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Policies and Interventions to Improve Access to Next-Generation Antimicrobials in Low- and Middle-Income Countries

India Case Study

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Abbreviations

AB-PMJAY	Ayushman Bharat–Pradhan Mantri Jan Arogya Yojana
ABSSSI	Acute bacterial skin and skin structure infections
AMRSN	Antimicrobial Resistance Surveillance and Research Network
AMSP	Antimicrobial Stewardship Program
APC	Advanced purchase commitments
AST	Antimicrobial susceptibility testing
BIRAC	Biotechnology Industry Research Assistance Council
CDSCO	Central Drugs Standard Control Organization
CRE	Carbapenem-resistant enterobacterales
DBT	Department of Biotechnology
DPCO	Drug prices control order
EDL	Essential drugs list
FDC	Fixed drug combination
FDI	Foreign direct investment
FNDR	Foundation for Neglected Disease Research
GARDP	Global Antibiotic Research and Development Partnership
GAVI	Global Alliance for Vaccines and Immunization
GLASS	Global Antimicrobial Resistance Surveillance System
GLP	Good laboratory practice
HAI	Healthcare-associated infection
ICH	International Council of Harmonization
ICMR	Indian Council of Medical Research
IPA	Indian Patent Act
IPC	Infection prevention and control
IPPL	Indian priority pathogen list
JAK	Jan Aushadhi Kendra
KMSCL	Kerala Medical State Corporation Limited
MARC	Mission for AMR Containment
MRSA	Methicillin-resistant staphylococcus aureus
MSC	Medical Service Corporation

NABH	National Accreditation Board for Hospitals & Healthcare Providers
NABL	National Accreditation Board for Testing and Calibration Laboratories
NCE	New chemical entity
NCDC	National Center for Disease Control
NDCT	New drugs and clinical trials
NHM	National Health Mission
NLEM	National List of Essential Medicines
NPPA	National Pharmaceutical Pricing Authority
OTC	Over the counter
PLI	Production-linked incentive
SDL	Special drug list
SEC	Subject expert committees
SOP	Standard operating procedure
TPP	Target product profile
UHC	Universal health coverage

Key messages

1. More than a million people die in India every year with a drug-resistant pathogen. Addressing this issue requires the enhancement of antimicrobial innovation, accessibility, and stewardship practices.
2. The National Action Plan on antimicrobial resistance (AMR) aims to combat antimicrobial resistance, but there is insufficient focus on drug procurement, access, and stewardship practices, as well as scarce implementation and inadequate uptake by the states; only four states have state action plans.
3. Recommendations aim to enhance access to relevant Watch and Reserve antimicrobials (drugs that the WHO recommend should receive greater protection from overuse and should only be used as a last resort, respectively) to treat critical-priority pathogens in India and ensure appropriate stewardship practices. Proposals include modifying procurement practices in national and state AMR action plans, including essential antimicrobials in state drug procurement lists; improving inter-state coordination; enhancing surveillance; and improving diagnostics facilities in all hospitals. Hospitals must be aligned to utilize accreditation, certification, and empanelment systems alongside an assurance program.
4. Creating an innovation ecosystem for antimicrobial R&D involves developing targeted antimicrobial profiles for the Indian context and making procedural changes to facilitate R&D of relevant Watch and Reserve antimicrobials to treat critical-priority pathogens in India.

Executive summary

Antimicrobial resistance (AMR) is a major public health issue that poses a threat to global health security, with India carrying one of the largest burdens of drug-resistant pathogens worldwide. The widespread misuse and overuse of antimicrobials, both in the home and in hospital settings, is a major cause of the emergence and spread of resistant microorganisms. To tackle this threat, we must fill the gaps in our knowledge regarding the prevalence of AMR in India. Moreover, it is essential that antimicrobial innovation is enhanced, accessibility is increased, and stewardship practices are dramatically improved. This study aimed to assess the current situation of AMR in India, evaluate the scope of the National Action Plan on AMR (NAP-AMR), and suggest policy recommendations to improve innovation and reduce the overuse and misuse of "high-end" antimicrobials (defined here as relevant Watch and Reserve categories of the WHO AWaRE list that treat critical-priority pathogens in the Indian Priority Pathogen List (IPPL)). This study used several approaches, including compiling an antimicrobial surveillance database, creating a drug pipeline and approval database, reviewing the NAP-AMR and state action plans, conducting stakeholder interviews, and identifying literature through systematic searches. The findings reveal that the Indian healthcare system faces significant challenges in terms of accessibility, affordability, and drug procurement, with the decentralized regulatory process leading to inefficiencies and delays.

The Indian healthcare system

Drug registration in India faces multiple challenges due to the complex regulatory framework split between the central and state governments. A lack of clarity regarding regulations has also been identified as a barrier to conducting clinical trials in India. To expedite new drug clinical trials, the central government has enacted the New Drugs and Clinical Trials Rules (NDCT 2019). It has also launched several initiatives to foster innovation in biotechnology, such as Startup India and the Atal Innovation Mission, and in 2017, it developed the National Action Plan on AMR (NAP-AMR). However, more work is required on supply-side interventions. Market entry mechanisms such as push and pull mechanisms have been implemented globally, but challenges like limited funds and regulatory oversight need to be addressed locally. Overall, there is a need to improve the coordination and regulation of the healthcare system and to implement comprehensive policies to combat AMR. The study's policy recommendations include improving the quality and accessibility of healthcare, promoting responsible antimicrobial use, strengthening regulatory oversight and capacity, enhancing research and development, and implementing market entry mechanisms specific to AMR. By adopting these policy recommendations, India can effectively tackle the threat of AMR and improve global health security.

The prevalence of antimicrobial resistance in India

The Global Research on Antimicrobial Resistance (GRAM) group estimates that in 2019, 1.8 million deaths in India were related to a bacterial infection. Of these infections, just over a million deaths are associated with drug-resistant pathogens, and almost 300,000 are estimated to be caused by drug resistance. We created an antimicrobial surveillance database to understand the prevalence of AMR in India. The results show that critical-priority class pathogens demonstrate more than 50 percent resistance to over half of the available antimicrobials. This highlights the urgent need for new high-end antimicrobials that target these pathogens. Pathogens listed as high priority show low resistance to most antimicrobials, and stewardship strategies can help reduce resistance levels for these.

Review of national and state action plans on antimicrobial resistance

The NAP-AMR was approved in 2017, with its first official duration ending in 2021. The plan prioritizes improving awareness of AMR, strengthening knowledge and evidence through surveillance, reducing infection incidence, optimizing antimicrobial use, promoting investments in AMR activities, research, and innovations, and strengthening India's leadership on AMR. However, the plan lacks detailed roadmaps for collaboration between private and medical service corporations to improve drug procurement and access. The plan could be expanded by including mechanisms such as pooled procurement through public pharmacies like Jan Aushadhi Kendras to make medicines affordable and ensure a continuous supply of high-end antimicrobials. Additionally, there is a lack of verification mechanisms to bolster stewardship and ensure the rational use of high-end antimicrobials. The plan could explore different pathways for improving the accessibility of antimicrobials while ensuring better stewardship practices.

Challenges to improving access to watch and reserve (high-end) antimicrobials

There are several challenges associated with improving access to highly effective antimicrobials in India. More than half of the states have only one or no Reserve category antimicrobials listed in their essential drug list; Reserve and Watch category drugs cost over 32 and 9 times more, respectively, than Access category drugs. Decentralized and limited public procurement of high-end antimicrobials reduces bargaining power, and state medical stores corporations (MSCs) working in silos with little interaction cause critical drugs to be procured on an ad hoc basis, leading to soaring prices. Small-sized private sector hospitals also face the issue of low-volume demand for high-end antimicrobials, which makes procurement difficult and costly, and the lack of flexibility to include high-end drugs in national- and state-funded insurance schemes creates further barriers to access. These issues can all place financial burdens on patients and increase out-of-pocket (OOP) expenditure.

Challenges in improving stewardship for existing and high-end antimicrobials

Healthcare facilities are high-risk environments for drug resistance, and evidence suggests that the unnecessary use of antimicrobials is high in India. Challenges with stewardship in India include poor implementation of infection prevention and control practices, limited data on AMR, gaps in diagnostic capabilities, and improper prescribing patterns among clinicians. Concerns also exist regarding the limited access to rapid diagnostics, which are only available in a limited number of hospitals charging high fees. While the government has introduced free drug and diagnostic initiatives, there is a shortage of infrastructure and workforce to conduct antimicrobial susceptibility testing.

Challenges associated with the innovation of high-end antimicrobials

The Indian pharmaceutical industry is well known for its production of generic medicines, vaccines, and biosimilars. However, when it comes to pharmaceutical innovation, it is not yet considered a major player. Challenges associated with innovating next-generation antimicrobials in India were identified by stakeholders, including weak regulation, a lack of patent-friendly policies, difficulty creating a target product profile, and a nascent innovation ecosystem. These challenges result in delays and significant costs associated with conducting clinical trials, difficulties meeting criteria and sample size, delays in patent grants, and limited funding for R&D. These challenges must be addressed if India wants to become a major player in pharmaceutical innovation, particularly in next-generation antimicrobials.

Recommendations

To combat AMR in India, we propose two categories of recommendations:

1. Enhancing access to high-end antimicrobials (relevant Watch and Reserve categories of the WHO AWaRE list that treat critical priority pathogens in the IPPL) while ensuring appropriate stewardship practices:

    - Modify national and state action plans to explicitly outline the guidelines for important Watch and Reserve antimicrobial procurement.
    - Include all essential Watch and Reserve antimicrobials in state drug procurement lists to regularize their procurement.
    - Enhance inter-state coordination to increase transparency, reduce duplication, and gain from economies of scales.
    - Use alternate channels to procure low-volume drugs.
    - Utilize AB-PMJAY to introduce the use of essential Watch and Reserve antimicrobials.

- Ensure that hospitals follow stewardship practices using an assurance system that goes beyond accreditation programs.
- Improve diagnostics facilities.
- Enhance surveillance of high-end antimicrobials to prevent future resistance.

2. Creating an innovation ecosystem that supports antimicrobial R&D:

    - Develop targeted antimicrobial profiles tailored to the Indian context.
    - Enact procedural changes to facilitate high-end antimicrobial innovation.

The fight against AMR in India requires innovative thinking to address access and innovation challenges. Procurement systems must be modified to effectively procure high-end antimicrobials and provide them promptly at the point of care. Innovative financing solutions are needed to incentivize the development of high-end antimicrobials and reduce the OOP burden for marginalized populations. This will require a well-coordinated response from different stakeholders in India.

1. Introduction

Antimicrobial resistance (AMR) is a major public health issue, with India carrying one of the largest burdens of drug-resistant pathogens worldwide (Mogasale, et al. 2021). Agricultural and commercial application of antimicrobials in the animal sector and human behaviour are both key factors in the growing threat of AMR. However, it is the rampant overuse and misuse of antimicrobials in the home and in hospital settings that is the biggest culprit in the emergence and spread of resistant microorganisms.

To adequately tackle the threat of AMR, it is imperative to fill the gaps in our knowledge regarding the prevalence of AMR in India. We must also ensure that innovation is enhanced, accessibility is increased, and stewardship practices are greatly improved.

Goals of the study

The objectives of this study are as follows:

- Assess the current healthcare structure and the situation of AMR in India (Sections 2 and 3).
- Evaluate the scope of the National Action Plan on AMR (NAP-AMR) and assess the progress of its implementation (Section 4).
- Outline problems of the antimicrobial market in India about innovation, access, and appropriate use (Sections 5–7).
- Suggest policy recommendations from India's perspective to improve innovation, increase access, and reduce overuse and misuse of "high-end" antimicrobials (defined here as relevant Watch and Reserve categories of the WHO AWaRE list that treat critical-priority pathogens in the Indian Priority Pathogen List (IPPL)) (Section 8).

Methodology

The methodology used in this study involved several approaches, including the compilation of an antimicrobial surveillance database using data from two sources—the mapping of the Indian surveillance list against the World Health Organization's (WHO) classification of antimicrobials, and the creation of the Indian Priority Pathogen List (IPPL). The study also involved the creation of a drug pipeline and approval database, which compared the IPPL list with the drugs approved by the Food and Drug Administration (FDA) and the Central Drugs Standard Control Organization (CDSCO) in the same period. The researchers reviewed the NAP-AMR and state action plans, summarized their strategic objectives, and analysed their current implementation status. Literature for secondary review was identified through a systematic search of peer-reviewed journals using seven online databases. Gray literature was identified by searching the references of key review articles and the archives of key organizations and advocacy groups. Finally, the researchers conducted thirty-two stakeholder interviews, using the snowballing technique to explore viable solutions to reduce the risk of antimicrobial resistance. Of the thirty-two, four were executives from

pharmaceutical companies, eighteen were subject matter specialists, and ten of the government agency representatives were interviewed. The detailed methodology used for this study is described in Appendix 1.

2. The Indian healthcare system

2.1 Drug development, approval, and registration

Drug registration in India faces multiple challenges due to the complex regulatory framework split between the central and state governments. While the central government is responsible for clinical trials, imports, and approvals, state authorities oversee the manufacture, sale, and distribution of drugs in their respective states. A lack of coordination among these bodies often leads to delays in the approval process. According to a recent study, the average time lag between drugs being approved in the US and India was twenty-one months (Konwar, et al. 2021). Decentralization in the regulatory process creates inefficiencies and delays in approvals. A lack of clarity on regulations has also been identified as a barrier to conducting clinical trials in India. To expedite new drug clinical trials, the central government has enacted the New Drugs and Clinical Trials Rules (NDCT 2019). The government has also launched several initiatives to foster innovation in biotechnology, such as Startup India and the Atal Innovation Mission, led through the Biotechnology Ignition Grant and the Biotechnology Industry Research Assistance Council under the Department of Biotechnology (Biotechnology Industry Research Assistance Council 2023, Ministry of Health and Family Welfare 2016, Ministry of Commerce and Industry 2022, Sivanandan, et al. 2019, Konwar, et al. 2021).

See Appendix 2 for more information.

2.2 Policies related to AMR containment

Approved in 2017, and aligned with the global action plan, India's first 5-year NAP-AMR ended in 2021. (Indian Council of Medical Research 2021)

The plan focused on the following strategic priorities:

- improving awareness of AMR through effective communication, education, and training;
- strengthening knowledge and evidence through surveillance;
- reducing the incidence of infection through effective infection prevention and control;
- optimizing the use of antimicrobial agents in health, animals, and food;
- promoting investments in AMR activities, research, and innovations; and
- strengthening India's leadership on AMR.

Although the plan is thought to achieve its targets from both the demand and the supply side, emphasis is seen mostly from the demand side rather than supply-side interventions. (National Centre for Disease Control 2022, Ranjalkar and Chandy 2019)

See Appendix 3 for more information.

2.3 Health systems

The Indian healthcare system faces challenges in terms of accessibility and affordability. Private hospitals account for 62 percent of the total hospitals in India. Of this, 80 percent are small clinics and nursing homes (less than thirty beds), 6–7 percent are 100–200 bed size hospitals, and only 2–3 percent of hospitals have 200-plus beds (Chatterjee and Srinivasan 2013).

Rural and urban India has very different experiences with healthcare. These disparities can be seen in the quality of the health infrastructure and the availability of healthcare practitioners. Reports suggest that 62 percent of the healthcare infrastructure is in urban areas, as well as 74 percent of doctors.

According to current estimates, over 80 percent of the Indian population is still not covered under any form of insurance. Total health expenditure in India is just 3 percent of GDP, far lower than the low- and middle-income country (LMIC) average of 5.3 percent. Of the total expenditure, the Indian government contributes 33 percent to the country's total, while the rest is out-of-pocket (OOP). By contrast, the average government health spending in LMICs is much higher at 52 percent (The World Bank 2022a, The World Bank 2022b). This is a huge financial burden and pushes 55 million people further into poverty each year. Access to high-end antimicrobials is challenging, as the diagnosis and treatment of AMR in India is currently limited to tertiary and quaternary facilities in the public and private sectors. Reimbursement rates have proven difficult for private hospitals accepted under the AB-PMJAY scheme, but adjustments are planned. The system could potentially lower OOP payments due to the change in reimbursement rates and increase in the number of operations and beneficiaries covered under the scheme. (Ministry of Finance 2023, Ambade, et al. 2022, Montaigne 2020, Ministry of Health and Family Welfare 2022a, Kadarpeta 2022, Dwivedi and Bhargava 2022, National Health Authority 2022)

See Appendix 4 for more information.

BOX 1. Evolving practice of Ayushman Bharat—Pradhan Mantri Jan Arogya Jan Arogya Yojana

Launched in 2018, AB-PMJAY is a government-funded health insurance scheme to support eligible, poor, and vulnerable entitled families seeking secondary and tertiary care in public and private hospitals. It marks a step towards Universal Health Coverage (UHC).

AB-PMJAY was created to provide high-quality preventive and therapeutic treatment without placing an undue financial burden on India's lowest socioeconomic groups, who make up close to 40 percent of the population. It is a jointly funded initiative by the union and state governments which cover three days of pre-hospitalization and fifteen days of post-hospitalization, including diagnostic care and expenses on medicines.

2.4 Procurement systems

India's pharmaceutical sector is growing rapidly. It serves around 40 percent of generics demand in the United States and 25 percent in the United Kingdom, yet vast numbers of citizens in India are denied basic access to healthcare and essential medicines (Singh, et al. 2013). Drug procurement in India is divided into the public and private sectors, with private hospitals and retail pharmacies accounting for 85–90 percent of all drug consumption in India (Fazaludeen, et al. 2022). Private hospitals and large pharmacy chains have multiple avenues to procure drugs through clearing and forwarding agents, distributors, and stockists, whereas retailers and smaller pharmacies rely on wholesalers and hospitals for their stock. Branded generic antimicrobials purchased from private retail markets typically cost 82–193 percent more than generic medications purchased from the public market (Kotwani and Holloway 2013).

Despite drug procurement in the public sector being aimed at providing free medicines for government-funded programs, each state in India creates and updates its own essential drug list independently. This leads to a multitude of independent systems for drug procurement, which can make the procurement process more difficult. To streamline this, most states have set up medical service corporations (MSCs). However, the efficiency of drug procurement varies between states and is influenced by factors such as procurement type and the autonomy of the procurement organization. State essential drug lists usually include only generic drugs, with the provision to procure patented drugs if demand arises. The special drug list consists of expensive, patented, and non-generic medications that the medical service corporation purchases, primarily for state-run hospitals at the tertiary level. If demand for these medicines is high enough, the same open tender procedure as the essential drug list is used for procurement; otherwise, hospitals can buy the medication by negotiating directly with manufacturers. (Lal 2014, Chokshi, et al. 2015)

The central government has also established dedicated outlets known as Jan Aushadhi Kendras to improve access to generic drugs for the poor. However, each state receives funding from the National Health Mission (NHM) in addition to using its own budget to procure drugs. The ratio of the budget that comes from the NHM and the states varies between states. Most states have their own IT-based inventory management system that deals with the purchase, inventory management, and distribution of medicines to various regional/district drug warehouses of states, district hospitals, community health centers, primary health centers, and sub-centers to distribute drugs.

To ensure stewardship and price control, an innovative approach of restrictive availability of drugs was attempted for tuberculosis (TB) drugs (bedaquiline and delamanid), which were prescribed for patients diagnosed with multidrug-resistant TB (MDR-TB) and exclusively drug-resistant TB (XDR-TB). These drugs were introduced under stringent regulatory approval from multiple stakeholders under the National TB Elimination Program (formerly known as the Revised National Tuberculosis Control Program). This method of restrictive drug access and compassionate use has helped combat the misuse of drugs.

The box below details the utilization of one state's budget and medical service corporation to introduce high-end antimicrobials in the public sector.

BOX 2. Evolving practice in kerala medical service corporation limITED

Evolving practice

Kerala EDL has 66 antibiotics, including high-end drugs. While most medications are obtained by open tendering, if any of these drugs do not attract a bidder, they are procured through Karunya Pharmacy. Karunya Pharmacy is an initiative by Kerala Medical State Corporation Limited (KMSCL) and runs a for-profit chain of pharmacies that competes with other retail pharmacies. The advantage Karunya may have over other pharmacies is lower prices through bulk procurement for the entire state and the streamlined procurement practices of KMSCL.

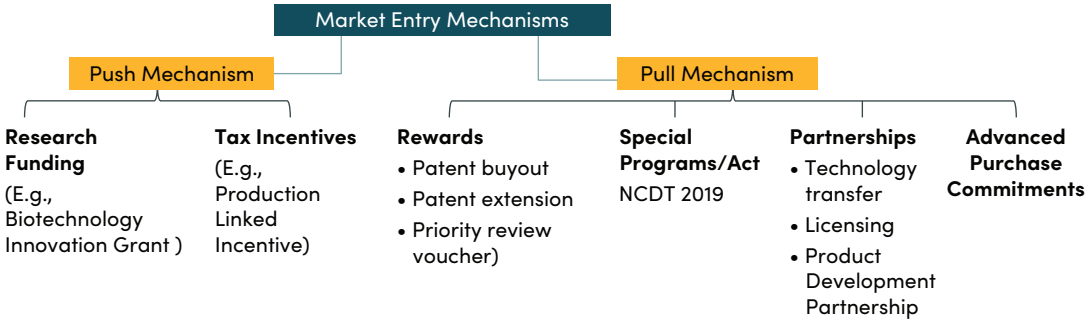
If high-end antimicrobials are requested, there is a separate purchase order or that which needs approval. If the amount is less than 125 percent of the total drug procurement budget, it is approved by an internal board. If it exceeds that amount, it needs approval from the state government.

See Appendix 5 for more information.

2.5 Market entry mechanisms

Various literature suggests that any new or innovative drug introduced in India faces challenges in terms of weak institutional and regulatory capacity, fragmented procurement mechanisms, poor patent protection, and ineffective policy frameworks (Langer 2013, Wockhardt 2020). To combat the growing threat of AMR, India needs to introduce market entry mechanisms that entail push and pull mechanisms (see Figure 1).

FIGURE 1. Market entry mechanisms



Different market entry mechanisms have been tried across various therapeutic areas in India, as shown in Table 1. However, these mechanisms have not been tested for AMR.

TABLE 1. Market entry mechanisms that have been implemented in India (not in AMR context)

Mechanism	Instruments Implemented Globally	Mechanisms Implemented in India (Not in AMR Context)
Push mechanism	Subsidized research through: i. Direct funding (research grants) ii. Tax incentives	i. Biotechnology Ignition Grant Scheme funded by BIRAC; the Indian Government supports early-stage biotech, agricultural startups (Biotechnology Industry Research Assistance Council 2023) ii. Department of Biotechnology (DBT), India, and Wellcome Trust, UK (India Alliance), fund research in health and biomedical sciences (India Alliance 2021) iii. Production-linked incentive (PLI) and Desh Bill 2.0 are tax incentive schemes to improve manufacturing capabilities (Department of Pharmaceuticals 2023)
Pull mechanism	Reward research output rather than research input through: i. Prizes/rewards ii. Priority review vouchers iii. Patent extensions iv. Patent buyouts	i. Gates Foundation's X prize for developing TB diagnostics (Bill and Melinda Gates Foundation 2008) ii. Priority review voucher exists for tropical disease and rare pediatric disease (US Food and Drug Administration 2020)

TABLE 1. (Continued)

Mechanism	Instruments Implemented Globally	Mechanisms Implemented in India (Not in AMR Context)
Product development partnerships (PDPs)	Long-term collaborations between academia, public sector, and private pharmaceutical companies	i. Rotavac vaccine was developed by Bharat Biotech, wherein R&D was supported by AIIMS, DBT, and IISc (Bharat Biotech 2022) ii. TB Alliance (TB Alliance 2023) iii. Shantha Biotech's cholera vaccine was developed in partnership with IVI (Chakma, et al. 2010)
Technology transfer and licensing	Allows sharing and eventual acquisition of knowledge, technology, and skills with another individual or institution	i. Hib (Haemophilis influenza b) vaccine technology was transferred by the Netherlands Vaccine Institute (NVI) to Biologicals E and Serum Institute of India (Biological E 2020) ii. Serum Institute's COVID vaccine (Astra Zeneca 2021) iii. Jubilant's non-exclusive licensing agreement with Gilead to manufacture Remdesivir (Gilead 2023) iv. Gilead's generic licensing agreement for hepatitis C drugs in India (Gilead 2014)
Advanced purchase commitments (with/without differential pricing)	Ex ante commitments by national governments/international organizations/private foundations to purchase a certain quantity of a drug/vaccine that has yet to be invented at a certain price	i. Advanced market commitment for pneumococcal vaccine by GAVI (Global Alliance for Vaccines and Immunization 2021) ii. APC for COVID vaccine (COVAX) (World Health Organization 2020)

Anticipated challenges to these mechanisms include:

- Push mechanism incentives, such as research grants, are provided by the Biotechnology Industry Research Assistance Council and the Department for Biotechnology under various schemes like the Biotechnology Innovation Grant. However, they are not specific to innovations of high-end antimicrobials, and the fund value is limited.
- The subscription model, a form of pull mechanism, could be attempted in India under AB-PMJAY. However, the challenge would be unlike the UK's National Health Service (NHS); India's PMJAY is not a sole service provider, and the insurance coverage is not as exhaustive.
- Schemes like advanced purchase commitments and priority review vouchers would require stringent oversight and changes in regulatory actions, which would not be feasible in upcoming years.

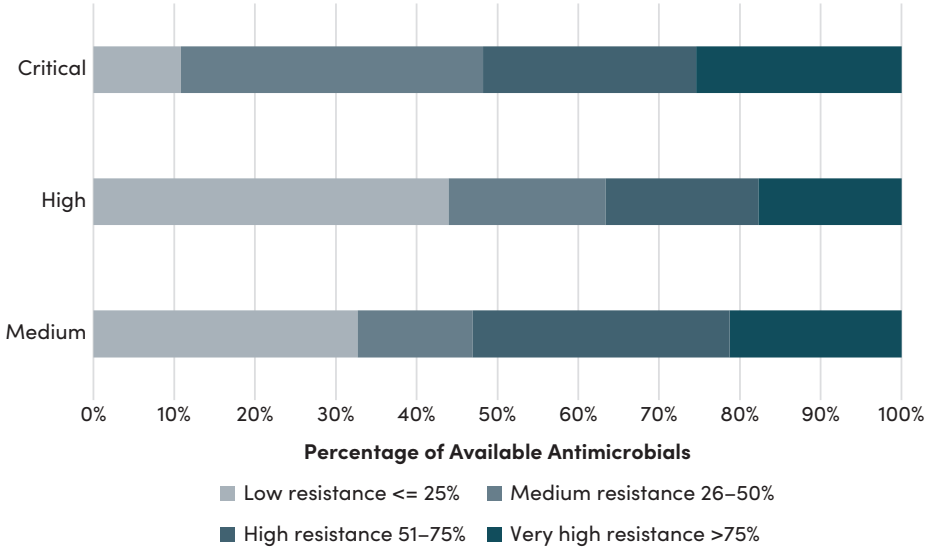
3. Antimicrobial resistance prevalence in India

The Global Research on Antimicrobial Resistance (GRAM) group estimates that in 2019, 1.8 million deaths in India were related to a bacterial infection. Of these infections, just over a million deaths are associated with drug-resistant pathogens, and almost 300,000 are estimated to be caused by drug resistance. This means that bacterial infections are associated with 19 percent of all deaths in India, and resistance is associated with 11 percent of deaths, causing 3.2 percent of them. Because the burden of AMR is disproportionately young compared to other illnesses, resistance is associated with 13.5 percent of disability-adjusted life years (DALYs) lost and causes 4.1 percent of DALYs lost. This is a death rate caused by resistance that is almost 40 percent higher than the global average of 2.2 percent of deaths.

To understand this further, we curated an antimicrobial surveillance database using two sources to understand the prevalence of AMR in India. The IPPL list, featuring the top ten pathogens for which there is an urgent need to develop novel drugs, is classified into three priority tiers: critical, high, and medium (World Health Organization, Department of Biotechnology 2017) (refer to Methodology).

Figure 2 shows the antimicrobial resistance for the three IPPL priority categories.

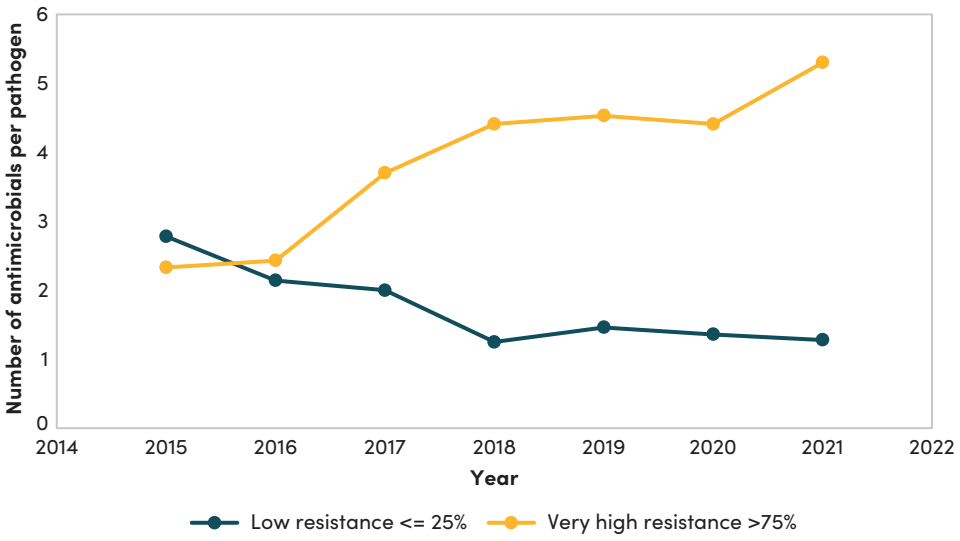
FIGURE 2. Antimicrobial resistance amongst three IPPL categories



Critical-priority pathogens are those that the IPPL considers to be the highest priority for the research and development of new antibiotics due to their prominent levels of resistance to existing treatments, high mortality rates, and the potential for widespread transmission. Our analysis shows that critical-priority class pathogens show more than 50 percent resistance to more than half of the available antimicrobials (antimicrobials reported in the surveillance data). On average, critical-priority class pathogens show low resistance to two or fewer antimicrobials. These findings suggest the following:

- A need for high-end antimicrobials for the pathogens listed under critical-category IPPL.
- Although stewardship can help curb the spread of AMR in the long term, the introduction of high-end antimicrobials for critical-priority pathogens is required immediately because of alarmingly elevated levels of resistance to available antimicrobials. In contrast, for pathogens listed as high priority, most antimicrobials are still effective, and pathogens show low resistance.
- Consequently, a surveillance strategy with strict monitoring of the usage of these antimicrobials will help reduce the increasing resistance to high-priority pathogens.

FIGURE 3. Temporal trend of critical categories (low and very high resistance)—number of antimicrobials per pathogen in 2015–2021



On analysing the temporal trends of resistance in critical-priority pathogens from 2015–2021, it was found that the number of antimicrobials per pathogen that show low resistance has dropped over time, whereas the number of antimicrobials per pathogen that exhibit exceedingly high resistance has increased (see Figure 3). These findings suggest the need to:

- Prioritize access to high-end antimicrobials for critical-category pathogens because the overall resistance is extremely high.
- Prioritize stewardship for antimicrobials targeting high-category pathogens to prevent resistance levels from rising.

4. Evaluation of national and state action plans on antimicrobial resistance

The government is making progress in improving awareness of the appropriate use of antimicrobials among healthcare professionals (doctors, nurses, hospitals, pharmacists, and microbiologists) and

the public. In the sphere of strengthening knowledge and evidence through surveillance (as included in NAP-AMR), two separate surveillance networks at the hospital and community levels have been established: NARS-Net and AMRSN. Most hospitals under AMRSN and NARS-Net are government-run tertiary and quaternary service providers, such as AIIMS and PGIMER. In these surveillance networks, private hospitals are commonly not included (National Centre for Disease Control 2022), (Ranjalkar and Chandy 2019), (Indian Council of Medical Research 2021).

Procurement and access to high-end antimicrobials have received limited attention in national and state action plans. States are encouraged to collaborate, but the national plan lacks a detailed roadmap for collaboration to improve access to expensive and critical drugs. Despite the public–private partnerships mentioned in the state action plans, there has been a lack of collaboration between private and medical service corporations, which must be addressed to improve drug procurement and access. Furthermore, the plan can also be expanded by including detailed roadmaps for mechanisms, such as pooled procurement through public pharmacies like Jan Aushadhi Kendras, which in turn would make the medicines affordable and ensure a continuous supply of high-end antimicrobials. The NAP-AMR briefly discusses diagnostics, but there is a considerable gap to be filled in terms of AMR-related diagnostic tools.

There is a lack of verification mechanisms to bolster stewardship, which would ensure the rational use of high-end antimicrobials at the point of care. Additionally, reimbursements under the AB-PMJAY scheme to ensure quality treatment and a continued supply of antimicrobials in private sector hospitals (small- to medium-sized) are not included in the current NAP-AMR. Although national and state action plans focus on several dimensions of access, innovation, and establishing quality management supply chain systems, there is a need to explore different pathways for easing the accessibility of antimicrobials (Watch and Reserve) while ensuring better stewardship practices.

See Appendix 6 for more information.

5. Challenges to improving access to existing and innovative antimicrobials

While eight antimicrobials are listed in the WHO Essential Medicine List (EML) under the Reserve category of AWaRe, more than half of the states have only one or no such antimicrobials in their corresponding essential drug lists (EDLs) (see Figure 4). Under the antimicrobials that treat Indian priority pathogens, we find that Reserve and Watch category drugs are more than 32 and 9 times more expensive, respectively, than Access category drugs, on average (see Figure 5) (Chokshi, et al. 2015), (World Health Organization n.d.), (Alsan, et al. 2015).

FIGURE 4. Average online retail price for AWaRe antimicrobials in India

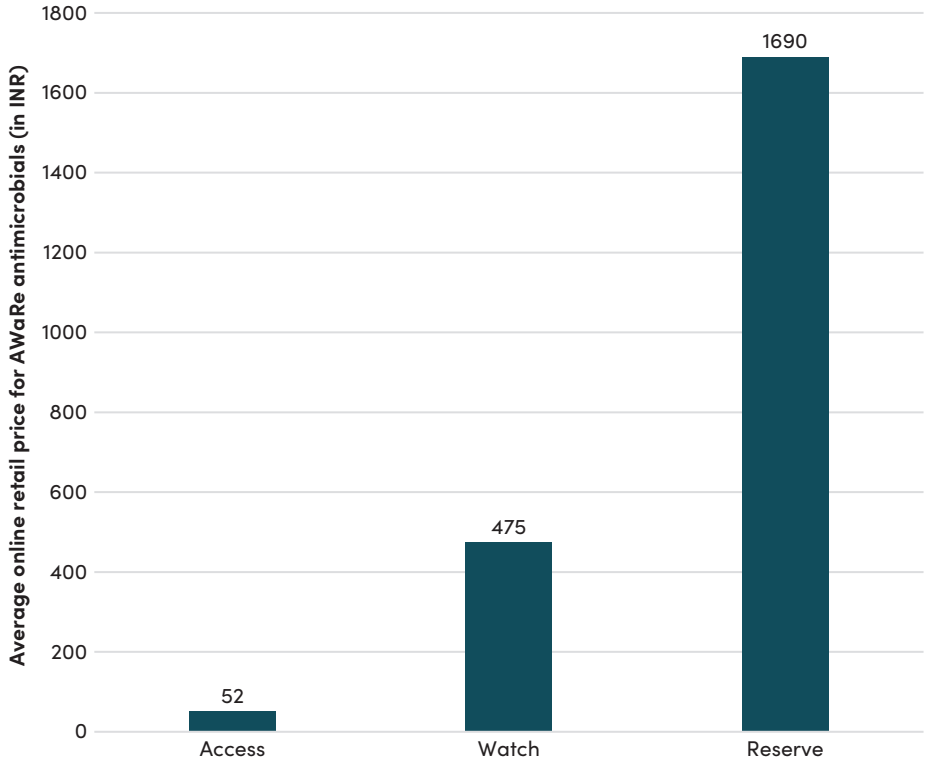
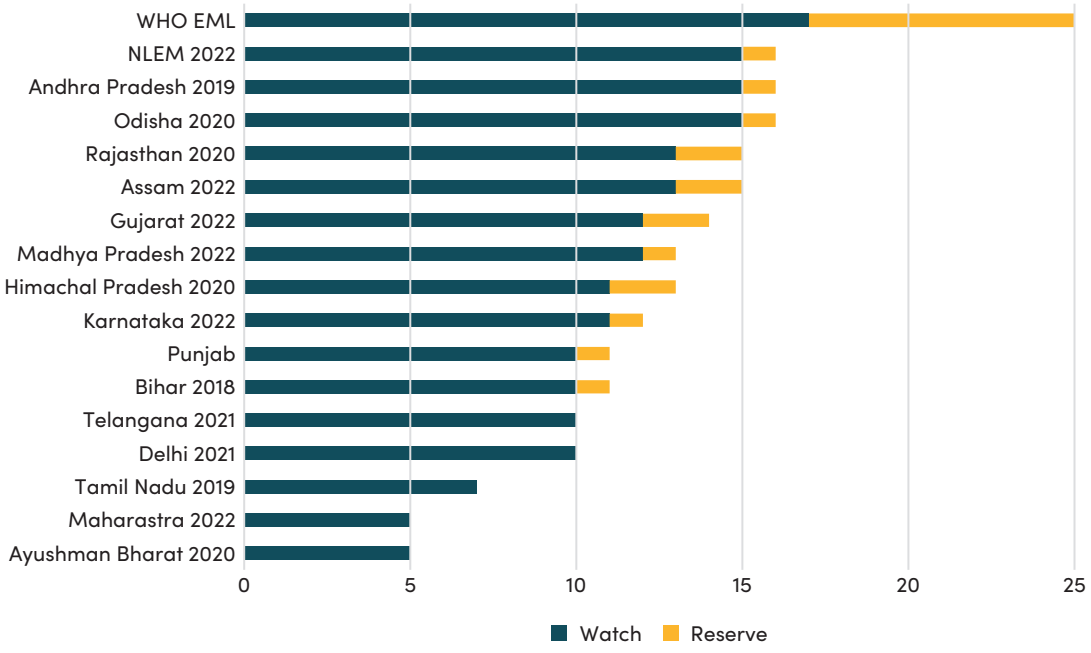


FIGURE 5. Comparing inclusion watch and reserve category antimicrobials in WHO EML, NLEM 2022, and EDL



This section provides insights from various groups of stakeholders regarding the challenges associated with access to next-generation antimicrobials in the Indian context:

- **Lack of Reserve category antimicrobials in state EDLs:** Currently, most state EDL and National List of Essential Medicines (NLEM) are focused on the Access category of the WHO AWaRe list, and rarely list Reserve category antimicrobials. Literature and stakeholder interactions indicated that unaffordable prices for Reserve and Watch category antimicrobials create access barriers to high-generation drugs.
- **Decentralized and limited public procurement of high-end antimicrobials:** A consequence of low-volume, high-end drugs not appearing in state EDLs is that they are procured by each health facility on a need basis. This independent and decentralized procurement reduces bargaining power, meaning that high-end antimicrobials remain costly. Since MSCs remain the primary source of drug procurement, the low-volume requirements of such medicines limit their availability. Even alternative outlets like Jan Aushadhi Kendras do not have the ability to procure these medicines.
- **State MSCs working in silos:** India's intricate procurement structure offers each state the freedom to operate autonomously. Although autonomy allows states the opportunity to design their own EDL and procurement strategies, this strategy is not advantageous for acquiring high-end (Watch and Reserve category) antimicrobials. States working in silos with little interaction cause these critical drugs to be procured on an ad hoc basis by each state, meaning that the prices of such drugs remain high. Lack of knowledge sharing between states also fails to reduce the information gap that states face when dealing with low-volume drugs. Moreover, the lack of demand for high-end drugs fails to attract competitive bidding, meaning that price discovery becomes a challenge for procurement agencies.
- **Scarcity of high-end drugs in small-sized private sector hospitals:** Small-sized hospitals in the private sector are plagued by low-volume demand for high-end antimicrobials. These hospitals do not have the bargaining power to reduce the price for such antimicrobials; thus, they either fail to procure such drugs or procure them at an exorbitant cost. This, in turn, places financial burdens on patients and increases OOP expenditures.
- **Lack of flexibility to include high-end drugs in national and state-funded insurance schemes:** National insurance schemes like the PMJAY currently do not have room to modify pre-existing rates as in other programs, such as Employee State Insurance (ESIs) and Ex-Servicemen Contributory Health Scheme (ECHS). The pre-determined packages (health benefits packages that include medicines, diagnostics, etc.) are fixed and do not have any option to substitute drugs with those of higher potency.

See Appendix 7 for more information.

6. Challenges to improving stewardship for existing and innovative antimicrobials

Healthcare facilities are high-risk environments for the development and spread of drug resistance and frequently have the highest burden of multidrug-resistant organisms (Ministry of Health and Family Welfare 2020). There is currently no good metric for measuring the level of unnecessary antimicrobial use in India, or indeed anywhere. However, the evidence that exists suggests that it is high. A 2013 study in Prune found that 92 percent of pharmacies were willing to dispense antibiotics to patients who did not have a prescription, and 55 percent of antibiotics prescribed were Watch antibiotics. This is contrary to the advice of WHO, which suggests that these should only account for 30 percent of doses consumed (Salunkhe, et al. 2013), (Fazaludeen, et al. 2022) (Ombelet, et al. 2018).

Stakeholders identified the following challenges associated with stewardship in the Indian context:

- **Infection, prevention, and control practices:** Several stakeholders stated that the implementation of infection, prevention, and control (IPC) practices was not stringent; therefore, there is a need to focus on the implementation and maintenance of IPC in hospitals, building an effective surveillance network to capture data on sensitivity, utilizing diagnostics, and ensuring the appropriate use of existing antimicrobials. Stakeholders also mentioned that NABH accreditation is currently limited to tertiary and quaternary service providers across public and private sector hospitals.
- **Antimicrobial consumption and surveillance:** There are limited data on AMR among different pathogens (AMRSN and NARS-Net), and this paucity of data makes it difficult to understand the magnitude of the problem. A lack of surveillance data from small- and medium-sized hospitals, which cater to the larger population in both the public and private sectors, adds to the challenge, as does self-medication among consumers.
- **Diagnostics:** Stakeholders raised concerns around two aspects of diagnostics: gaps in existing diagnostic capabilities and innovation regarding rapid/point-of-care diagnostics. Several stakeholders were of the view that only limited hospitals offering tertiary and quaternary services in the public and private sectors had access to such rapid diagnostics, for which they charged patients highly. Although the government has introduced free drugs and diagnostic initiatives, there is a shortage of workforce, infrastructure, and reagents to conduct antimicrobial susceptibility testing (AST).
- **Prescribing pattern/knowledge of clinicians:** Administration of broad-spectrum antimicrobials as an empirical therapy leads to the emergence of resistant strains. Empirical therapy relates to the practice of symptomatic treatment, whereby a broad-spectrum antimicrobial is administered to provide immediate relief to patients according to the symptoms, without clinicians confirming the underlying causative organism leading to the disease.

- **Financial burden/implications:** Owing to imprecise empirical treatment by healthcare professionals, the duration of in-patient stay is prolonged, which in turn increases bed occupancy and treatment costs. Overall costs include clinician fees, bed and drug costs, and overhead charges, leading to high OOP expenses. Hospitals may be loath to investment in stewardship measures, despite the long-term cost savings this can reap.

7. Challenges associated with the innovation of antimicrobials

As outlined in Section 2.4, the Indian pharmaceutical industry is strong in the fields of generic medicines, vaccines, and biosimilars, but is not yet a major player in pharmaceutical innovation. When interviewed, stakeholders identified the following challenges associated with the innovation of next-generation antimicrobials in the Indian context:

- **Regulation:** The Indian regulatory system is weak in terms of supporting clinical trials for any new drug, including high-end antimicrobials, and the regulations are not tailored to the Indian context. First, the introduction of any new drugs already approved outside India requires additional India-based clinical trials, which are an expensive and lengthy process. These significant additional costs often render an innovative drug unviable and unfeasible for the innovator firm. Second, fulfilling the requirements for conducting clinical trials, such as criteria and sample size, is difficult. Third, several stakeholders mentioned that the drug approval process is often delayed due to a fragmented regulatory process, causing a lag of up to two years in some cases. Finally, the lack of supervision on the availability of scheduled drugs is another challenge due to the injudicious antimicrobial usage and poor policy regulation in India. This can cause drug resistance to develop more quickly. Hence, stakeholders were of the view that companies selling antimicrobials are reluctant to introduce drugs into the Indian market, fearing that resistance will emerge in India and spread to more lucrative markets, undermining sales elsewhere.
- **Intellectual property:** Several stakeholders indicated that India is not very patent friendly. They also stated that under intellectual property law, patent infringement is a major challenge because TRIPS Plus and patent linkage do not exist in India. Due to a lack of coordination between the state and the central regulators, patent infringement occurs because there is currently no provision to check the patent registry, and by the time the innovator realizes that the patent has been infringed upon, they can already see their product in the market. Other concerns about IP laws relate to opposition proceedings in India, that is, the pre- and post-grant opposition process, which depends on the stage of the grant of the patent. Stakeholders also shared that there were delays of up to eight years in the grant of a patent due to misuse of the pre-grant opposition window. Serial pre-grant opposition, sometimes by unknown entities, further adds to the delay.

- **Target product profile (TPP):** Resistance trends vary by geographical region, meaning that diverse types of new antimicrobials are of higher demand in different regions. To best meet India's needs, there should be a TPP that encourages innovation in the products most useful for India. To date, India has not yet been able to create a TPP because there are different molecular mechanisms involved, and there is insufficient information to pinpoint resistance across different diseases.
- **Innovation ecosystem:** India's innovation ecosystem is at a nascent stage, where a limited pool of venture capitalists engages in supporting early-stage innovations. Most domestic innovators concentrate on developing drugs that generate high margins; hence, the antimicrobial drug pipeline is thin in comparison to other therapeutic areas because it does not have a desirable RoI. Equally, there is no provision by the Indian government to fund private manufacturers. Even with the support of organizations like BIRAC, the funding amount is limited and is not available for the entire R&D but focuses on a few phases, resulting in unpredictable funding patterns.

See Appendix 8 for more information.

8. Recommendations

To combat AMR in India, our recommendations focus on two key areas:

1. Enhancing access to high-end antimicrobials (relevant Watch and Reserve categories from the WHO AWaRe list that treat critical-priority pathogens in the IPPL) while ensuring appropriate stewardship practices
2. Creating an innovation ecosystem that supports antimicrobial R&D

8.1 Enhancing access to high-end antimicrobials in the public and private sectors while ensuring appropriate stewardship practices

To ensure access to these Watch and Reserve category antimicrobials, we recommend their inclusion in state drug procurement lists that cater to the public sector. To foster drug accessibility in private sector hospitals, alternative procurement pathways need to be explored. Simultaneously, stewardship practices should be undertaken by improving diagnostic facilities in all hospitals and aligning these hospitals to utilize accreditation, certification, and empanelment systems alongside an assurance program.

As the procurement of essential drugs in India is primarily handled autonomously by the states, key prerequisites for improving access to high-end antimicrobials in the public sector are to develop or modify state action plans and state EDLs. State action plans should include clear procurement guidelines covering access and stewardship provisions, while EDLs should include Watch and

Reserve category antimicrobials that are essential for treating critical-priority pathogens of IPPL. These inclusions will facilitate coordination among MSCs in the short term but will also pave the way for MSCs to potentially pool procure these medicines in the long run.

Coordination can be further enhanced by increasing the transparency of rate contracts. MSCs should share information about their drug procurement (drug name, supplier, contract price, and volume) in a centralized portal where every MSC can access all procurement history. This portal could be a new open-access dashboard or a modification of the current "Drugs and Vaccine Distribution Management System (DVDMS) Central Dashboard," which currently only allows states to access their own procurement information.

Implementing these changes will standardize and simplify the procurement process, alleviate the sporadic and ad hoc-based procurement of high-end antimicrobials, and, by aggregating demand, strengthen the MSC's bargaining power, reducing prices and stockouts and increasing affordability.

Additionally, and acknowledging the challenge of exceptionally low volumes in certain cases, alternate procurement channels could also be deployed. State-owned pharmacies, autonomous entities that manage pharmacy outlets outside government budgets, private aggregators, group purchase organizations that can negotiate prices for smaller public and private hospitals, and Jan Aushadhi pharmacies can all play a role in improving access to high-end antimicrobials while securing stewardship. For example, states could learn and expand from experiences such as those of Karunya pharmacies, a state-owned pharmacy that is part of the Kerala Medical Services Corporation (KMSCL). This self-revenue-generating state pharmacy chain leverages centralized demand pooling to offer drugs at a discounted rate for patients with prescriptions as well as public hospitals. Karunya procures meropenem, an antimicrobial from the Watch category, at half of the MRP, and colistin, an antimicrobial from the Reserve category, at one-third of the MRP. Private aggregators, funded by third-party donors, could also aggregate demand for smaller private hospitals when the state lacks the infrastructure to pool demand centrally at the inter- or intrastate level (Applied Policy 2014). Private aggregators can collect data from low-demand nodes and negotiate prices for pooled demand.

PMJAY can also play an important role in increasing access and securing stewardship by creating variants of existing packages for high-end antimicrobials that should require verified and validated diagnostic test results, indicating the need for the high-end drug to avoid potential misuse or overuse. Current AB-PMJAY reimbursement norms are restrictive in that the package rates are low and rigid; that is, they do not account for the possibility that some patients under the same package may need more expensive drugs. As a result, these drugs may have to be financed through state procurement mechanisms, or their costs may have to be borne by the patients.

Embedding stewardship in any access initiative

Stewardship will need to be an essential part of any access strategy to prevent the misuse and overuse of antibiotics, especially in small- and medium-sized hospitals that are less likely to have strong stewardship programs. A new assurance mechanism within NABH, improved availability of diagnostics, and enhanced surveillance of resistance are three key strategic policy options to support this goal. The assurance mechanism, which would go beyond the three broad themes of NABH guidelines (accreditation, certification, and empanelment), would request that hospitals report data on antibiotic use and stewardship practices to NABH, which would then verify it. The mechanism could be a prerequisite for accessing antibiotics or could be used as an incentive for hospitals to get preferential prices. The Association of Healthcare Providers of India (AHPI) could take a lead role in mobilizing support for this program, with large hospitals "handholding" smaller hospitals to support them in enacting antimicrobial stewardship practices. Evidence could also be shared with smaller hospitals to demonstrate the long-term financial benefits of improved stewardship practices.

A good point-of-care diagnostic test can also reduce the inappropriate use of antibiotics by enabling early detection of the pathogen and facilitating rapid testing of antimicrobial susceptibility. The Free Diagnostic Service Initiative in India aims to augment the development and deployment of diagnostics in the Indian healthcare system. However, access to rapid diagnostics remains a challenge. Importing diagnostic tools is costly and requires extensive human resources (Sharma 2022), so it is essential to develop low-cost tests locally (World Health Organization 2019). For these efforts to be successful, adequate mandatory accreditation requirements in the diagnostic industry must be put in place. Increasing the number of quality-approved facilities with qualified personnel will also help with the early detection and subsequent control of antimicrobial resistance (Public Health Agency of Sweden 2023).

Finally, monitoring resistance and susceptibility patterns is necessary to ensure that everyone has fair access to effective drugs. The existing surveillance network should be expanded so that a larger network of hospitals conducts consistent sampling. In addition, surveillance must be expanded in scope to include any newly added antimicrobials.

8.2 Creating an innovation ecosystem that supports antimicrobial R&D

> While India has shown its exemplary presence in manufacturing generic medicines and contributing to global consumption, promoting innovation of high-end antimicrobials requires the development of a customized target antimicrobial profile to serve Indian needs and facilitate procedural changes.

To combat the current dearth of innovation, the Government of India needs to create an innovation ecosystem that supports drug and diagnostics R&D in the country. This includes developing targeted

antimicrobial profiles tailored to the Indian context and implementing procedural changes to facilitate high-end antimicrobial innovation. The proposed profiles will be modelled on the WHO TPP, which includes estimates of disease burden, target population, expected price, and intended use, and highlights other desirable attributes of the products related to safety and efficacy. In addition, the target antimicrobials profile (TAP) should list the prominent resistance molecular mechanisms present in India to guide innovators' investments in the drug pipeline. The government could also link push and pull incentives (e.g., grants for conducting exploratory research, making a robust public infrastructure available for conducting trials, ease of approval for Phase III/IV trials, and extended patent protection) to pharmaceutical firms developing drugs that fit the TAP. In addition, the TAP may aid access to antimicrobials that are present outside India but have not yet reached the Indian market by actively seeking innovators with regulator-approved (e.g., FDA) drugs that meet the TAP.

The government should also signal its intent to get high-end antimicrobials into the Indian market through different initiatives, such as expedited approvals, assurance of a minimum price (e.g., Sweden, PHAS pilot study), and access to essential R&D infrastructure. The NDCT 2019 rules, which have helped to expedite clinical trials in India, could be used as a model to allow companies to avoid repeating clinical trials in India if the disease targeted is prevalent in the country. An online record system accessible to regulators and pharmaceutical companies could improve coordination and reduce the delay in providing information sought by regulators to provide approval. Access to good laboratory practices (GLP) and centers for toxicology studies at a reduced cost could also support private companies in investing in antibiotic R&D. To increase transparency and efficiency, an independent body should review and regulate these processes.

Finally, a network, preferably funded by a multinational research organization, could be established to conduct solidarity trials. One example of this is the successful engagement of the Gates Foundation in the Serum Institute's Covishield production (Jaju 2019).

9. Conclusion

The complicated nature of AMR calls for a multifaceted strategy. India is struggling to contain rising resistance rates, and it is necessary to create a favourable ecosystem that will increase antimicrobial access and foster innovation. Any attempt to combat AMR through increased accessibility and innovation must be accompanied by superior stewardship techniques.

This report identifies three key challenges in combating AMR in India: improving access to high-end antimicrobials, enhancing stewardship practices, and fostering innovation in high-end antimicrobials. The lack of Reserve category antimicrobials in state EDLs, decentralized procurement of high-end antimicrobials, and limited availability in small-sized private sector hospitals constrict access. Inadequate implementation of infection, prevention, and control

practices, limited data on AMR, and the prescribing patterns of clinicians pose challenges to improving stewardship practices. The weak regulatory system, patent infringement, and inadequate innovation ecosystem hinder innovation in high-end antimicrobials.

To address these challenges and combat AMR in India, our recommendations focus on two key areas: enhancing access to high-end antimicrobials while ensuring appropriate stewardship practices, and creating an innovation ecosystem that supports antimicrobial R&D. The first set of recommendations involves modifying national and state action plans to outline guidelines for high-end antimicrobial procurement and improving inter-state coordination to increase the transparency of rate contracts. The use of alternate channels to procure low-volume drugs, utilization of AB-PMJAY to introduce the use of high-end antimicrobials, and improvement of diagnostic facilities are also recommended. Additionally, enhancing surveillance of high-end antimicrobials and ensuring appropriate stewardship practices is critical for preventing future resistance. The second set of recommendations involves developing targeted antimicrobial profiles, linking push and pull incentives to pharmaceutical firms, and making procedural changes to facilitate high-end antimicrobial innovation.

Successfully implementing these recommendations to improve access to high-end antimicrobials and ensure adequate stewardship while encouraging innovation requires a multi-pronged, integrative, and well-coordinated response from both public and private stakeholders in India to avoid a catastrophic AMR situation in the future.

Bibliography

Ackley, Renee, Danya Roshdy, Jacqueline Meredith, Sarah Minor, William E Anderson, Gerald A Capraro, and Christopher Polk. 2020. "Meropenem-Vaborbactam versus Ceftazidime-Avibactam for Treatment of Carbapenem-Resistant Enterobacteriaceae Infections." *Antimicrobial agents and Chemotherapy, 64,* 5.

Alhifany, Abdullah A, Nisrin Bifari, Yasser Alatawi, Saad U Malik, Thamer A Almangour, Ali F Altebainawi, Thamir M Alshammari, Amal F Alotaibi, Ahmad J Mahrous, Fahad S Alshehri, Ejaz Cheema. 2022. "Efficacy and safety of delafloxacin, ceftaroline, ceftobiprole, and tigecycline for the empiric treatment of acute bacterial skin and skin structure infections: A network meta-analysis of randomized controlled trials." *Science Direct* 195–204.

Alsan, Marcella, Lena Schoemaker, Karen Eggleston, Nagamani Kammili, Prasanthi Kolli, and Jay Bhattacharya. 2015. "Out-of-pocket health expenditures and antimicrobial resistance in low-income and middle-income countries: an economic analysis." *The Lancet Infectious Diseases, 15,* 10.

Ambade, Mayanka, Rakesh Sarwal, Nachiket Mor, R Kim, Rockli Kim, and S.V. Subramanian. 2022. "Components of Out-of-Pocket Expenditure and Their Relative Contribution to Economic Burden of Diseases in India." *JAMA Open Network, 5,* 5.

Applied Policy. 2014. "GPOs: Helping to Increase Efficiency and Reduce Costs for Healthcare Providers and Suppliers." *Suppply Chain Association.* Accessed February 12, 2023. https://www.supplychainassociation.org/wp-content/uploads/2018/05/Applied_Policy_Report_2014.pdf.

Astra Zeneca. 2021. *Serum Institute of India obtains emergency use authorisation in India for AstraZeneca's COVID-19 vaccine.* January. Accessed February 12, 2023. https://www.astrazeneca.com/media-centre/press-releases/2021/serum-institute-of-india-obtains-emergency-use-authorisation-in-india-for-astrazenecas-covid-19-vaccine.html

Bharat Biotech. 2022. *Rotavac.* Accessed February 12, 2023. https://bharatbiotech.com/rotavac.html.

Bill and Melinda Gates Foundation. 2008. *X PRIZE Foundation, Inc.* Accessed Februray 12, 2023. https://www.gatesfoundation.org/about/committed-grants/2008/09/opp51217.

Biological E. 2020. *Partnerships.* Accessed February 12, 2023. https://biologicale.com/partnerships.html.

Biotechnology Industry Research Assistance Council. 2023. *Biotechnology Ignition Grant Scheme.* Accessed Febraury 12, 2023. https://birac.nic.in/big.php.

Chakma, Justin, Hassan Masum, Kumar Perampaladas, Jennifer Heys, and Peter A Singer. 2010. "India's billion dollar biotech." *Nature Biotechnology, 28,* 783.

Chatterjee, Chirantan, and Vasanthi Srinivasan. 2013. "Ethical issues in health care sector in India." *IIMB Management Review* 49–62.

Chokshi, Maulik, Habib Hasan Farooqui, Sakthivel Selvaraj, and Preeti Kumar. 2015. "A cross-sectional survey of the models in Bihar and Tamil Nadu, India for pooled procurement of medicines." *WHO South-East Asia Journal of Public Health* 78–85.

Department of Pharmaceuticals. 2023. *Production Linked Incentive (PLI) Scheme for Promotion of Domestic Manufacturing of critical Key Starting Materials (KSMs)/ Drug Intermediates and Active Pharmaceutical Ingredients (APIs) in the Country.* Accessed February 12, 2023. https://pharmaceuticals.gov.in/schemes/production-linked-incentive-pli-scheme-promotion-domestic-manufacturing-critical-key.

Dwivedi, Neelima, and Ruma Bhargava. 2022. "How public-private partnerships could be the booster dose for India's healthcare ecosystem." *World Economic Forum.* Accessed January 15, 2023. https://www.weforum.org/agenda/2022/09/public-private-partnerships-india-healthcare-ecosystem/.

Fazaludeen, Koya Shaffi, Senthil Ganesh, Sakthivel Selvaraj, Veronika J. Wirtz, Sandro Galea, and Peter C Rokers. 2022. "Consumption of systemic antibiotics in India in 2019." *The Lancet Regional Health—Southeast Asia.*

Gilead. 2014. *Gilead Announces Generic Licensing Agreements to Increase Access to Hepatitis C Treatments in Developing Countries.* Accessed January 23, 2023. https://www.gilead.com/news-and-press/press-room/press-releases/2014/9/gilead-announces-generic-licensing-agreements-to-increase-access-to-hepatitis-c-treatments-in-developing-countries.

Gilead. 2023. *Voluntary Licensing Agreements for Remdesivir.* Accessed Febraury 12, 2023. https://www.gilead.com/purpose/advancing-global-health/covid-19/voluntary-licensing-agreements-for-remdesivir?ftag=MSF0951a18.

Global Alliance for Vaccines and Immunization. 2021. *Pneumococcal AMC*. Accessed February 12, 2023. https://www.gavi.org/investing-gavi/innovative-financing/pneumococcal-amc.

Global Antibiotic Research & Development Partnership. 2022. *Shionogi, GARDP and CHAI announce landmark license and collaboration agreements to treat bacterial infections by expanding access to cefiderocol in 135 countries.* Accessed February 12, 2023. https://gardp.org/shionogi-gardp-and-chai-announce-landmark-license-and-collaboration-agreements-to-treat-bacterial-infections-by-expanding-access-to-cefiderocol-in-135-countries/.

India Alliance. 2021. *India Alliance.* Accessed February 12, 2023. https://www.indiaalliance.org/about-us/about-ia.

Indian Council of Medical Research. 2021. "India's Antimicrobial Resistance Surveillance & Research Initiative." *AMR ICMR.* Accessed Feb 12, 2023. https://iamrsn.icmr.org.in/index.php/resources/amr-icmr-data.

Institut Montaigne. 2020. *Private Healthcare in India: Boons and Banes*. November. Accessed February 12, 2023. https://www.institutmontaigne.org/en/analysis/private-healthcare-india-boons-and-banes.

Jaju, Mahesh. 2019. *Implications of updated who essential medicines list*. Accessed February 12, 2023. https://clarivate.com/blog/implications-updated-essential-medicines-list/.

Jeffery, Roger. 2007. *Pharmaceutical Distribution Systems in India*. Accessed February 12, 2023. https://assets.publishing.service.gov.uk/media/57a08c0a40f0b652dd00108e/60336-WP1a.pdf.

Kadarpeta, Dr. Rahul S Reddy. 2022. "Can a government health insurance program reduce out-of-pocket expenditures on medicines in India?" *PLOS BLOGS*. Accessed February 12, 2023. https://yoursay.plos.org/2022/10/can-a-government-health-insurance-program-reduce-out-of-pocket-expenditures-on-medicines-in-india/.

Konwar, Mahanjit, Mitesh R Maurya, Tushar B Nishandar, Urmila M Thatte, and Nithya J Gogtay. 2021. "An evaluation of drug lag for new drugs approved by the Indian regulator relative to the United States, European Union, and Japanese regulatory agencies: A 15-year analysis." *Perspectives in Clinical Research* 159–164.

Kotwani, Anita, and Kathleen Holloway. 2013. "Access to antibiotics in New Delhi, India: implications for antibiotic policy." *Journal of Pharmaceutical Policy and Practice* 6.

Lal, Shanker. 2014. *Here is a model Indian States can implement to ensure smooth flow of medical supplies to health facilities*. https://blogs.worldbank.org/governance/here-model-indian-states-can-implement-ensure-smooth-flow-medical-supplies-health-facilities.

Langer, Frank. 2013. "Neglected infectious diseases: are push and pull incentive mechanisms suitable for promoting drug development research?" *Health Economics, Policy and Law* 185–208.

Ministry of Commerce and Industry. 2022. *Startup India*. Accessed December 15, 2022. https://www.startupindia.gov.in/.

Ministry of Finance. 2023. *Economic Survey 2022–2023*. Accessed February 12, 2023. https://www.indiabudget.gov.in/economicsurvey/doc/echapter.pdf.

Ministry of Health and Family Welfare. 2016. "The Drugs and Cosmetics Act and Rules." *CDSCO*. Accessed 15 2023, February. https://cdsco.gov.in/opencms/export/sites/CDSCO_WEB/Pdf-documents/acts_rules/2016DrugsandCosmeticsAct1940Rules1945.pdf.

Ministry of Health and Family Welfare. 2020. "National Guidelines for Infection Prevention and Control in Healthcare Facilities." Accessed February 12, 2023. https://main.mohfw.gov.in/sites/default/files/National%20Guidelines%20for%20IPC%20in%20HCF%20-%20final%281%29.pdf.

Ministry of Health and Family Welfare. 2022a. *National Health Estimates (2018–19) released*. September. Accessed January 23, 2023. https://pib.gov.in/PressReleasePage.aspx?PRID=1858770.

Ministry of Health and Family Welfare. 2022b. *Dr Mansukh Mandaviya launches National Lists of Essential Medicines (NLEM) 2022.* Accessed December 18, 2022. https://pib.gov.in/PressReleasePage.aspx?PRID=1858931.

Ministry of Health and Family Welfare, Central Drugs Standard Control Organisation (CDSCO). 2019. "New Drugs and Clinical Trials Rules 2019." https://cdsco.gov.in/opencms/export/sites/CDSCO_WEB/Pdf-documents/NewDrugs_CTRules_2019.pdf

Mogasale, VV, Pai V Saldanha P, Rekha PD, and Mogasale V. 2021. "A descriptive analysis of antimicrobial resistance patterns of WHO priority pathogens isolated in children from a tertiary care hospital in India." *Nature Scientific Reports* 5116.

National Centre for Disease Control. 2022. *Annual Reports by National Antimicrobial Resistance Surveillance Network NARS-NET.* Annual Report, Ministry of Health and Family Welfare. Accessed February 12, 2023. https://ncdc.gov.in/index1.php?lang=1&level=2&sublinkid=3938&lid=349.

National Health Authority. 2022. *National Health Authority (NHA) organises Southern Regional Review Meeting at Mahabalipuram, Tamil Nadu to discuss progress and implementation of Ayushman Bharat Pradhan Mantri Jan Arogya Yojana (AB PM-JAY) and Ayushman Bharat Digital Mission (ABDM) in the Southern States and UTs.* Accessed February 12, 2023. https://pib.gov.in/PressReleasePage.aspx?PRID=1814806.

Ombelet, S, JB Ronat, T Walsh, CP Yansouni, J Cox, E Vlieghe, D Martiny, M Semret, O Vandenberg, J Jacobs, & Bacteriology in Low Resource Settings working group. 2018. "Clinical bacteriology in low-resource settings: today's solutions." *The Lancet Infectious Diseases, 18*(8), 248–258.

Peacocke, Elizabeth F, Sonja L. Myhre, Hakan Safaralilo Foss, and Unni Gopinathan. 2022. "National adaptation and implementation of WHO Model List of Essential Medicines: A qualitative evidence synthesis." *Plos Medicine.*

Pragasam, Agila Kumari, S. Lydia Jennifer, Dhanalakshmi Solaimalai, Dhiviya Prabaa Muthuirulandi Sethuvel, Tanya Rachel, Divyaa Elangovan, Karthick Vasudevan, Karthick Gunasekaran, and Balaji Veeraraghavan. 2020. "Expected Plazomicin Susceptibility in India Based on the Prevailing Aminoglycoside Resistance Mechanisms in Gram-Negative Organisms Derived from Whole-Genome Sequencing." *Indian Journal of Medical Microbiology* 313–318.

Public Health Agency of Sweden. 2023. *Availability of antibiotics.* Accessed February 27, 2023. https://www.folkhalsomyndigheten.se/the-public-health-agency-of-sweden/communicable-disease-control/antibiotics-and-antimicrobial-resistance/availability-of-antibiotics.

Ranjalkar, Jaya, and Sujith J. Chandy. 2019. "India's National Action Plan for antimicrobial resistance—An overview of the context, status, and way ahead." *Journal of Family Medicine and Primary Care* 1828–1834.

Salunkhe, S. D., Vijaya Pandit, Shriram Jayshree Dawane, and Kushal Sarda. 2013. "Study of over the counter sale of antimicrobials in pharmacy outlets in Pune, India: A cross sectional study." *International Journal of Pharma and Bio Sciences* 616–622.

Sharma, Priyanka. 2022. *ICMR seeks proposals for manufacture of antimicrobial resistance diagnostic kits.* Accessed December 24, 2022. https://www.livemint.com/news/india/icmr-seeks-proposals-for-manufacture-of-antimicrobial-resistance-diagnostics-kits-11668515442483.html.

Singh, Prabal Vikram, Anand Tatambhotla, Rohini Kalvakuntla, and Maulik Chokshi. 2013. "Understanding public drug procurement in India: a comparative qualitative study of five Indian states." *BMJ Open 3*(2), e001987.

Sivanandan, Sindhu, Kajal Jain, Nishad Plakkal, Monika Bahl, Tanushree Sahoo, Shirshendu Mukherjee, Yogendra Kumar Gupta, and Ramesh Agarwal. 2019. "Issues, challenges, and the way forward in conducting clinical trials among neonates: investigators' perspective." *Journal of Perinatology* 20–30.

TB Alliance. 2023. *Antimicrobial Resistance.* Accessed February 12, 2023. https://www.tballiance.org/why-new-tb-drugs/antimicrobial-resistance.

The World Bank. 2022a. *Current Health Expenditure (% of GDP).* Accessed March 24, 2023. https://data.worldbank.org/indicator/SH.XPD.CHEX.GD.ZS.

The World Bank. 2022b. *Domestic general government health expenditure (% of current health expenditure).* Accessed March 24, 2023. https://data.worldbank.org/indicator/SH.XPD.GHED.CH.ZS.

US Food and Drug Administration. 2020. *Tropical Disease Priority Review Voucher Program.* Accessed February 12, 2023. https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/tropical-disease-priority-review-voucher-program.

Wockhardt. 2020. *Wockhardt gets DGCI approval for 2 new antibiotics.* Accessed February 12, 2023. https://economictimes.indiatimes.com/industry/healthcare/biotech/pharmaceuticals/wockhardt-gets-dgci-approval-for-2-new-antibiotics/articleshow/73293398.cms?from=mdr.

World Health Organization. 2020. *COVAX Announces additional deals to access promising COVID-19 vaccine candidates; plans global rollout starting Q1 2021.* https://www.who.int/news/item/18-12-2020-covax-announces-additional-deals-to-access-promising-covid-19-vaccine-candidates-plans-global-rollout-starting-q1-2021.

World Health Organization. 2019. "Landscape of diagnostics against antibacterial resistance, gaps and priorities." Accessed February 12, 2023. https://apps.who.int/iris/handle/10665/326480.

World Health Organization. n.d. *Model List of Essential Medicines.* Accessed February 12, 2023. https://list.essentialmeds.org/.

World Health Organization, Department of Biotechnology. 2017. "Indian Priority Pathogen List." DBT. Accessed February 12, 2023. https://dbtindia.gov.in/sites/default/files/IPPL_final.pdf.

Appendix 1. Methodology

This study aimed to explore pathways for improving access to new and existing antimicrobials and fostering antimicrobial innovation while ensuring appropriate stewardship practices. To do this, we curated databases to understand existing pathogen resistance levels, reviewed action plans to depict current policy directions, and spoke to stakeholders for insights. The methods used to compile databases, review national and state action plans, and interview stakeholders are as follows:

For the quantitative research, an antimicrobial surveillance database was created from two sources:

- The ICMR's AMR Surveillance and Research Initiative (AMRSN); and
- The National AMR Surveillance Network (NARS-Net), coordinated by the NCDC.

This data set was then mapped against the WHO Access, Watch, and Reserve (AWaRe) classification of antimicrobials in its Essential Medicines List and the WHO list of Critically Important Antimicrobials for Human Medicine (WHO CIA list). Using these data, antimicrobials were categorized into distinct categories based on the prevalence of resistance in the isolates evaluated in the AMRSN and NARS-Net surveys.

Simultaneously, another data set was created using the IPPL category pathogens. Pathogens under IPPL were mapped against US FDA- and CDSCO-approved medicines to understand the availability of medicines in India. This was undertaken for all antimicrobials approved by the US FDA between 2015 and 2022 and was compared with their approval by CDSCO in India.

For the qualitative research, national and state action plans were reviewed against each of their strategic priorities, established goals, and current implementation status. Thirty-two stakeholder interviews with executives from medical service corporations, pharmaceutical companies, subject matter specialists, and representatives of government agencies were conducted. These participants were identified when reviewing secondary literature on the Indian pharmaceutical ecosystem, with an emphasis on antimicrobials.

Appendix 2. Drug quality and price control

The Central Drugs Standard Control Organization (CDSCO), assisted by the Drugs Technical Advisory Board (DTAB) and the Drugs Consultative Committee (DCC) under the central government, oversees clinical trials, approvals, and imports in India. The drugs controller general of India (DCGI), head of the CDSCO, reviews submitted clinical trial applications in conjunction with two subject expert committees (for antiviral and antimicrobial applications) and has the final regulatory authority for clinical trial approvals. At the state level, the state drug regulatory authority (SDRA) is responsible for the manufacture, sale, and distribution of drugs in their respective states. Each state is independent in formulating its regulatory processes.

Drug quality: The Indian Pharmacopeia Commission deals with drug quality standards by updating monographs regularly. The IPC runs the Pharmacovigilance Program of India (PvPI), a flagship drug safety and monitoring program of the Government of India. Through the PvPI, data related to adverse drug-related events are recorded and analyzed to improve patient safety. CDSCO provides periodic updates on the list of substandard drugs by conducting regular testing.

Price control: The National Pharmaceutical Pricing Authority (NPPA) was established in 1997 to enforce the Drugs Price Control Order (DPCO) 1995/2013. The Ministry of Health and Family Welfare (MoHFW) creates and revises its list of essential medicines known as the NLEM. It promotes the judicious use of drugs while considering three essential attributes: cost, safety, and efficacy. The simple average of all available identical medications on the market is the ceiling price for drugs marketed under NLEM.

Appendix 3. Review of national and state action plan on AMR

Table 2 below provides a snapshot of the goals and current implementation status of various strategic priorities under NAP-AMR.

TABLE 2. Strategic priorities of NAP-AMR and their current implementation status

Strategic Priority	Goals	Current Implementation Status
Improve awareness of AMR through effective communication, education, and training	• Assess awareness among key stakeholders • Utilize communications to promote awareness • Knowledge and capacity building among stakeholders • Include AMR-related topics in the educational curriculum • Improve interdepartmental and intersectoral communication	• Antimicrobial stewardship activities: a series of sensitization and training workshops were organized. • ICMR Pfizer Center for AMR Research and Education was set up to improve public awareness. • World Awareness Week is held every year on November 18–24, aimed at raising awareness of and commitment to tackling the emergence of AMR. • Activities such as quiz competitions in schools, participation in perfect health mela posters, and quiz competitions for healthcare workers have been organized. • Media material related to AMR education and awareness has been developed.
Improve awareness of AMR through effective communication, education, and training; Strengthen knowledge and evidence through surveillance	• Strengthen microbiology laboratory capacity in human, animal, food, and environment sectors • Designate national reference laboratories in human, animal, food, and environmental sectors • Establish standards and coordination mechanisms for national surveillance, standardizing data analysis and information management • Antimicrobial residues/contaminants in food and environment	• India was enrolled in the Global Antimicrobial Resistance Surveillance System (GLASS). • Two separate surveillance networks were established. NARS-Net AMR Surveillance Network (run by NCDC) comprises 35 labs in 26 Indian states to track seven priority bacterial pathogens. Indian Council of Medical Research's AMRSN network of 30 tertiary hospitals report resistance data for six pathogen groups. • Annual reports of national AMR surveillance have been published since 2015. • ICMR undertook a project on an "Integrated One Health Surveillance Network for Antimicrobial Resistance" in collaboration with the Indian Council of Agriculture Research (ICAR) to assess the preparedness of Indian veterinary laboratories to participate in an integrated AMR surveillance network. • ICMR created veterinary standard operating procedures (Vet-SOPs) to enable the comparison of antimicrobial resistance patterns in animals and humans.

TABLE 2. (Continued)

Strategic Priority	Goals	Current Implementation Status
Reduce the incidence of infection through effective infection prevention and control	• Strengthen the national plan for IPC in health care, veterinary settings, animal husbandry, and in the community • Reduce environmental contamination with resistant pathogens and antimicrobial residues • Align the healthcare support industry with the IPC	• National guidelines on IPC in healthcare facilities were released in Jan 2000. These guidelines have been used in training modules for country-wide training.
Optimize the use of antimicrobial agents in health, animals, and food; Regulate access to high-quality antimicrobials	• Strengthen national regulatory authorities for improved quality, safety, and efficacy of antimicrobials • Ensure uninterrupted access to high-quality antimicrobials by strengthening the drugs control department • Ensure intersectoral coordination to regulate and optimize the use of antimicrobials in humans, animals, and food • Establish a national surveillance system for antimicrobial use • Implement monitoring system to assess antimicrobial consumption in humans, animals, and food sectors • Implement antimicrobial stewardship programs in healthcare facilities • Improve the appropriate use of antimicrobials in the community	• To improve the appropriate use of antimicrobials, the NCDC published the National Treatment Guidelines for Antimicrobial Use in Infectious Diseases in 2016. Hospital authorities are expected to disseminate the guidelines to all staff members and ensure compliance by practicing antimicrobial stewardship. • On the recommendation of ICMR, DCGI banned 40 fixed-dose combinations (FDCs) targeting human health. • Steps were taken to ban the use of colistin as a growth promoter in animal feed in poultry. • ICMR has initiated an antimicrobial stewardship program on a pilot project basis to control the misuse and overuse of antimicrobials. • ICMR Pfizer Center for AMR Research and Education was set up to improve awareness, strengthen surveillance, and develop AMR stewardship capabilities.

TABLE 2. (Continued)

Strategic Priority	Goals	Current Implementation Status
Promote investments for AMR activities, research, and innovations for AMR containment	• Sustainable investments for AMR interventions • Secure sustainable funds for the implementation of NAP-AMR • Access impact of AMR • Develop an operational plan to implement NAP-AMR • Identify priorities for basic and operational research to optimize the use of antimicrobials and improve IPC in human and animal health • Encourage basic and operational research for AMR containment • Develop an operational plan to secure funds, which will be utilized to implement state action plans (SAPs) • Have One Health approach reviewed by top leadership under Mission for AMR Containment (MARC) through the advisory and technical committee • Encourage basic and operational research for AMR containment • Conduct research for evidence-informed policymaking in all sectors	• ICMR signed an MOU with the Research Council of Norway (in 2017) to promote joint R&D on AMR. • ICMR, along with the Federal Ministry of Education and Research (BMBF), Germany, has a joint Indo–German collaboration for research on AMR. • WHO, in collaboration with India's Department of Biotechnology, developed the IPPL to guide the development of new antimicrobials in India. • ICMR and the Global Antibiotic Research and Development Partnership (GARDP) announced a partnership in 2021 to facilitate the development of new drugs.
Strengthening India's commitment and collaborations on AMR at international, national, and sub-national levels	• Launch state-level action plans • Strengthen intersectoral coordination of AMR activities • Review India's existing collaborations, international, national, and sub-national collaborations on AMR • Identify priority areas of action to strengthen coordination mechanisms	• Delhi Declaration on AMR, an inter-ministerial consensus, was signed by the ministers of the concerned ministries pledging their support in AMR containment. • In line with NAP-AMR, three states (Kerala, Madhya Pradesh, and Delhi) have launched their state action plan.

We reviewed the plans created by three states in India (Delhi, Kerala, and Madhya Pradesh) and compared them with each other. The fourth state to have developed an action plan, Andhra Pradesh, has not yet made this available in the public domain. Table 3 below provides a summary of the key goals of the state plans. We did not find adequate information to assess the progress of implementation for these three states.

TABLE 3. Summary of key goals of SAP-AMR of Delhi, Madhya Pradesh, and Kerala

Strategic Priority	Objective	Delhi	Madhya Pradesh	Kerala
1	Awareness and understanding, communication, education, and training	• Focus on knowledge, attitude, practice (KAP), and behavioural studies • Mass media, drive for safe water, sanitation, and hygiene (WASH)	• Focus on role plays, social media advertisements, and social media awareness generation • FM radio platform • Focus group discussions • KAP and behavioural studies, seminars, workshops, audio-visual aids, and social media for awareness generation • One Health approach	• Focus on social media • World Antibiotic Awareness Week • Online platform for One Health approach • School, colleges, universities curricula • Training programs
2	Strengthen knowledge and evidence through surveillance	• Antimicrobial susceptibility testing • Quality accreditation for all surveillance laboratories • One Health approach	• NABH, NABL accreditation • Promotion and procurement of equipment as per the need of SOPs • Quality accreditation for all surveillance laboratories	• Strengthening microbiology laboratories • Standardizing AMR surveillance • Establishing AMR databases • One Health AMR surveillance system
3	Effective infection prevention and control	• IPC Campaign under Swachh Bharat Abhiyan, Kayakalp Program • Developing and implementing IPC guidelines and programs in human health, animal, and food sectors	• Formation of IPC committees in all hospitals as per directives of the Government of India • Assigning infection control nurses in all hospitals and strengthening capacity for diagnostic stewardship	• Reducing the healthcare-associated infection rates by 20% of the existing rate by one year 50% by 3 years and attaining international benchmarks by 5 years • Antimicrobial Stewardship Program and adherence to antimicrobials policy
4	Optimize the use of antimicrobial agents in health, animals, and food and regulate access to high-quality antimicrobials	• Strengthen the drugs control department for quality, safety, use, and access to antimicrobials • Strengthen Food Safety and Pollution Control Departments	• Stop the OTC sale of drugs for human/animal use • Ban substandard and spurious drugs in the state • Stop sale of antimicrobials without a valid prescription	• Reduce OTC sale of drugs • Institutional antibiogram • Formulate antimicrobials policy based on institutional antibiogram

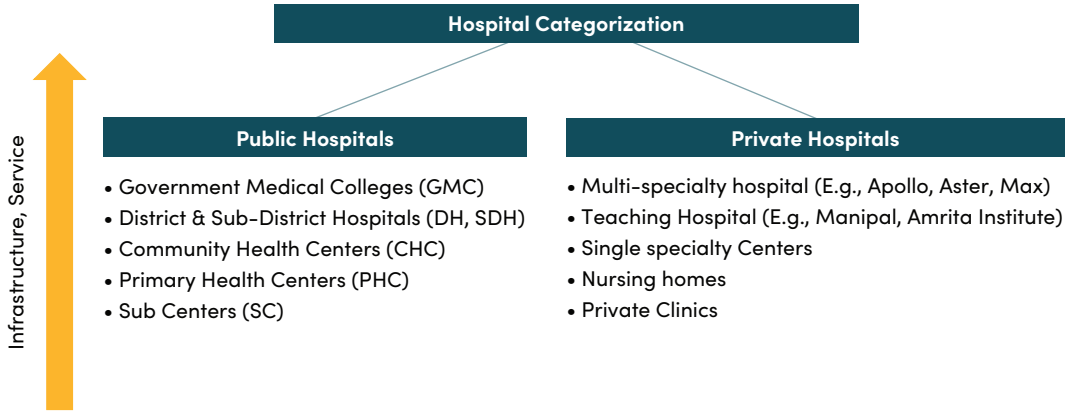
TABLE 3. (Continued)

Strategic Priority	Objective	Delhi	Madhya Pradesh	Kerala
		• Intersectoral coordination to regulate and optimize the use of antimicrobials in humans, animals, and food • AMC tool for antimicrobial consumption • Monitoring system-antimicrobial consumption • Antimicrobial Stewardship Program (AMSP) in healthcare facilities	• App for H1 drugs made by Food and Drugs department for TB to be expanded for all H1 drugs, including antimicrobials • Review and implement regulations regarding the use of antimicrobials • Antimicrobial stewardship program in healthcare	• Antimicrobial stewardship committee • Electronic prescriptions • Kerala AMR state action plan implementation • Prescription audits • AMC tool to measure the consumption of antimicrobials
5	Promote investments for AMR activities, research, and innovations	• Sustainable funds for state action plan implementation • Focus on One Health approach • Mission for AMR containment plan • Artificial intelligence to monitor surveillance data • Research for evidence of informed policy making	• Baseline data on the status of current research on AMR • Compilation of research activities and list of stakeholders • Promote research to develop new antimicrobials • Facilitate evidence-based policy formulation • Generate investment to fund research on rapid diagnostic kits • App for mobile phones to ensure easy access to treatment guidelines	• Define research priorities on AMR • Identify potential research institutes • Screening of phytochemicals/ herbal extracts • Information technology for AMR and HAI surveillance • Development of probiotics of human origin • Biofilm inhibition
6	Research and Collaborations on AMR	• Interdepartmental and Inter-State Collaboration • Partnership with the private sector, professional associations, and civil society organizations • Annual consultation on AMR	• State-level governance mechanism, other state collaboration • Antimicrobial stewardship • Sharing of knowledge and resources among district division and central level • Intersectoral mechanisms • Private sector engagement	• Partnership with private hospitals • Information sharing on drug resistance in state disease control program

Appendix 4. Hospital categorization

Hospitals can be categorized into public and private sectors. Rural India is predominantly public sector hospitals (like sub-centers and primary health centers) and private nursing homes that provide basic healthcare services like immunization and referrals to tertiary and quaternary (higher) centers. Urban India has an abundance of tertiary and quaternary care centers in both the public and private sectors.

FIGURE 6. Hospital categorization



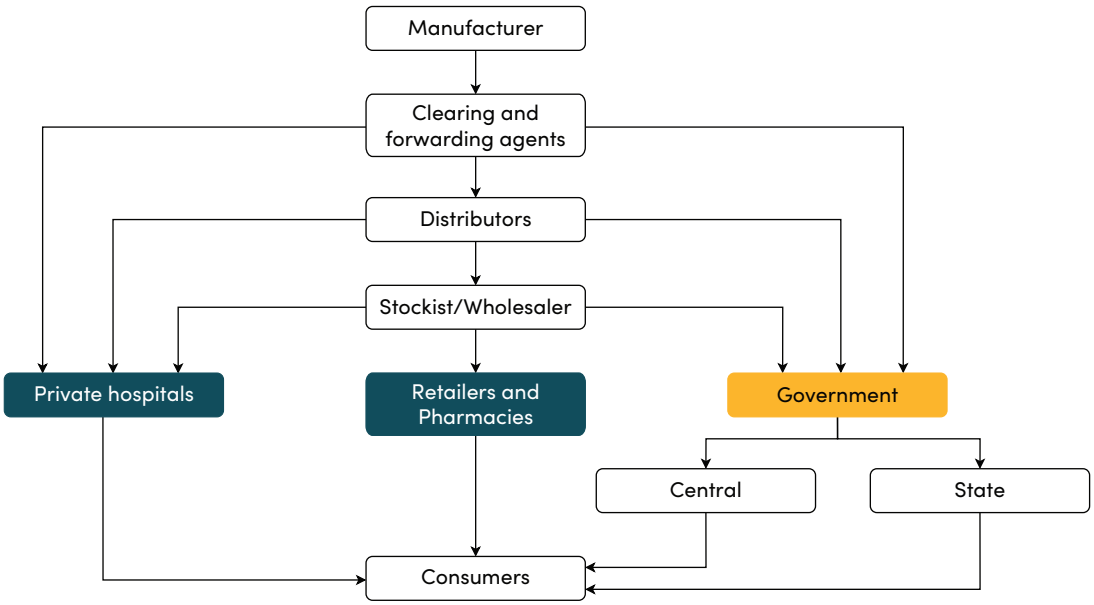
In India, the availability of quality healthcare services varies significantly with income disparities. As per the current estimates from the National Sample Survey (NSS, 75th round) conducted in 2020, 86 percent of the rural Indian population and 81 percent of the urban population are still not covered under any form of insurance. However, this does not take AB-PMJAY into consideration.

Appendix 5. NLEM and drug procurement mechanism

The primary purpose of the NLEM is to promote the rational use of medicines, considering their cost, safety, and efficacy. It also helps optimize healthcare resources and budgets, drug procurement policies, health insurance, prescribing habits, medical education and training, and the drafting of pharmaceutical policies. The DPCO brings all the drugs listed in the NLEM under price control. Through this order, drug ceiling prices are fixed (Ministry of Health and Family Welfare 2022b).

Like the NLEM, the World Health Organization Essential Medicines List (WHO EML) bases its drug selection on the drug's cost effectiveness, efficacy, and safety. Drugs are divided into core and complementary lists by the WHO EML. A list of the bare minimal medications required for a basic healthcare system makes up the core group. The complementary list includes the necessary drugs for priority diseases requiring specialized diagnosis, treatment, and training. The WHO Essential Medicines Committee considers input from external partners, including governments, pharmaceutical companies, medical associations, and subject matter experts (Peacocke, et al. 2022). The WHO EML list is an evidence-based reference list for countries to consult when establishing their essential medications, along with country-specific factors like disease burden and pharmaceutical cost. Drug procurement consists of multiple stages before reaching the consumer. An overview of the supply chain and drug procurement in India is depicted in Figure 7 (Jeffery 2007).

FIGURE 7. Overview of supply chain and drug procurement



Appendix 6. Critical evaluation of national action plan

The government's efforts are visible in improving awareness among various stakeholder groups. Various information, education, and communication (IEC) activities, such as quiz competition in schools, distribution of pamphlets, social media and print media awareness sessions, and talks related to the appropriate use of antimicrobials are being held. States like Jammu, Kashmir, and Haryana are organizing World Awareness Week every year on 18–24 November. The Indian Council of Medical Research and Pfizer Ltd. announced a partnership in 2017 to set up a center for AMR Research and Education within the Department of Health Research campus in New Delhi. The joint initiative entailed implementing a series of comprehensive interventions, ranging from AMR stewardship programs for nursing homes to scaling up of the ongoing AMR surveillance network and creating awareness around the responsible use of antimicrobials. Although various interventions have been undertaken by the government to raise awareness about AMR, efforts are required to make the public aware of the overuse and self-administration of antimicrobials, their harmful effects, and the rise in community-based antimicrobial resistance patterns.

In the sphere of strengthening knowledge and evidence through surveillance, two separate surveillance networks at the hospital and community levels have been established. The NARS-Net AMR surveillance network was established and is run by the National Center for Disease Control at both the community and hospital levels. It comprises thirty-five labs in twenty-six Indian states to track seven priority bacterial pathogens. The Indian Council of Medical Research AMRSN network was established at the hospital level and comprises thirty tertiary hospitals to report resistance data for six pathogen groups. The data from NARS-Net and AMRSN assist in understanding the level of pathogen resistance at the community and hospital levels and are a highly effective strategy undertaken by the government to combat AMR. The hospitals included under AMRSN and NARS-Net are mostly government hospitals, and there seems to be less inclusion of private hospitals. Thus, there is a need to include more secondary and tertiary private sector hospitals under AMRSN and NARS-Net to gain more precise and consistent surveillance data. This resistance level data could also be utilized by the industry and academia to foster innovation and develop drugs for pathogens that show the highest resistance, and hospitals providing these data can also serve as clinical trial networks to speed up drug development in India.

To regulate access to high-quality antimicrobials and improve the appropriate use of antimicrobials, the National Center for Disease Control (NCDC) published the National Treatment Guidelines for Antimicrobial Use in Infectious Diseases in 2016, and they were updated in 2019. Hospital authorities are expected to disseminate the guidelines to all staff members and ensure compliance by practicing antimicrobial stewardship. The government banned pesticides and fertilizers to prevent AMR. On the recommendation of the Indian Council of Medical Research (ICMR), DCGI banned 40 fixed-dose combinations (FDCs) targeting human health. The ICMR has also initiated an antimicrobial stewardship program on a pilot project basis to control the misuse and overuse of antimicrobials. Further, small- and medium-sized hospitals, which cater to 70 percent of the Indian population,

lack a strong stewardship program, and this could eventually increase the usage of broad-spectrum antimicrobials and lead to their overuse. Thus, about building strong stewardship to combat AMR, the NAP-AMR can also define a verification mechanism that would ensure rational use of high-end antimicrobials at the point of care. To ensure quality treatment and continued supply of antimicrobials in private sector hospitals (small- and medium-sized), the NAP-AMR could consider the inclusion of reimbursements under the AB-PMJAY scheme.

The NAP-AMR emphasizes uninterrupted access to high-quality antimicrobial medicines, but the plan lacks a focus on how India is planning to streamline and track the process of access to ensure an uninterrupted supply of high-end antimicrobials. The NAP-AMR can be expanded by including a novel procurement mechanism that could address the challenge of access, especially of Watch and Reserve category antimicrobials. Although substantial research has shown that pooled procurement and alternative mechanisms like Jan Aushadhi Kendra's could make medicines affordable and ensure a continuous supply of high-end antimicrobials, such alternatives have not been explored in the NAP-AMR.

To promote investments in AMR activities, research, and innovations for AMR containment, ICMR signed a memorandum of understanding (MOU) with the Research Council of Norway (in 2017) to promote joint R&D on AMR. ICMR, along with the Federal Ministry of Education and Research (BMBF) in Germany has a joint Indo–German collaboration for research on AMR. The WHO, in collaboration with India's Department of Biotechnology, developed the IPPL to guide the development of high-end antimicrobials in India. ICMR and the Global Antimicrobials Research and Development Partnership (GARDP) announced their partnership in 2021 to facilitate the development of new drugs. The plan focuses on developing and implementing a strategy/plan to promote/fast-track research for innovations. The NAP-AMR needs to be expanded in terms of developing a strategy for target product profiles required for the Indian ecosystem to encourage innovation in the right direction. Drug development would require exhaustive data from rigorous surveillance to develop appropriate novel medicines that can work in India. Hence, developing an India-specific TPP is crucial. India needs visibility in terms of the molecular mechanism, patient profiles, pathogen type, and other technical details that could eventually help in developing a TPP.

Although the national action plan emphasizes establishing AMR as a state-level priority and developing state action plans on the containment of antimicrobial resistance (SAP-CAR) aligned to NAP-AMR, only a few states (i.e., Delhi, M.P and Kerala) have implemented their state action plans. Further, the state action plans mention developing partnerships with private hospital groups and individual hospitals on AMR and healthcare-associated infection (HAI) surveillance, research, and capacity building. Data from our primary stakeholder interviews suggest that there has been no collaboration between private and medical service corporations to date to ensure the efficient procurement of drugs. Also, due to the autonomous functioning of MSCs and private hospitals, there are still gaps in estimating the required demands and ensuring the supply of medicines.

Appendix 7. Access to high-end antimicrobials

A dried-out clinical pipeline and lack of access to quality antimicrobials affect healthcare systems. To understand the availability of next-generation antimicrobials in high-income countries, we used data sets to compare the timeline of their approval by the FDA and CDSCO. The basic premise in comparing FDA- and CDSCO-approved drugs was that FDA approval is considered the gold standard for approval and serves as a benchmark to assess CDSCO approvals and obtain a clear idea about the antimicrobial drug landscape in India.

TABLE 4. Antimicrobials approved by FDA but not by CDSCO

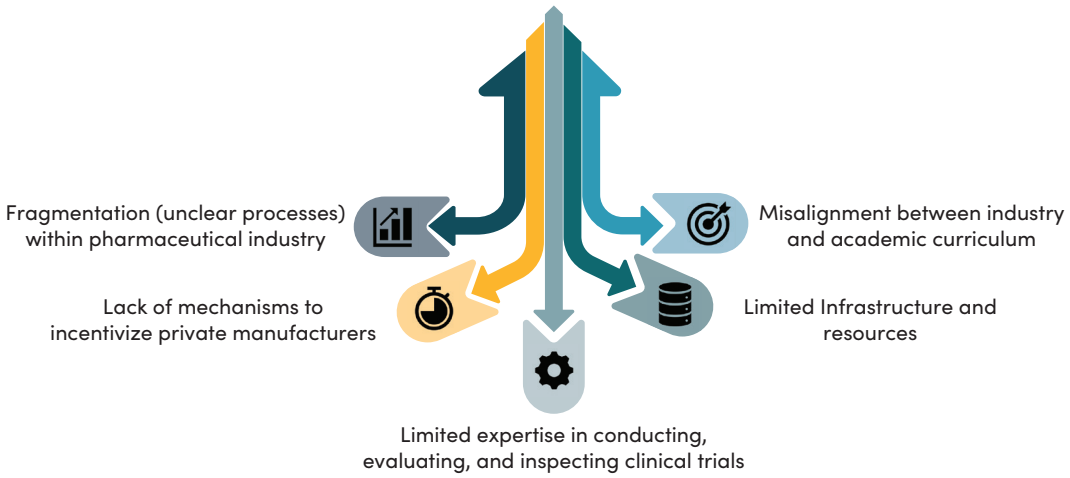
Composition	Targeted Pathogen	Comment
Imipenem/cilastatin/ relebactam	E. coli Klebsiella pneumoniae	Although imipenem, cilastatin, and relecbatam are available in India individually, the combination remains unavailable.
Omadacycline	Klebsiella pneumoniae	According to a UMich Drug Monograph, although omadacycline exhibits non-inferior results compared to linezolid for the treatment of ABSSSI and moxifloxacin for Community-acquired bacterial pneumonia (CABP), it should not be recommended for regular use given the availability of similarly effective agents.
Plazomicin sulfate	E. coli Klebsiella pneumoniae	A study predicted plazomicin efficacy in India to be around 53% against NDM-producing E. coli and 47% and 60% against NDM and Oxa-48-like-producing K. pneumoniae, respectively (Pragasam, et al. 2020).
Meropenem-Vaborbactam	E. coli Klebsiella pneumoniae	A study measured the efficacy of ceftazidime-avibactam (available in India) and meropenem-vaborbactam for the treatment of carbapenem-resistant Enterobacteriaceae (CRE) infections and found no significant difference in clinical success (Ackley, et al. 2020).
Delafloxacin	E. coli Klebsiella pneumoniae	The efficacy of delafloxacin has mixed reviews. While considering delafloxacin to be a promising new antimicrobial for acute bacterial skin and skin structure infections (ABSSSI), demonstrating greater improvement (composite clinical response) than ceftobiprole, fusidic acid, iclaprim, telavancin, and vancomycin, no statistically significant differences were found with ceftaroline, ceftobiprole, or tigecycline in terms of efficacy and safety (Alhifany, et al. 2022).
Cefiderocol	E. coli Klebsiella pneumoniae	GARDP, CHAI, and Shionogi are currently attempting to understand the market landscape to introduce the drug in India (Global Antibiotic Research & Development Partnership 2022).

Appendix 8. Innovation high-end antimicrobials

Globally, the pipeline of antimicrobials is lean. When comparing the WHO's pipeline of antimicrobials in phase trials of clinical research to the IPPL list, only sixteen medications in Phase I, three in Phase II, eight in Phase III, and one in preregistration that are effective against pathogens in the IPPL were in the pipeline.

Figure 8 illustrates some of the key challenges associated with drug development and innovation.

FIGURE 8. Key challenges associated with drug development and innovation



Although Indian pharmaceutical companies have the expertise to understand molecular mechanisms and identify drug targets, they lack requisite R&D facilities. The drug development process also requires exhaustive data from rigorous surveillance to develop an appropriate novel medicine that can work in India. Hence, developing an India-specific target antimicrobials profile (TAP or TPP) is crucial.

A TPP outlines the desired profile and characteristics of a product that treats a particular disease. It includes the desirable attributes of the product, including its safety- and efficacy-related features, and acts as a guide for research and development in the industry. In the regulatory context, TPPs are planning tools that guide the development of such products, and in the public health context, TPPs set R&D targets for funders and developers. Apart from providing desired information on product development, TPPs developed by the WHO support the development of health products that focus on public health priorities. They provide information for funders and developers on the performance and operational characteristics expected of products if they are to meet the WHO's needs.

Wockhardt is a global pharmaceutical and biotechnology organization that aims to provide high-quality medicines for a healthier world. The organization is committed to innovating high-end antimicrobials and has proven its technical excellence by developing patented modified-release formulations and

recombinant biotechnology products. It is the first Indian company to achieve approval for newly discovered antimicrobials EMROK (IV) and EMROK O (Oral) for acute bacterial skin and skin structure infections, including diabetic foot infections and concurrent bacteremia, based on a Phase III study involving 500 patients in forty centers across India. The high-end antimicrobial will target superbugs like methicillin-resistant staphylococcus aureus (MRSA), a leading cause of rising antimicrobial resistance (AMR).

Bugworks Research India Private Limited is one of the leading startups focusing on antimicrobial activity for developing novel drugs. The organization aims to develop high-end antimicrobials and to be the first innovator of safe, effective, and robust antimicrobials. Its goal is a breakthrough in innovating a high-end antimicrobial for combating antimicrobial resistance (AMR). The Bugworks research receives funding from CARB-X, a public–private initiative that supports the development of high-end antimicrobials against multidrug-resistant diseases worldwide.

Aurigene Pharmaceutical Services, a drug discovery biotech, was established in Bangalore in 2002. It is a clinical-stage biotech company committed to drug discovery and novel therapeutics development. The biotech company has ten drug discovery collaborations, a pipeline of sixteen discovery programs at various stages, from hit generation to late-stage pre-clinical optimization and has filed sixteen patents across six programs. The company has delivered fifteen clinical programs currently in Phase I/II global clinical trials. It has also executed over eighty discovery programs using small molecules, peptides, and peptidomimetic approaches. Aurigene has developed deep expertise in cancer and inflammatory disorders and has continuously invested in its human resources and infrastructure. Aurigene has recently entered into a global license agreement with Olema Oncology for the research, development, and commercialization of novel small molecule inhibitors against an undisclosed oncology target.

Vitas Pharma is a drug discovery and development company that started in 2011. It is involved in identifying and developing next-generation antimicrobials to treat multidrug-resistant diseases. The company filed two international patents and one in India. Vitas has received seed funding from the Indian Angel Network and two grants from the Biotechnology Industrial Research Assistance Council. It also has a research collaboration with Biocon. The drug is in the toxicology study stage.

Peptris Technologies Private Limited has created a platform technology that uses artificial intelligence and machine learning to improve efficiencies throughout the drug discovery and development process. Their neural network models aid in rationalizing and providing insights into experimental data in molecular biology and making predictions to generate hypotheses for newer experiments. ABAC Therapeutics, Peptris, the Foundation for Neglected Disease Research (FNDR), and Medicines for Malaria Venture (MMV) are leading an international project to optimize a new chemical structure that has demonstrated effectiveness against Gram-negative bacteria.