  - Nitrofurans (furan)
  - Chloramphenicol (phenylpropanoid)
  - Polymyxin (lipopeptide)
  - Chlorotetracycline (tetracycline)
  - Cephalosporin (β-lactam)

- **1950-60**
  - Erythromycin (macrolide)
  - Isoniazid (niticnic acid)
  - Vancomycin (glycopeptide)
  - Virginiamycin (streptogramin)
  - Cycloserine (aminocyclitol)
  - Nalidixic acid (quinolone)
  - Tetracycline (tetracycline)
  - Rifamycin (ansamycin)
  - Teicoplanin (strepogranin)
  - Metronidazole (nitroimidazole)

- **1960-70**
  - Metyllin (β-lactam)
  - Ampicillin (β-lactam)
  - Nalidixic acid (quinolone)
  - Trimethoprim (pyrimidine)
  - Fusidic acid (tetacyclic tetracerpenoid)
  - Fusidic acid (tetracycline)
  - Fosfomycin (phosphoenoxypryvurate)
  - Aminoglycoside (aminoglycoside)
  - Lincomycin (lincomamide)

- **1970-90**
  - Gentamicin (aminoglycoside)
  - Mupirocin (polyene)
  - Carbapenem (β-lactam)
  - Imipenem (β-lactam)
  - Ciprofloxacin (quinolone)
  - Oxazolidinone (cycloheximide)

- **1990-2010**
  - Linezolid (oxazolidinone)
  - Telithromycin (macrolide)
  - Daptomycin (lipopeptide)
  - Tigecycline (tetracycline)
  - Retapamulin (pleuromutilin)
  - Garenoxacin (quinolone)
  - Telavancin (glycopeptide)
  - Besifloxacin (quinolone)
  - Ceftline (xenosum)

- **2010-16**
  - Fidaxomicin (lactam)
  - Bedaquiline (diarylquinoline)
  - Teixobactin (depsipeptide)
Reflected owing to poor surveillance, the crisis of AMR in India is not properly documented. A nationwide surveillance of AMR pathogens in India would provide a better guide to understanding the mechanisms of resistance and rapid emergence of AMR. The World Health Organization (WHO) recently launched the Antimicrobial Resistance Surveillance Network (AMRSN) in 2013 to explore data on resistant pathogens in India and from 169 member countries. The report mentioned the lack of national surveillance data on resistant pathogens in India and 14 other member countries. Systematic nationwide surveillance of AMR pathogens in clinical settings, animals, and the environment is inadequate or lacking. A national repository of AMR pathogens in India does not exist.

The Indian Council of Medical Research launched the Antimicrobial Resistance Surveillance and Research Network (AMRSN) in 2013 to explore prevalence of resistance in six pathogenic bacterial and fungal species, including Klebsiella pneumoniae, Escherichia coli, Salmonella enterica serovar typhi, Staphylococcus aureus, and enterococci and candida species. Twenty healthcare institutions, comprising 12 public and eight private agencies from various states and union territories were included in the network. At present, the programme is limited to only 10 laboratories in eight states of India, while the five year plan is for a network of 30 laboratories. Although, the AMRSN is active, the crisis of AMR in India is not properly reflected owing to poor surveillance infrastructure and gaps in coordination with healthcare systems.

Public sector funding for research has been inadequate owing to lack of awareness of the gravity of the problem and of political will. The national action plan calls for at least 2% of the total budget towards research. A similar allocation would help donor agencies to mobilise their resources and plan an effective research programme.

Insufficient funds are available for research and surveillance, possibly because immediate returns on investment for antimicrobial drugs are small. Over the past 10 years, major pharmaceutical companies in India have increased their research and development expenditure almost 40-fold, but none is directly related to new antimicrobial drugs. Pharmaceutical companies and academic laboratories have focused on chemical modification of existing antimicrobial compounds rather than on attempting to discover new therapeutic agents. In the past 60 years, more than 80 ß-lactam derivatives have been introduced, but no new classes of antibiotics were launched between 1960 and 2000.

The national action plan recommends conducting comprehensive surveillance, sentinel surveillance, and point prevalence studies on AMR with descriptive methods. There is emphasis on strengthening the capacity for laboratory based surveillance of AMR in humans, animals, food, and the environment. This includes situational analysis of microbiology laboratories in the public and private sectors, quality assurance, capacity building, designating national reference laboratories for AMR surveillance—a prerequisite for enrolment in the Global AMR Surveillance System, developing standardisation and coordination mechanisms for national surveillance, and standardised data management.

A robust surveillance network is fundamental to monitor resistance patterns in pathogens of public health importance through a chain of regional laboratories that report data to a central system. This must be linked to research into the complexity and mechanisms of resistance. Audits of antibiotic use in public and private health facilities and in the community can provide information on the impact on resistance and reinforce the need for initiatives to curb inappropriate use. An updated national database of resistance profiles of tuberculosis, sepsis, and diarrhoeal pathogens through advanced real time tracking is vital. Additionally, it is important to bridge the interdisciplinary research among different domains and organisations working on human, animal and environmental sciences. Transparent policies and improved communication and collaboration on projects could be helpful. Figure 2 shows the key factors to promote AMR research in India. The national action plan should encourage different regulatory bodies across health, environment, animal, agriculture, and environment sectors to work together on shared objectives for AMR research and control.

For research to be effective, it will be vital to strengthen coordination between different types of research and share the results within a realistic time to guide clinical decisions, interventions, and policies. The national plan does not outline a mechanism for depositing and sharing data nationally or regionally, but this will be crucial to strengthen academic research and convert findings into interventions and policies for AMR.

Finally, a national sustained initiative to invest and incentivise public-private partnerships for product development, and align biological, engineering, and medical science research for development of disruptive innovations in antimicrobial diagnostic and therapeutic agents is required to deal with the current AMR crisis.

Key factors to promote AMR research
- Robust AMR surveillance
- Updated AMR database
- Faster approval process
- AMR diagnostic R&D
- IP protection cost incentive
- Multidisciplinary R&D efforts
- Stakeholder participation
- Incentivisation
- National privatisation

Schematic presentation of key factors to promote antimicrobial research in India (IP=intellectual property)
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Susmita Chaudhuri, scientist
Rahul Srivastava, consultant
G Balakrish Nair, adviser
Thandavaramay Ramamurthy, national chair
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