

Fostering research into antimicrobial resistance in India

Bhabatosh Das and colleagues discuss research and development of new antimicrobials and rapid diagnostics, which are crucial for tackling antimicrobial resistance in India

India is among the world's largest consumers of antibiotics.¹ 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.²

The Global Action Plan on AMR emphasises the need to increase knowledge through surveillance and research.³ 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,¹¹⁻¹² mechanisms of AMR,¹³⁻¹⁵ natural sources of AMR,¹⁶⁻¹⁷ development of new antimicrobials from uncultured bacteria,¹⁸ expanding the chemical diversity of existing antimicrobials,¹⁹ resensitising resistant pathogens against available antibiotics,²⁰ and development of non-antibiotic agents as substitutes.²¹ 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.

KEY MESSAGES

- Antimicrobial resistance research in India is focused on burden and patterns of resistance, yet nationwide surveillance is lacking
- More research is needed to discover new antibiotics and develop rapid diagnostic tests
- Investment in research and national surveillance of resistant pathogens must be prioritised

Box 1: Examples of the impact of antimicrobial resistance research and interventions globally

- In 2011, the Chinese Ministry of Health implemented a campaign for rational use of antibiotics in healthcare, accompanied by supervision audits and inspections. Over a year, superfluous prescription of antimicrobials was reduced by 10-12% for patients in hospital and for outpatients, as were drug sales for antimicrobials.⁴⁵
- The Swedish Strategic Programme against Antibiotic Resistance (STRAMA) led to a decrease in antibiotic use for outpatients from 15.7 to 12.6 daily doses per 1000 inhabitants and from 536 to 410 prescriptions per 1000 inhabitants per year from 1995 to 2004.⁶ The decrease was most evident for macrolides (65%)
- The effect of WHO essential medicines policies was studied in 55 countries. These policies were linked to reductions in antibiotic use of $\geq 20\%$ in upper respiratory tract infections. A national strategy to contain antibiotic resistance was associated with a 30% reduction in the use of antibiotics in acute diarrhoeal illness⁷
- An antimicrobial stewardship programme (2009-2014) in 47 South African hospitals led to a reduction in mean antibiotic defined daily doses per 100 patient days from 101.4 to 83.04⁸
- In the US, infections with carbapenem resistant Enterobacteriaceae declined after the Antimicrobial Resistance Monitoring and Research Programme was started. In addition, there were no further reports of outbreaks caused by colistin resistant *Acinetobacter* spp⁹
- In the Netherlands, a decrease of CTX-M-1-1-like ESBL genes (from 44% to 25%) in livestock was seen during 2010-14, possibly linked to considerable (>60%) reduction in antibiotic use in livestock¹⁰

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.³¹ 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

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

Category of research	Types of studies included	Role of this research	Potential effect
Epidemiology	Disease burden studies for various micro-organisms in the community or hospitals Incidence studies, reports of new resistance strains	To understand the trend in emergence of AMR	To guide actions locally, regionally, and nationally To guide clinical decisions and appropriate use of antimicrobials through data gathering and real time data sharing throughout national public health systems
Clinical	AMR related to healthcare set-up, treatment regimen, drug evaluation, evaluation of diagnostics	To understand the effectiveness of interventions and trends of AMR in health	To help to develop strategies to combat AMR
Mechanistic	Mechanism of emergence of resistance and spread across species and from environment, characterisation of resistance traits/strains	To understand factors contributing to emergence and transmission of resistance	To provide knowledge of the mechanism of emergence to enhance readiness for emergence of new resistance traits
Intervention	New drug development, diagnostics, alternative antimicrobial treatment, assay development, evaluation of antibiotic properties of herbal preparations	To rapidly and efficiently diagnose resistant traits and pathogens, and develop medications to treat infections	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
Policy	Policies and priorities and opinion articles, health systems research to improve effectiveness of stewardship programmes, regulatory research	To monitor impact of policies and programmes and guide further interventions	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
Review	Review of literature on AMR	To provide update of knowledge and comparison of research into AMR	-

Council of Scientific and Industrial Research, Indian Institutes of Technology, the Defence Research and Development Organisation, and universities are among the top patent applicants.

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

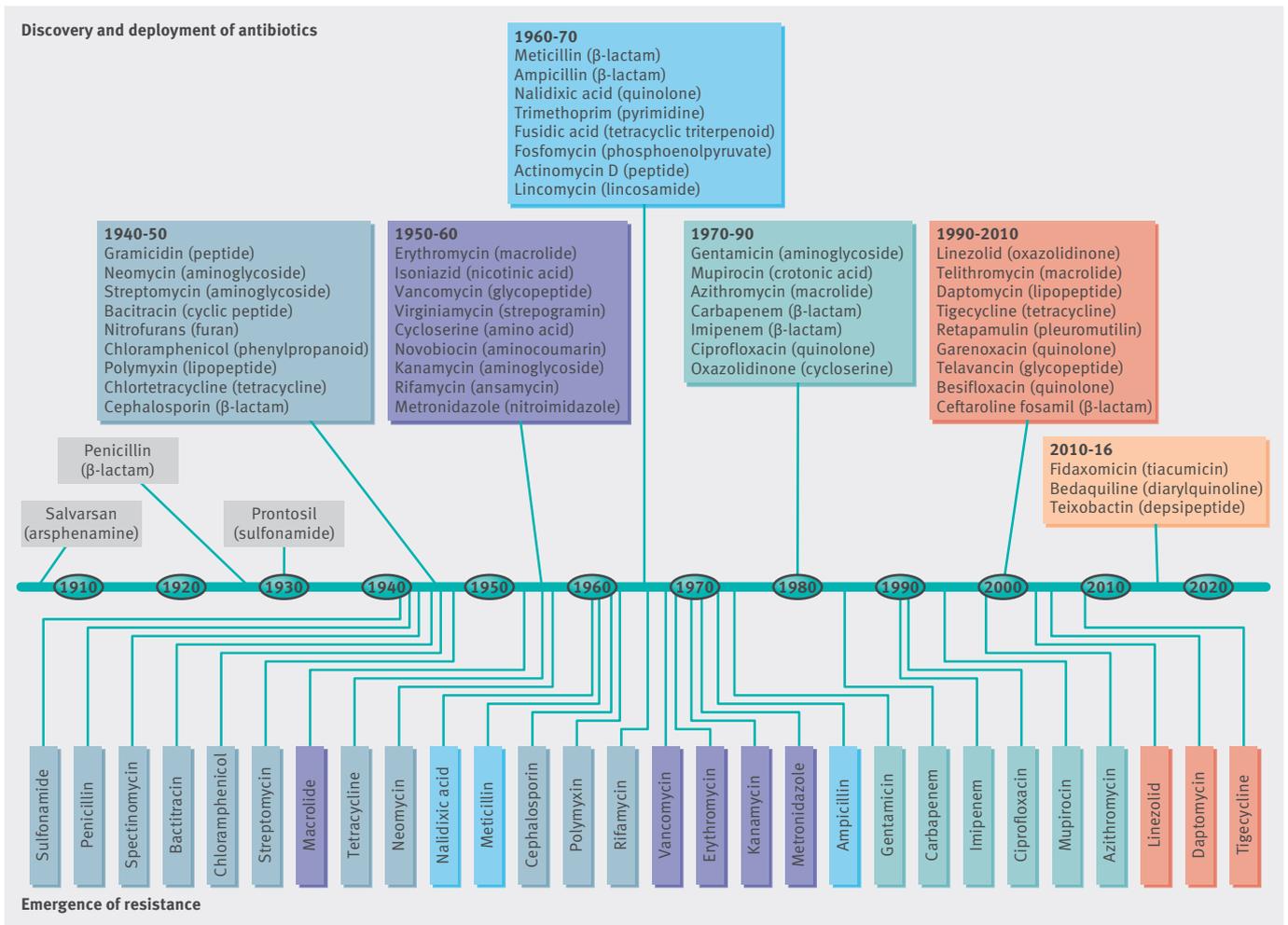


Fig 1 | Introduction of antibiotics in clinical practice and emergence of antimicrobial resistance. The timeline shows that most new antibiotics (scaffolds) were discovered up to the 1970s. In subsequent years, these scaffolds were expanded chemically by introducing new functional groups. Few clinically used antibiotics with new scaffolds (<5) were discovered in the past 50 years. Resistance to almost all antibiotics was reported shortly after introduction in clinical practice. Relevant information was obtained from multiple sources, including <https://card.mcmaster.ca/>

limited to in vitro experiments or small animal studies. No clinical evaluation of any new antimicrobial agent has been published, suggesting that the stage of clinical evaluation has not been reached. Figure 1 shows how the introduction of antibiotics into clinical practice and emergence of resistance has developed. As resistance increases, research into newer antimicrobial formulations becomes more urgent.

There is insufficient research into the mechanisms of resistance and rapid antimicrobial susceptibility diagnostics, which would provide a better guide to prescribing for treatment of infections.

Poor surveillance

The World Health Organization (WHO) recently published AMR surveillance data from 169 member countries. The report mentioned the lack of national surveillance data on resistant pathogens in India and 14 other member countries.²² 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.²³ 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.²⁴ 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.²⁵

Research funding

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 investments in initiatives to contain AMR, but does not make clear what proportion should be allocated for AMR research.²⁶ WHO advocates allocating 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.

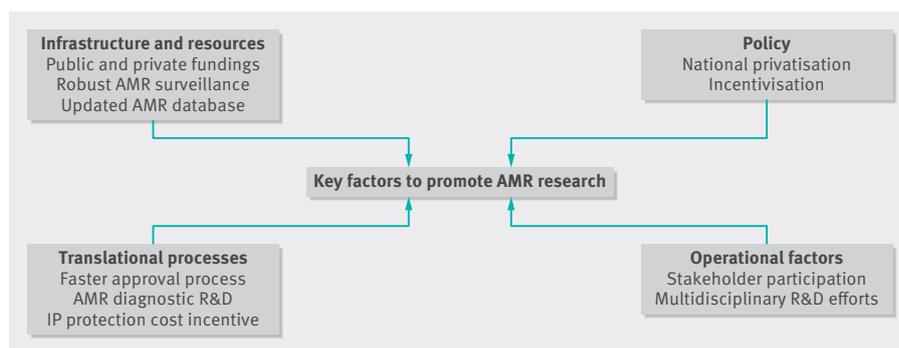


Fig 2 | Schematic presentation of key factors to promote antimicrobial research in India (IP=intellectual property)

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.²⁷ Pharmaceutical companies and academic laboratories have focused on chemical modification of existing antimicrobial compounds rather than on attempting to discover new therapeutic agents.²⁸ In the past 60 years, more than 80 β -lactam derivatives have been introduced,²⁹ but no new classes of antibiotics were launched between 1960 and 2000.³⁰

Recommendations

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 standards 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.

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