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# Antimicrobial resistance and its containment in India

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# **Antimicrobial resistance and its containment in India**

*Background paper*

**Inter-Ministerial Review Meeting on Antimicrobial Resistance**



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## Abbreviations

AGP	antibiotic growth promotor
AMR	antimicrobial resistance
AMRSN	Antimicrobial Resistance Surveillance Research Network
AMSP	antimicrobial stewardship programme
ARB	antibiotic resistance breakers
ASPIC	Antimicrobial Stewardship, Prevention of Infection and Control
AYUSH	Ayurveda, Yoga and Naturopathy, Unani, Siddha & Homoeopathy
CDSCO	Central Drugs Standard Control Organization
CSIR	Council of Scientific and Industrial Research
ESBL	extended spectrum beta-lactamase
FDC	fixed dose combination
FSSAI	Food Safety and Standards Authority of India
GAP-AMR	Global Action Plan on Antimicrobial Resistance
HAI	health care associated infection
HCI	health care institution
HIC	hospital infection control
HICC	hospital infection control committee
ICAR	Indian Council of Agricultural Research
ICMR	Indian Council of Medical Research
IPC	infection prevention and control
MDR-TB	multi-drug resistant tuberculosis
MoHFW	Ministry of Health & Family Welfare
MRSA	methicillin resistant <i>Staphylococcus aureus</i>
NAP-AMR	National Action Plan on Antimicrobial Resistance
NCDC	National Centre for Disease Control
NDMI	New Delhi Metallo-beta-lactamase-1
NVBDCP	National Vector Borne Disease Control Programme
OPPI	Organization of Pharmaceutical Producers of India
OSDD	Open Source Drug Discovery
OTC	over-the-counter

RNTCP	Revised National Tuberculosis Control Programme
STG	standard treatment guidelines
TB	tuberculosis
UNGA	United Nations General Assembly
VRE	vancomycin resistant enterococci
VRSA	vancomycin resistant <i>Staphylococcus aureus</i>
WHA	World Health Assembly
WHO	World Health Organization
XDR-TB	extensively drug resistant tuberculosis

# Executive summary

## Background

The relentless march of antimicrobial resistance (AMR) has emerged as a public health concern, especially in the light of the fact that newer antibiotic classes have been slow to develop and investments in novel antimicrobial drug classes have been receding. The AMR problem transcends international borders and is not limited to nations with limited capacity to manage pathogen emergence or antibiotic stewardship. In keeping with this, the Sixty-eighth World Health Assembly (WHA) came up with the Global Action Plan to contain AMR (GAP-AMR) in May 2015. The plan outlined activities to be streamlined along five major strategic objectives:

1. Improve awareness and understanding of AMR through effective communication, education and training
2. Strengthen the knowledge and evidence base through surveillance and research
3. Reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures
4. Optimize the use of antimicrobial medicines in human and animal health
5. Develop the economic case for sustainable investment that takes account of the needs of all countries and to increase investment in new medicines, diagnostic tools, vaccines and other interventions.

Aligning national interests with the global context, member states have been tasked to develop a National Action Plan to contain AMR (NAP-AMR), aligned with the GAP-AMR, by May 2017. This report discusses the magnitude of the AMR issue in India, focussing on providing evidence to assist in the framing of the NAP-AMR.

## AMR in man and animals

India is among the nations with the highest burden of bacterial infections. An estimated 410 000 children aged 5 years or less die from pneumonia in India annually; accounting for



almost 25% of all child deaths in India. The crude mortality from infectious diseases in India today is 417 per 100 000 persons. Consequently, the impact of AMR is likely to be higher in the Indian setting. AMR is a major public health concern in India. The emergence of resistance is not limited to the older and more frequently used classes of drugs. There has also been a rapid increase in resistance to the newer and more expensive drugs, like carbapenems. Available data indicates rising rates of AMR across multiple pathogens of clinical importance. An indicator of the rising tide of AMR in India is the rapidly increasing proportion of isolates of *Staphylococcus aureus* that are resistant to methicillin. In 2008, about 29% of isolates were of methicillin-resistant *Staphylococcus aureus* (MRSA), and by 2014, this had risen to 47%. In contrast, countries that have established effective antibiotic stewardship and/or infection prevention and control programmes, the proportion of MRSA isolates has been decreasing.

The burden of AMR in livestock and food animals has been poorly documented in India. Aside from sporadic, small, localized studies, evidence that can be extrapolated to the national level is lacking. Given that there are few regulations against the use of antibiotics for non-therapeutic purposes in India, with no stringent implementation protocols even when there are regulations, the emergence of AMR from antibiotic overuse in the animal sector is likely to be an unmeasured burden in India.

Drug resistant bacteria have been isolated from dairy cattle as early as the 1970s. One of the most common clinical issues encountered in dairy farms is mastitis, which maybe sub-clinical or overtly symptomatic. Commonly thought to be a disease of production, milk from mastitic cows and buffaloes has been shown to contain a wide range of bacteria, with a wide spectrum of resistance against commonly used antibiotics. In some cases, multi-drug resistant bacteria have been seen to co-infect animals suffering from mastitis.

As with the dairy sector, there is limited evidence available on the exact amount of antibiotics consumed within the poultry industry, and the various indications for which the medications were prescribed. In many cases, since the antibiotics are given as a growth promoter through the premixed feed, which comes with added antibiotics, it is difficult to estimate exactly the dose or the consumption levels of antibiotics in the poultry sector. Individual studies have consistently shown that bacteria isolated from animals or seafood has high levels of resistance.

The legislative conditions regulating the aquaculture processes are different from those in the poultry or the dairy industry. The Food Safety and Standards Authority of India (FSSAI) has

placed an extensive ban on the use of antibiotics and several pharmacologically active substances in fisheries. Also, in contrast to the poultry industry where many of the commercially available pre-mixed feeds come with antibiotics added, none of the feed in the fisheries sector contain antibiotics. These drugs can, of course, be added to the feeds separately by the farmers. Compared to the poultry and dairy sector, antibiotic resistance has been scrutinized more closely in the aquaculture sector. Due to the existence of stringent legislative provisions to contain the inappropriate and non-therapeutic use of antibiotics, it is expected that the problem of AMR in the aquaculture sector should be smaller compared to the dairy or poultry sectors. However, in a recent study that examined over 250 samples, it was seen that multi-drug resistant bacteria were isolated from over two-thirds of the samples.

There exists a large body of evidence that comprises of studies investigating the resistance profiles of bacteria isolated from both sick and healthy cattle. However, these studies cannot be compiled to obtain a representative picture of the problem at the national level. Driven by local contexts, these studies can at best provide a rough overview of the magnitude of the problem of drug resistance in bacteria, but for obtaining a more comprehensive and holistic understanding, it is imperative to have a broad based surveillance system in place.

## Awareness and understanding of AMR

The GAP-AMR states that the first strategic objective in effectively containing AMR is to improve awareness and understanding of AMR through effective communication, education and training (1). The strategy envisions that the awareness building has to proceed on several fronts at the same time. On one hand it has to leverage public communication programmes to encourage behaviour change in target populations, namely, stakeholders in human health, animal health and agriculture; and on the other, there needs to be concerted efforts to incorporate AMR as a core component in the professional education of medical and veterinary professionals.

The need to focus on awareness building, both in consumers and providers, was highlighted by the results of the multi-country public awareness survey that was conducted by the World Health Organization (WHO). The findings of the study highlight important deficits in the understanding of what antibiotics are, how they should be used and when to take them. There

is ample evidence to suggest that there is a certain “pull” from patients which forces medical practitioners to overprescribe antibiotics, especially for conditions like viral illnesses, upper respiratory tract infections and diarrhoea, for which antibiotic therapies are not the recommended first line of approach.

Given the financial incentives to prescribe antibiotics, and the role of the pharmaceutical industry in encouraging prescription of antibiotics in India, there is a need to approach the process of awareness generation with additional legislative support. Internationally, there is evidence that awareness generation campaigns, in combination with other interventions, organized at the national level may be successful to reduce antibiotic use.

There is also a need to increase the awareness about the need to contain AMR at the higher levels of policy making, so that this aspect may emerge as a priority in the health policies of the nation. In 2011, the health ministers of the South-East Asia Region’s Member States articulated their commitment to combat AMR through the Jaipur Declaration. This was a high-level commitment to prioritize AMR control programmes at the highest levels of national policy-making.

## Surveillance of AMR

India has previously instituted surveillance of the emergence of drug resistance in disease causing microbes in the context of vertical programmes, like the Revised National Tuberculosis Control Programme, the National Vector Borne Disease Control Programme, and the National AIDS Control Programme, to name a few. However, a cross-cutting programme dealing with resistance across multiple microbes, especially common bacterial infections, has been lacking.

The National Programme on the Containment of Antimicrobial Resistance was launched under the aegis of the National Centre for Disease Control (NCDC) under the Twelfth Five-Year Plan (2012–2017). The objectives of this programme were to – establish a laboratory based AMR surveillance system of 30 network laboratories; generate quality data on AMR for pathogens of public health importance; strengthen infection control guidelines and practices, and promote rational use of antibiotics; and generate awareness about the use of antibiotics in both health care providers and in the community (2). The policy focus included – situation analysis

regarding the manufacture, use and misuse of antimicrobials; creating a national surveillance system; identifying prescription patterns and establishing a monitoring system for the same; enforcing enhanced regulatory provisions with respect to marketing of antimicrobials; developing specific intervention measures such as antibiotic policies for health care facilities; and development of diagnostic aids related to monitoring AMR.

At present, 10 network laboratories have been identified in the first phase of the programme, in the course of which four pathogens of public health importance are being tracked: *Klebsiella spp*, *E. coli*, *Staphylococcus aureus*, and *Enterococcus spp*. The network intends to extend testing of resistance to two more index bacteria: *Pseudomonas aeruginosa* and *Acinetobacter spp*. Reporting from the 10 laboratories puts overall resistance rates to be very high, against the commonly used fluoroquinolones, third generation cephalosporins and carbapenems, although resistance against reserve drugs like vancomycin was not noted in isolates of *Staphylococcus aureus*, or against colistin in Gram negative bacteria. A strategy to scale up the programme in order to carry out surveillance of hospital acquired infections and antibiotic use patterns in health care settings has also been outlined; additional focus on building awareness about rational use of drugs on a continuous basis is also being planned.

The Indian Council of Medical Research (ICMR) has established a national network on surveillance of AMR in laboratories based at academic centres, targeting medically important index microbes which have been identified by WHO (3). The Antimicrobial Resistance Surveillance Research Network (AMRSN) established by the ICMR has six reference labs for six pathogenic groups that are located in four tertiary care medical institutions. The network is being expanded to include 15 more medical colleges/corporate hospitals. ICMR has also developed a real time online AMR data entry system for its network and will have AMR data analysis capacity specific for bacterial species in relation to point of origin of pathogens as well as various patient demographic parameters.

The AMRSN also incorporates in depth understanding of clonality of drug-resistant pathogens and the transmission dynamics to enable better understanding of AMR in the Indian context and devise suitable interventions. The AMRSN, although currently limited to human health, plans to scale up on a national scale and expand its ambit to include samples from a wider spectrum of sources, including animal, environmental and food samples, to reflect the One

Health approach to surveillance. It is planned to expand the laboratory network to include 10 centres.

Like most low- and middle-income countries, India is in the process of developing a national surveillance network. In addition, the move to establish a NAP-AMR aligned with the principles outlined in the GAP-AMR will serve to streamline the process and ensure that a One Health approach to surveillance is adopted.

Aside from the absence of a One Health approach to surveillance, another weakness of the existing surveillance systems for AMR in India is that it does not account for antibiotic use. The existence of a surveillance system that can establish the relationship between the antibiotic consumption patterns and emergence of AMR is vital to produce evidence that may help in the designing and evaluation of effective interventions.

## Infection prevention and control

The background report on the role of infection prevention and control (IPC) programmes in order to contain AMR, which was commissioned by WHO, has highlighted the critical nature of this issue. Functional infection control programmes not only cut down the rates of nosocomial infections, but also reduce the volume of antibiotic consumption and have been identified to be part of any comprehensive strategy to contain AMR.

An international conference on “Combating AMR: Public Health Challenge and Priority”, which was organized in February 2016, in New Delhi, by the Ministry of Health and Family Welfare (MoHFW) in collaboration with WHO, released the ICMR Guidelines on Infection Control, which are locally relevant and implementable for India. The international conference further identified the need to develop IPC standards for each level of health care facility, and not just tertiary care centres. It noted the need to establish functional hospital infection control committees (HICCs) to provide leadership to the IPC programmes at the institutional level. The need to integrate IPC programmes, both from the policy-making and implementation angles, was also stressed. Establishing IPC focal experts at the policy-making levels, linking of IPC programmes to surveillance of AMR and HAIs were identified as key policy integrations to drive more successful IPC programmes in India. NCDC has recently developed Guidelines for

Hospital Infection Prevention and Control and is also developing a policy on infection control, which is in the final phases of preparation.

ICMR launched the programme on Antimicrobial Stewardship, Prevention of Infection and Control (ASPIC) in 2012 through collaboration between the office of the National Chair of Clinical Pharmacology, ICMR and the Christian Medical College, Vellore. A national workshop was hosted as a part of a 1-year programme to develop capacity of key stakeholders in antibiotic stewardship.

In addition to launching the AMRSN, the ICMR also instituted an evaluation of the antimicrobial stewardship programme (AMSP) through an in-depth facility survey in private and government health care institutions. The results showed that though there was a very high degree of adherence to the guidelines when it came to dealing with health care associated infections (HAIs) or hospital infection control (HIC) measures, compliance was poor with the other aspects of antibiotic stewardship, especially with respect to having a documented stewardship programme, antibiotic prescription guidelines, surveillance of antimicrobial use, and a truly multidisciplinary team. It was also seen that the stewardship programmes in private institutions were better equipped to deal with emerging crises like AMR or HAI outbreaks, as compared to the government facilities in the survey. It is suggested that the accreditation mandates, which certain private institutes adhere to on account of financial compulsions, may have a positive impact on the programme. The evaluation report recommends that government health care facilities also need to seek mandatory accreditations to improve their stewardship programmes. The survey revealed a paucity of implementation strategies, including formulary restrictions and drug rotation policies. Prescription audits were conducted in very few institutions; efforts in development, dissemination and regularly updated prescription policies were also deficient; absence of computer-assisted programmes, especially in government facilities, also hampered the work of the stewardship programme.

## Use of antimicrobials

At  $12.9 \times 10^9$  units of antibiotics consumed in 2010, India was the largest consumer of antibiotics for human health. Although the per capita consumption of antibiotics in India (10.7 units per

capita) was lower than that seen in many other countries (e.g. 22 units per capita in USA), the overall population and infection load led to higher total consumption.

With respect to consumption of antimicrobials in food animals, the global consumption was estimated to be 63,151 ( $\pm$ 1,560) units in 2010; India accounts for 3% of the global consumption and is the fourth highest in the world, behind China (23%), the United States (13%) and Brazil (9%). The consumption of antimicrobials in the food animals sector in India is expected to double by 2030.

The absence of stringently framed and implemented regulatory frameworks to limit the use of antimicrobials in livestock and food animals, especially for non-therapeutic purposes like growth promotion has been one of the drivers of antibiotic overuse at the community level. A directive was issued in January 2015, by the FSSAI which outlines certain principles that include limiting the use of antibiotics in livestock rearing; it does little besides reiterating the directives of a previous advisory from the Department of Animal Husbandry, Dairying and Fisheries. The National AMR Containment Policy also highlighted the need to establish a separate Schedule H1 under the Drugs and Cosmetics Rules to regulate the sales of antibiotics. Guidelines for punitive actions against agencies that are in contravention of such policies are also outlined. The national policy also outlined the proposal for colour-coding antibiotic strips and newer molecules (carbapenems, tigecycline, daptomycin, etc.) to eliminate their use outside of tertiary care settings. The Red Line Campaign was launched in February 2016.

## Research and innovations

In 2004, in the 15 largest pharmaceutical companies, only 1.6% of the drugs in the development stages were antibiotics, and none of them were from novel classes, nor were they targeted to treat multidrug resistant agents. Despite the obvious need to develop newer classes of drugs to respond to the challenges of emerging AMR, there are few late stage candidates in the process of development. Additionally, pharmaceutical agencies have been reluctant to invest in research and development of antibiotics owing to the nature of the market, the current policies on conservation of newer classes of antimicrobials and the nature of antibiotic chemotherapy for infectious diseases.

The Cadila approach of developing the antibiotic resistance breakers (ARBs) to restore effectiveness of older classes of antibiotics has also emerged as an innovative way around the issue of resistance. ARBs can be known compounds as well as novel molecules which have no or minimal antibacterial activity, but which help in restoring the effectiveness of drugs to which the microbes would otherwise be resistant. The current consensus seems to be that there is a need to develop ARBs that are likely to salvage key members of each group of antibiotics, especially those that target Gram negative bacteria.

## Conclusion

Historically, AMR has not received adequate focus and attention in India. However, recent trends clearly illustrate the growing political commitment at the highest levels to have a cogent response in place that can provide the necessary gravitas for nation-wide surveillance and stewardship for containment of AMR. Efforts are being made to incorporate the One Health approach into these plans. WHO's National Action Plan framework is a template that can aid in systematizing AMR containment in India and make it comparable to global efforts.

The MoHFW has recently notified three governance mechanisms towards this – an intersectoral coordination committee, a technical advisory group and a core working group on AMR. The political declaration/UN resolution at the High Level Meeting on AMR at the United Nations General Assembly (in September 2016) provides an opportunity for the technical leadership in India to leverage the current conducive policy environment.



## I. Background

There is a rapid accumulation of evidence from all across the world that the effectiveness of antimicrobials is waning. Resistance against all groups of antimicrobials, both first line and last resort drugs, is on the rise. This relentless march of antimicrobial resistance (AMR) has emerged as a major public health concern, especially in the light of the fact that development of newer classes of antibiotics has been slow. The crisis of AMR today has assumed a global context, and is no longer limited to one particular group of nations. For example, strains of *Escherichia coli* bearing the resistance gene *mcr-1*, which made it resistant to almost all clinically important antimicrobials in use today, was first identified from China in the course of routine surveillance activities (4). Soon after, these multidrug resistant (MDR) bacteria were isolated from both animal and clinical samples from the United States (5). This rapid transmission of resistance, especially with respect to resistance encoded by mobile genetic elements like plasmids, has become a major source of concern.

The Sixty-eighth World Health Assembly (WHA) in May 2015 took cognizance of this crisis and adopted the global action plan on AMR (GAP-AMR), which outlined five strategic objectives (1):

1. Improve awareness and understanding of AMR through effective communication, education and training;
2. Strengthen the knowledge and evidence base through surveillance and research;
3. Reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures;
4. Optimize the use of antimicrobial medicines in human and animal health; and
5. Develop the economic case for sustainable investment that takes account of the needs of all countries and to increase investment in new medicines, diagnostic tools, vaccines and other interventions.

The WHA resolution has also set a target that all Member States should develop National Action Plans on AMR (NAP-AMR), which are aligned to the principles outlined in the GAP-AMR, by May 2017. In order to develop a customized NAP-AMR, it is in the interest of the Member States to conduct systematic evaluation of the AMR situation in the national context. Additionally, in order to ensure the delivery of the outputs planned in the GAP-AMR, the

strategic objectives adopted at the global level need to be adapted to the country context, along with embedded systems of monitoring and evaluation in the NAP-AMR.

At the United Nations General Assembly High-Level Meeting on AMR, held in September 2016, heads of state/delegations addressed the seriousness and scope of the situation (6). For the first time, global leaders and heads of states committed to taking a broad, coordinated approach to address the root causes of AMR across multiple sectors, especially human health, animal health and agriculture. They pledged to strengthen regulation of antimicrobials, improve knowledge and awareness, and promote best practices, as well as to foster innovative approaches using alternatives to antimicrobials and new technologies for diagnosis and vaccines.

This report presents a situation analysis of AMR in the Indian context. The primary objective of this report is to review and collate the current evidence on the AMR situation in India and capture the information on the lines of the five strategic objectives of the GAP-AMR, including identifying bilateral and international collaborations with partner agencies and other countries, focussing on the issue of containment of the emergence of AMR. It is expected that this report will provide information that will contribute to the framing of a NAP-AMR aligned with the GAP-AMR.

## 2. AMR situation in India

A combination of factors – rising incomes, unregulated access to antibiotics, including over-the-counter sale as well as sale without prescription or with invalid prescription; and perverse financial incentives for providers to prescribe antibiotics, often driven by patient demand and expectations – have played a major role in the emergence of AMR in India.

The issue of AMR drew global attention through the controversy of the nomenclature of the New Delhi Metallo-beta-lactamase-1 (NDM-1), and has since received a lot of attention as a major public health concern. All the factors like the high burden of bacterial infections, poor sanitary and hygiene conditions and the increasing proportion of intensive animal farming, especially in small holder settings with minimal oversight and quality control makes emergent AMR a cause of special concern in the country. The problem is no longer restricted to the clinical or hospital setting, and is now emerging as a wider concern involving the animal/food/livestock sector, as well as environmental contamination as a source for the spread of resistance genes and antibiotic residues promoting selection pressure (7).

### 2.1 AMR in humans

AMR is a major public health concern in India. The emergence of resistance is not only limited to the older and more frequently used classes of drugs but there has also been a rapid increase in resistance to the newer and more expensive drugs, like carbapenems, which is worrisome. Carbapenems are a class of antibiotics widely considered to be the last-resort antibiotics, which are pressed into use when first and second line treatment options have failed. The emergence of carbapenem resistance, particularly carbapenem resistant *Enterobacteriaceae* (CRE), has been a major concern in developed countries, especially in the hospital/health care setting. Although available data indicates only mild increase in carbapenem resistant isolates of *E. coli* from India (from 10% in 2008 to 13% in 2013), there has been a much larger increase in carbapenem resistant isolates of *Klebsiella pneumoniae* (from 29% in 2008 to 57% in 2014) and *Acinetobacter baumannii* (8).

India is among the nations with the highest burden of bacterial infections (9). An estimated 410 000 children aged 5 years or less die from pneumonia in India annually (10); accounting for almost 25% of all child deaths in India (11). The crude mortality from infectious diseases in India today is 417 per 100 000 persons (3). Consequently, the impact of AMR is likely to be higher in the Indian setting.

An indicator of the rising tide of AMR in India is the rapidly increasing proportion of isolates of *Staphylococcus aureus* that are resistant to methicillin. In 2008, about 29% of isolates were of methicillin-resistant *Staphylococcus aureus* (MRSA), and by 2014, this had risen to 47% (8). In contrast, in countries that have established effective antibiotic stewardship and/or infection prevention and control programmes, the proportion of MRSA isolates has been decreasing.

A study has shown that as much as 78% of clinical isolates of *Neisseria gonorrhoeae* are resistant to ciprofloxacin. Although all were ceftriaxone sensitive, about 25% were beta-lactamase producers (12). The impact of antibiotic use on emerging resistance patterns in India is exemplified by the resistance profile of *Salmonella Typhi* isolates. Resistance to fluoroquinolones has increased from 8% in 2008 to 28% in 2014, whilst the resistance against older antimicrobials, which are not used very commonly, is reducing (8).

In India, extended spectrum beta-lactamase (ESBL) producing strains of Enterobacteriaceae have emerged as a challenge in hospitalized patients as well as in the community. In a multicentric study conducted in seven tertiary care hospitals in Indian cities, 61% of *E. coli* were ESBL producers. In the same study, 31–51% *Klebsiella* species were carbapenem resistant, 65% *Pseudomonas* sp. were resistant to ceftazidime and 42% were resistant to imipenem (13). *Acinetobacter* species isolated from hospitalized patients in a tertiary care hospital in Delhi showed 57–80% resistance to imipenem/meropenem while 70% isolates were resistant to tigecycline (14).

In a study conducted at 15 tertiary care centres on *S. aureus* isolates, the Indian Network for Surveillance of Antimicrobial Resistance (INSAR) found MRSA prevalence rate of 41% which also showed a high rate of resistance to ciprofloxacin, gentamicin, cotrimoxazole, erythromycin, and clindamycin (14).

Another study showed incidence of CA-MRSA at about 10% and reduced susceptibility to vancomycin in about 12% of the isolates of *Enterococcus fecalis* (15). Among blood culture isolates of *Salmonella Typhi* at a tertiary care hospital in Delhi, resistance was observed to nalidixic acid (96.7%), ciprofloxacin (37.9%) and azithromycin (7.3%) and multi-drug resistance in 3.4% isolates (16).

Recent studies in India show that most isolates of *Vibrio cholerae* O1 are resistant to the commonly-used antibiotics, such as ampicillin, furazolidone, ciprofloxacin, and tetracycline (17, 18). Resistance of *V. cholerae* to ceftriaxone has been reported from Delhi (18). A report of *Neisseria gonorrhoeae* isolated from males and female STD clinic at Delhi highlighted alarming increase in ciprofloxacin resistance (83.3%), penicillinase-producing *N. gonorrhoeae* (35.1%), tetracycline resistance (19.3%), ceftriaxone less-susceptible strains (5.5%) and multi-drug resistant isolates (23.3%) over 14 years from 1996 to 2008 (19).

Additionally, it has also been identified that the emergence of resistance against widely used and cheaper antibiotics, in addition to complicating the clinical burden, will also result in direct financial implications due to the cost constraints on replacing them with more expensive, newer generation antibiotics (20).

### Key messages

- Noticeable reduction in resistance against older antimicrobials, which are not used very commonly, indicates the possibility of reversing the AMR tide if indiscriminate antibiotic consumption can be curbed. However, rising incomes, increasing ability to purchase/access to antimicrobial agents is likely to impair effectiveness of newer and commonly use antibiotic groups.
- Enactment of enhanced regulatory and legislative measures to control over-the-counter (OTC) sales and invalid prescription based purchase is one of the major focus areas of the national policy for containment of AMR. However, implementation strategies remain spotty and limited availability of trained pharmacists, especially in rural and difficult-to-access areas remains a challenge.
- Institution of the National List of Essential Medicines (NLEM) and Essential Drug List at the state levels are likely to disengage perverse economic incentives associated with

over prescribing of antibiotics. However, drugs and generics made available at lower prices at government facilities need to be quality assured to prevent spurious drugs from flooding the system.

## 2.2 AMR in livestock/food animals

It was first noted in the 1940s that addition of small doses of antibiotics to the feed led to an increased rate of weight gain and a better “feed-conversion ratio” in animals. This led to the practice of non-therapeutic use of antibiotics either for prophylaxis or metaphylaxis (timely mass medication of a group of animals to eliminate or minimize an expected outbreak of disease), and for growth promotion. Over the years, it has been seen that with improving environments in which animals are reared and with the adoption of good agricultural norms, the effect of antibiotic growth promoters (AGPs) has become progressively smaller. However, in countries where animals are reared in unhygienic or unsanitary environments, which make them more prone to suffer from infectious diseases, antibiotics still have a role to play in growth promotion. The use of sub-therapeutic doses of antibiotics for this purpose has been widely viewed to be a driver for the emergence of AMR in countries with intensive animal farming where the use of antibiotics for growth promotion is not prohibited or controlled legally (3).

The burden of AMR in livestock and food animals has been poorly documented in India. Aside from sporadic, small, localized studies, evidence that can be extrapolated to the national level is lacking. Given that there are few regulations against the use of antibiotics for non-therapeutic purposes in India, with no stringent implementation protocols even when there are regulations, the emergence of AMR from antibiotic overuse in the animal sector is likely to be an unmeasured burden in India. India does not have a surveillance system that accounts for use and/or consumption of antibiotics in the animal/food/livestock sector. If the data from USA are indicative, then it is likely that a large proportion of the total antibiotic consumption may actually be accounted for through the livestock sector. According to a report issued by the US Food and Drug Administration (FDA), in 2011, 13.6 million kg of antibiotics were sold for use in food-producing animals in the United States, accounting for almost 80% of all the antibiotics sold or distributed in the country (21). In 2012, India manufactured about a third of the total antibiotics produced globally. Hence, it is likely that the consumption patterns and emerging AMR through antibiotic use in the livestock sector is an important target for policy-makers.

### **2.2.1. Antibiotic use: Cattle**

The detection of antibiotic residues in milk and dairy products has been the main approach for estimating the use of antibiotic use in dairy cattle, followed by non-compliance with withholding periods to allow the drug to be completely metabolised before initiating milking. A survey conducted by the National Dairy Research Institute (NDRI) identified that the most commonly used antibiotics in cattle were – tetracycline, oxytetracycline, gentamicin, ampicillin, amoxicillin, cloxacillin, and penicillin due to their lower costs (22). Use of enrofloxacin, lincomycin, streptomycin and chloramphenicol was also common when veterinarians treated for clinical conditions. More recent studies have shown that the most common indication for using antibiotics in dairy cattle is mastitis, and the preferred antibiotics include beta-lactams and streptomycin (23). This was supported by findings from Delhi, where similar trends were observed as beta-lactam antibiotic residues were detected from 11% of milk samples (24).

Although antibiotic residues in milk are an indicator that the animal had been provided with antibiotic drugs in the recent past, there is no way to elicit information on the indication for which the medication was given, who prescribed it, what duration the medication was given for, what dosage the medication was given in, and whether the use of antibiotics in that particular instance was justified or not. Hence, in the absence of more robust antibiotic consumption surveillance, it is difficult to elicit data on antibiotic consumption specific to the dairy industry.

### **2.2.2. Antibiotic use: Poultry**

As with the dairy sector, there is limited evidence available on the exact amount of antibiotic consumed within the poultry industry, and what were the various indications for which the medications were prescribed. In many cases, since the antibiotic is given as a growth promoter through the premixed feed, which comes with added antibiotics, it is difficult to exactly estimate the dose or the consumption levels of antibiotics in the poultry sector.

In a study where samples of chicken meat were drawn from the Delhi National Capital Region, it was seen that 40% of the samples contained the residues of one or more antibiotics and 17% of the samples contained more than one antibiotic residue in the meat (25). With the market for chicken meat growing at a rate of 10% per annum, intensification of poultry rearing is the way

to keep up with the demand, and may further increase the use of antibiotics as growth promoters.

### **2.2.3 Antibiotic use: Aquaculture**

The legislative conditions regulating the aquaculture processes are different from those in the poultry or the dairy industry. The Food Safety and Standards Authority of India (FSSAI) has placed an extensive ban on the use of antibiotics and several pharmacologically active substances in fisheries. Also, in contrast to the poultry industry where many of the commercially available pre-mixed feeds come with antibiotics added, none of the feed in the fisheries sector contain antibiotics. These drugs can, of course, be added to the feeds separately by the farmers.

Although the total amount of antibiotics used in fisheries may be much smaller in quantity than that used for terrestrial, intensive livestock rearing, the major problem is that more antibiotics which are clinically important in humans find use in the aquaculture sector (26). Although there is little evidence on the deleterious impact of using antibiotics in fisheries on the marine ecosystem, it has been seen that most antibiotics are toxic to native marine flora and fauna when given in excess. The long-term impact of the use of antibiotics for aquaculture not only has ramifications for emergence of resistance in marine bacteria, but also has a yet unmeasured impact on the marine ecology and the environment.

Based on usage trends in aquaculture, China is the largest consumer of antibiotics, and possible problematic usage patterns being noted in Indonesia, Thailand, Vietnam, India and Chile (27). However, like in most of the developing countries, scientific evidence is missing on antibiotic use patterns and residues in the fisheries industry in India (28).

### **2.2.4. Antimicrobial resistance: Cattle**

Drug resistant bacteria have been isolated from dairy cattle as early as the 1970s. A high level of AMR was reported from Shiga toxin-producing *E. coli* isolated from calves with diarrhoea in Gujarat and the Kashmir Valley (29, 30). All of the strains from Gujarat were resistant to at least three antibiotics, and almost half were resistant to eight or more of the 11 antibiotics tested. Resistance was ubiquitous for kanamycin and cephalixin and was above 50% for seven of the antibiotics tested (29).



One of the most common clinical issues encountered on dairy farms is mastitis, which may be subclinical or overtly symptomatic. Commonly thought to be a disease of production, milk from mastitic cows and buffaloes have been shown to contain a wide range of bacteria, with a wide spectrum of resistance against commonly used antibiotics. In some cases, MDR bacteria have been seen to co-infect animals suffering from mastitis (31). One study identified that almost all samples drawn from 105 sick cows showed bacteria that were resistant to ampicillin, carbenicillin and/or oxacillin (32). MRSA has also been isolated from the samples of milk drawn from cows suffering from mastitis (31). In a recent study, almost 13% of the milk samples exhibited the presence of MRSA. These samples were significantly more resistant to other groups of antibiotics than other bacteria that were also seen in the same samples (33). In this study, none of the isolated MRSA were seen to be resistant to vancomycin; however, recently the first report on the presence of vancomycin resistant *Staphylococcus aureus* (VRSA) in bovine and caprine milk has been published, indicating the rapidly growing issue of AMR (34). Recent studies have shown that samples drawn from mastitic cows also contained *E. coli* which carried the multi-resistant NDM-1 gene and other samples, which contained *E. coli* with ESBL genes (35).

Bovine source milk, especially from those animals suffering from mastitis, has been observed to have high levels of resistant bacteria. In a study conducted in eastern India, it was seen that 20% of the isolates demonstrated resistance to imipenem; samples were positive for plasmid-mediated quinolone resistance genes (qnrS). The samples also contained ESBL and AmpC type beta lactamase producing MDR *Klebsiella pneumoniae* (36).

There exists a large body of evidence, which comprises of studies investigating the resistance profiles of bacteria isolated from both sick and healthy cattle. However, these studies do not provide a representative picture of the problem at the national scale, for which it is imperative to have a broad based surveillance system in place.

#### **2.2.5. Antimicrobial resistance: Poultry**

There are gaps in the surveillance system monitoring antibiotic resistance in animals in India. However, individual studies have consistently shown that bacteria isolated from animals or seafood have high levels of resistance. It has been seen that for certain groups of antibiotics, *Staphylococcus* and *Pasteurella multocida* isolated from poultry may have up to 100% resistance (7).

A 2009 study reveals that a majority of isolates from poultry were resistant to at least one antibiotic, the highest rates being against streptomycin (75%) and erythromycin (57%). Resistance was also greater than 40% for kanamycin, ampicillin, tobramycin, and rifampicin, which were largely used for non-therapeutic purposes, the most important one of them being growth promotion (37). *Salmonella* isolated from eggs, has been shown to be resistant to multiple groups of antibiotics (38, 39).

A recent study found significant differences in the resistance profiles of broiler farms vs. layer farms<sup>1</sup> in the Punjab region of northern India, with drug resistance being far more common in broiler operations. Broiler farms ranged from twice as likely to more than twenty times as likely to harbour resistant *E. coli*, and prevalence of multi-drug resistance was much higher (94% in broiler farms vs. 60% in layers). ESBL prevalence in broiler farms was also higher at 87% vs. 42% among layers. Independent broiler operations had overall higher rates of resistant *E. coli*, while contracted layer farms (not independent) had higher prevalence of ESBL producers (7).

The first systematic study of MDR ESBL-producing *E. coli* in Indian poultry and cattle found 18 of 316 *E. coli* isolates sampled in Odisha to be ESBL producers. All ESBL-producing strains emerged as a single lineage through phylogenetic analysis and were resistant to cephalosporins and monobactam, as well as a host of other antibiotics (40). A more recent study from backyard layers has found high rates of resistance against chloramphenicol, ciprofloxacin, gentamicin, levofloxacin, norfloxacin and oxytetracycline (41).

#### 2.2.6. Antimicrobial resistance: Aquaculture

Compared to the poultry and dairy sector, antibiotic resistance has been scrutinized more closely in the aquaculture sector. Due to the existence of stringent legislative provisions to contain the inappropriate and non-therapeutic use of antibiotics, it is expected that the problem of AMR in the aquaculture sector should be smaller compared to the dairy or poultry sectors. However, in a recent study that examined over 250 samples, it was seen that MDR bacteria were isolated from over two-thirds of the samples (42).

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<sup>1</sup> Broiler farms are those farms in which chickens are raised for the purpose of poultry meat. Layer poultry farming refers to raising egg-laying poultry birds for commercial production of eggs.

The extent of multidrug resistance is a major issue in aquaculture. Two thirds of the samples of *Salmonella* isolates drawn from fish and shellfish obtained from the markets of Mangalore were seen to be resistant to at least two antibiotics; almost a quarter of the isolates were seen to be resistant to three or more antibiotics (43). These results reflect the poor implementation of the existing legislative provisions, as well as the polypharmacy practised in the aquaculture sector.

Almost 90% of the isolates of *Vibrio cholerae* from coastal southern India were resistant to ampicillin, penicillin, and streptomycin, whilst almost two-thirds of the samples were resistant to bacitracin (44).

### Key messages

- To whet the increasing appetite of India's rapidly expanding cities for animal source proteins, there has been a concurrent increase in intensive, industry-style animal rearing, even in small holders, with minimal quality control, oversight and support. Farmers functioning on razor-thin margins need to keep their animals healthy at any cost and hence they resort to inappropriate use of antibiotics, often through unprescribed routes.
- Few regulations and legislative measures are available against the non-therapeutic use of antibiotics in food animals. Limited legislations are available for control of antibiotics in the livestock sector, although some legislative tools are available for fisheries and poultry raised exclusively for export.
- There are increasing legislative tools against non-therapeutic use of antibiotics in animals, e.g. the directive issued by FSSAI in January 2015 outlines principles to limit the use of antibiotics in livestock rearing. However, it lacks a roadmap or implementation plan, making it difficult to translate it into actionable policy interventions.
- There is an absence of a One Health approach to AMR containment at a policy level, as the focus is more on human health issues and the scope of the problem in the veterinary sector, although acknowledged, is not outlined in granular details.

## 2.3 Awareness and understanding of AMR

The GAP-AMR states that the first strategic objective in effectively containing AMR is to improve awareness and understanding of AMR through effective communication, education and training (1). The strategy envisions that the awareness building has to proceed on several fronts at the same time. On one hand it has to leverage public communication programmes to encourage behaviour change in target populations, namely, stakeholders in human health, animal health and agriculture; and on the other, there needs to be concerted efforts to incorporate AMR as a core component in the professional education of medical and veterinary professionals. It is essential to identify stakeholders who can play a pivotal role in containing AMR in their professional capacity; this could include a wide spectrum of functionaries such as, physicians, nurses, AYUSH (Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homoeopathy) practitioners, pharmacists and chemists, veterinarians, para-veterinarians (including veterinary field assistants) and other health care support staff. Similar views were expressed in the situation analysis on antibiotic use and resistance in India conducted by the Global Antibiotic Resistance Partnership (GARP) – India Working Group (45). The GARP had identified that of the three critical areas of intervention in India and countries with similar resource limitations, a vital component is education and public awareness campaigns to improve the understanding of AMR in both providers as well as consumers.

The need to focus on awareness building, both in consumers and providers, was highlighted by the results of the multi-country public awareness survey that was conducted by WHO (46). The findings of the study highlight important gaps in the understanding of what antibiotics are, how they should be used and when to take them. There is ample evidence to suggest that there is a certain “pull” from patients which forces medical practitioners to overprescribe antibiotics, especially for conditions like viral illnesses, upper respiratory tract infections and diarrhoea, for which antibiotic therapies are not the recommended first line of approach (47). This irrational demand to be over-treated inappropriately with antibiotics can be explained through the findings from this survey, which could identify potential areas for which targeted messages could be developed. Surprisingly, a large proportion of the Indian respondents also admitted that they considered AMR to be a serious issue, but there seemed to be a wide dissonance between knowledge, attitudes and practices.

Although there is a dearth of evidence to assess baseline awareness levels, and use these levels to evaluate the impact of any awareness-building campaigns in India, limited evidence indicates that there is a definite felt need related to this issue in India, both from consumers and providers. In a self-reported survey of medical practitioners in Tamil Nadu, for example, 12% expressed the need to have focussed continuing medical education programmes targeting antibiotic use guidelines and resistance issues; an additional 6% felt that patient awareness on antibiotics was also critical as patient requests/expectations emerged as a major driver for antibiotic prescription in the clinical setting (48).

However, it is also widely recognized that given the easy availability of antibiotics OTC, without prescriptions, or with inappropriate prescriptions, pharmacists need to be identified as stakeholders in the process of awareness generation. Although there are a few programmes targeting continuing professional development of pharmacists, they are not on a scale that may impact OTC sales of antibiotics in India. Additionally, though a few studies have noted that in the immediate aftermath of meeting with pharmacists, through training programmes, there is a reduction in the sales volume of antibiotics, the long-term sustainability of such progress is suspect (45). Additionally, there is some evidence that, in the long run, intense training may not make a difference, as untrained pharmacy attendants are likely to mimic the prescription practices of the local providers, copying both the appropriate as well as the inappropriate prescribing-behaviours of trained providers (49). Whilst copying of desirable traits may be potentially beneficial, such uncontrolled diffusion of prescribing habits, especially if originating from unlicensed practitioners, could result in detrimental effects in the long run.

These findings were also bolstered by the report on the country-wise worldwide situation analysis that was conducted by WHO (50). This report identified that the awareness levels regarding prudent and appropriate use of antibiotics was low in all regions of the world. One of the points of concern was that even in countries that had conducted national awareness campaigns for AMR, there seemed to be a fair amount of misunderstanding about the therapeutic role of antibiotics. This points to the fact that there needs to be sustained, targeted awareness campaigns that not only look to improve knowledge and awareness of the target audience, but also have a strong behaviour change component along with appropriate measures for monitoring and evaluation, incorporated in it.

Given the financial incentives to prescribe antibiotics and the role of the pharmaceutical industry in encouraging prescription of antibiotics in India, there is a need to approach the process of awareness generation with additional legislative support. A major cause of concern is that despite their high costs and apparent access issues, the consumption of expensive classes of antibiotics like carbapenems is on the rise in India, largely driven by OTC sales and inappropriate prescribing practices (49). Evidence from the higher income countries exist, showing that if such perverse economic incentives linked to inappropriate and irrational prescribing of antibiotics are cut off, there is an immediate reduction in the antibiotic prescription volumes (51, 52). In China, the government launched the National Essential Medicine System (NEMS) advocating the use of essential medicines and promoting the rational use of antibiotics. The programme sought to eliminate the profit link between health institutions or doctors and medicine (prescriptions) by imposing the Essential Drug List (EDL), a compendium of low cost medicines for common, treatable illnesses affecting a large number of people (53).

Internationally, there is evidence that awareness generation campaigns, in combination with other interventions, organized at the national level may be successful to reduce antibiotic use. The “Antibiotics are not automatic” campaign, which was launched in France in 2001 as a part of a programme to conserve effective antibiotics for therapeutic purposes, achieved a reduction of antibiotic prescription to the tune of 27% (54). The common attributes of successful campaigns to reduce antibiotic prescription or consumption in human medicine should (55):

- be multifaceted programmes, targeting multiple groups, especially the parents of young children;
- have involvement/participation of health authorities;
- be publicly funded;
- last for at least one year; and
- utilize multiple channels to deliver information, suited to the target groups.

Education of medical, veterinary and agriculture professionals in the key tenets of AMR, sustainable and prudent antibiotic use, and antibiotic stewardship has also been identified as one of the key elements of reducing provider side “push” for overuse of antibiotics. As noted in the report on the State of the World’s Antibiotics, education pertaining to antibiotic stewardship is largely limited to the clinical setting at the hospital levels. It needs to be

incorporated as a core curriculum at the undergraduate and postgraduate medical education in the relevant disciplines. Surveys of European medical schools have established that almost all of them contain prudent antibiotic prescription, AMR and antibiotic stewardship as core components in the undergraduate curriculum (56).

The National Policy for Containment of AMR in India, outlined in 2011, acknowledged the shortcomings in medical education as far as training in the principles of rational antibiotic usage is concerned. One of the focus area of the policy document emphasizes the need to develop training modules on rational prescribing of antibiotics in India (57).

There is also a need to increase the awareness about the need to contain AMR at the higher levels of policy-making, so that it may emerge as a priority in the health policies of the nation. In 2011, the health ministers of WHO Member States of the South-East Asia Region articulated their commitment to combat AMR through the Jaipur Declaration. This was a high-level commitment to prioritize AMR control programmes at the highest levels of national policy-making.

The Red Line campaign emphasizes the following key issues:

- Raising awareness about how to identify a drug that should only be dispensed against a prescription from a licensed doctor;
- Curbing the practice of self-medication, which received an additional fillip through *Mann ki Baat* (a radio programme hosted by the Hon'ble Prime Minister of India, Shri Narendra Modi) in August 2016, in which the PM urged all Indians to avoid the practice of self-medication and take medications as prescribed; and
- Becoming aware of the potential harms that may result from the misuse of antibiotics.

### Key messages

- The pull from consumer/patient side (increased demand for antibiotics as a therapeutic right) and push from caregivers (overprescribing antibiotics either to satisfy patient expectations or driven by perverse economic interests) is a major hurdle in curbing irrational and inappropriate antibiotic use. To overcome this, focused multi-faceted programmes, targeting risk groups, to spread awareness and information need to be developed.

- There is a need to build and sustain interest in AMR containment at the highest level. Adherence to the principles outlined in the Jaipur Declaration of 2011 shall ensure prioritisation of AMR containment.
- The policy response to address AMR has been espoused at the highest levels through communication channels from Hon'ble Prime Minister's radio show.
- Launching the Red Line Campaign at the national level to raise awareness in people about the need to have prescriptions from medical/veterinary professionals before consumption of certain groups of colour-coded drugs, is part of a concerted effort to increase awareness of drugs that should not be consumed without prescriptions.

## 2.4 Surveillance of AMR in humans, animals and food

The global report on surveillance of AMR, having data reported from 114 countries, including India, reported serious lapses in the surveillance mechanisms in place in different countries (58). The report identified the lack of a global consensus on the methodology and data collection systems for AMR surveillance. It highlighted the fallacies of facility-based testing, which is what forms the foundation stone for AMR surveillance programmes in many countries. The concerns about under-reporting of AMR in community-acquired infections was also underlined in this report; and in course of the data collection process for compilation of the report, it was found that there are knowledge gaps and capacity issues in the process of sample/data collection needed to institute an effective surveillance programme.

Surveillance of AMR and antibiotic use on a national scale is a priority area for policy focus in any country grappling with the problem of AMR, including India (59). The rationale is that it will provide better information and assist in making evidence-based decisions for development of standard treatment guidelines, education and awareness programmes, and monitor the AMR situation longitudinally. The National Policy on AMR Containment (57) had outlined a roadmap with a two-pronged approach – surveillance of antibiotic use and consumption, both in the human and the animal sector; and that of the emergent patterns and trends of AMR in index bacteria against drugs which are of critical clinical significance for humans. The policy advocated a model of sentinel surveillance of AMR.



India has previously instituted surveillance of the emergence of drug resistance in disease causing microbes in the context of vertical programmes, like the Revised National Tuberculosis Control Programme (RNTCP), the National Vector Borne Disease Control Programme (NVBDCP), and the National AIDS Control Programme (NACP), to name a few. However, a cross-cutting programme dealing with resistance across multiple microbes has been lacking.

The National Programme on Containment of Antimicrobial Resistance was launched under the aegis of the National Centre for Disease Control (NCDC) under the Twelfth Five Year Plan (2012–17). The objectives of this programme were to establish a laboratory-based AMR surveillance system of 30 network laboratories, generating quality data on AMR for pathogens of public health importance; to strengthen infection control guidelines and practices, and promote rational use of antibiotics; and to generate awareness about the use of antibiotics in both health care providers and in the community (2). The policy focus included: situation analysis regarding the manufacture, use and misuse of antimicrobials; creating a national surveillance system; identifying prescription patterns and establishing a monitoring system for the same; enforcing enhanced regulatory provisions with respect to marketing of antimicrobials; developing specific intervention measures such as antibiotic policies for health care facilities and development of diagnostic aids related to monitoring AMR.

At present, 10 network laboratories have been identified in the first phase of the programme, in course of which four pathogens of public health importance are being tracked: *Klebsiella spp*, *E. coli*, *Staphylococcus aureus*, and *Enterococcus spp*. The network intends to extend testing of resistance to two more index bacteria: *Pseudomonas aeruginosa* and *Acinetobacter spp*. Reporting from the 10 laboratories shows overall resistance rates to be very high, against the commonly used fluoroquinolones, third generation cephalosporins and carbapenems, although resistance against reserve drugs like vancomycin was not noted in isolates of *Staphylococcus aureus*, or against colistin in gram negative bacteria. The NCDC is also drafting a National Infection Control Policy, which is in the final phases of preparation (2). A strategy to scale the programme up in order to carry out surveillance of hospital acquired infections and antibiotic use patterns in health care settings has also been outlined; additional focus on building awareness about rational use of drugs on a continuous basis is also being planned.

The Indian Council of Medical Research (ICMR) has also established a national network on AMR surveillance in laboratories based at academic centres, targeting medically important

index microbes which have been identified by WHO (3). The Antimicrobial Resistance Surveillance Research Network (AMRSN) established by the ICMR monitors AMR at six reference laboratories in four tertiary care medical institutions, in the following six pathogenic groups of bacteria (i) diarrhoeagenic bacterial organisms, (ii) enteric fever pathogens, (iii) Enterobacteriaceae causing sepsis, (iv) Gram negative non-fermenters, (v) Gram positives including MRSA, and (vi) fungal infections.

ICMR has also developed a real time online AMR data entry system for its network and will have AMR data analysis capacity specific for bacterial species in relation to point of origin of pathogens as well as various patient demographic parameters.

The AMRSN also incorporates in-depth understanding of clonality of drug-resistant pathogens and the transmission dynamics to enable better understanding of AMR in the Indian context and devise suitable interventions. The AMRSN is currently limited to the human health side and plans to scale up on a national scale and expand its ambit to include samples from a wider spectrum of sources, including animal, environmental and food samples, to reflect the principles of a One Health approach based surveillance system. The network is being expanded to include 15 more centres.

The data emanating from this network since the last quarter of 2014 has shown that *S. Typhi* multidrug resistance to ampicillin, chloramphenicol and trimethoprim-sulfamethoxazole is showing a downward trend and resistance to fluoroquinolones is being increasingly reported in *S. Typhi*. This finding is very promising as this provides evidence to start using first generation, simple and cheap drugs. Among the Enterobacteriaceae species, *Klebsiella* and *E. coli* cause most of the infections which are 100% sensitive to colistin, followed by imipenem and meropenem, but are resistant to third generation cephalosporins (80%). Most of the hospital-acquired infections are caused by *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. All isolates of *Pseudomonas aeruginosa* were susceptible to colistin, followed by imipenem (85%), amikacin (80%), ciprofloxacin (80%), piperacillin-tazobactam (58%) and meropenem (50%) In *Acinetobacter baumannii*, maximum susceptibility was to colistin (99%) followed by imipenem (53%) and meropenem (53%). Susceptibility to amikacin has increased by 27% from 2014 to 2015 (ICMR data, personal communication). ICMR is working with the Indian Council of Agricultural Research (ICAR) to standardize antimicrobial susceptibility testing in the

veterinary labs with the aim of creating tools and formats for integrating AMR surveillance in humans and animals.

Despite the process of scaling up the programme, there are several limitations that have hobbled rapid roll-out of the programme on a national scale. Data has mainly been obtained from tertiary care centres, which may provide only a glimpse of the whole picture, especially with respect to resistance in community acquired infections. Quality assurance measures need to be defined and implemented, right from the step of sample collection to final reporting. Frameworks for uniform reporting standards, including use of comparable diagnostics also need to be evolved. In the absence of universalization of an online platform for data entry, transmission and analysis, all these steps need to be carried out manually at each level, not only resulting in labour-intensive and time consuming processes, but also increasing the chances of human error. Exploring options for real time data sharing, and training in the use of the WHONET platform for reporting has been initiated to combat these limitations. Developing external quality assurance systems (EQAS) and data sharing protocols (anonymized) have also been accepted at the level of policy leadership as key areas that need to be focussed on.

A WHO pilot project, undertaken in three sites in India (Delhi, Vellore and Mumbai) and two sites in South Africa (Durban and Brits), concluded that it was feasible to establish community-based surveillance systems once the local factors had been addressed (60).

Site	Prescriptions with antibiotics (in %)	Most commonly used antibiotics	Antibiotics against which $\geq 50\%$ isolates showed resistance
Delhi	21.5%  Significant use of newer antibiotics	Fluoroquinolones Cephalosporins Extended spectrum penicillins Macrolides	Ampicillin (85%) Cephalexin (50%) Ciprofloxacin (57%) Cotrimoxazole (65%) Nalidixic acid (77%) Norfloxacin (59%)
Vellore	41%	Fluoroquinolones Extended spectrum penicillins Cephalosporins	Nalidixic acid (59%) Ampicillin (53%) Cotrimoxazole (60%) Tetracycline (53%)
Mumbai	36-40%	Extended spectrum penicillins Cotrimoxazole Tetracycline Fluoroquinolones	Ampicillin (52%) Nalidixic Acid (56%) Tetracycline (83%)

The study also found high levels of resistance in *E. coli* isolates from urine. Higher rates were observed, in general, against antibiotics that have been in use for the longest (e.g. cotrimoxazole, ampicillin, tetracyclines, and nalidixic acid). The table on the previous page mentions the antibiotics against which 50% or more of the isolates obtained from the three Indian sites were resistant.

Like most low- and middle-income countries, India is in the process of developing a national surveillance network. In addition, the move to establish a NAP-AMR aligned with the principles outlined in the GAP-AMR will serve to streamline the process and ensure that a One Health approach to surveillance is adopted.

The Invasive Bacterial Infection Surveillance (IBIS) project generated valuable information, especially related to pneumonia in India, but has failed to fulfil its objective of establishing a sustainable, permanent system of AMR surveillance in India (61). The GARP India Working Group identified several challenges to establishing a sustainable AMR surveillance network; these included securing cooperation from the various stakeholders across multiple sectors, establishing mechanisms for inter-state and cross-border coordination, and financial sustainability (20).

There is very limited surveillance of AMR in animals and food in India. There are isolated studies, which have indicated high levels of AMR across animal commodities and systems, but they are yet to be unified under a nationally scaled programme.

Aside from the absence of a One Health approach to surveillance, another weakness of the existing surveillance systems for AMR in India is that they do not account for antibiotic use. The existence of a surveillance system that can establish the relationship between the antibiotic consumption patterns and emergence of AMR is vital to producing evidence that may help in the designing and evaluation of effective interventions. Additionally, if such a link is established, then tracking antibiotic use or consumption data could be used as a surrogate marker for the risk of potential AMR emergence (20).

The need to establish a robust laboratory network at the national level has also been identified as one of the limiting features of the AMR surveillance programmes in India. The report submitted by the Task Force constituted by the Ministry of Health and Family Welfare (MoHFW) emphasizes the need to develop such a laboratory network. The task force also

recommended establishing prescription and sales monitoring for antibiotics, and outlined a plan to deploy these measures in Delhi, followed by scaling up over time (20).

To have an effective AMR containment programme, which is based on a NAP-AMR aligned with the principles outlined in the GAP-AMR, it is essential to have a robust surveillance system.

### *Key messages*

- There is a higher risk of emergence of AMR in microbes isolated from clinical settings where they represent a dual risk: higher selection pressure owing to the high use of antibiotics, especially newer antibiotics; and presence of potentially susceptible, sick patients, who can be infected with resistant organisms and perpetuate the infection transmission.
- Data sources are limited to tertiary medical centres. There are minimal quality assurance protocols implemented across the steps of the surveillance process – especially with respect to diagnostic tests. There are also limitations in data collection, storage, transmission and analysis.
- Surveillance of antibiotic use and consumption is also important, both in the human and the animal sector, and that of the emergent patterns and trends of AMR in index bacteria against drugs that are of critical clinical significance for humans.

## **2.5 IPC and surveillance of health care associated infections**

Health care facilities, particularly acute care settings, are a high-risk zone for emergence of drug resistant organisms. The high volume of drug use, combined with the presence of a population that is highly susceptible to infections makes this a particularly difficult setting to deal with. As such, it is vital to control the spread of infections, especially those caused by drug resistant microbes, within such settings. The background report on the role of IPC programmes to contain AMR, commissioned by the WHO has highlighted the critical nature of this issue (62). Functional infection control programmes not only cut down the rates of nosocomial infections,

but also reduce the volume of antibiotic consumption, and have been identified to be part of any comprehensive strategy to contain AMR.

The report identifies barrier practices, including the use of patient isolation protocols, and personal protective equipment like gloves, masks, and gowns, to have limited effectiveness in controlling AMR in the clinical settings. This is because several other parameters drive the drug-resistant infection rates in such a setting, including factors like prevalence of AMR organisms at the facility level, characteristics of the patient population (especially with respect to their susceptibility to infectious diseases), patient volume and staffing ratio, to name a few. The report emphasizes the need to adopt a holistic approach to IPC measures at the facility level in order to control emergence of and outbreaks caused by resistant organisms. Barrier practices may form one part of the whole, but by themselves have limited effectiveness in controlling AMR at the facility level. The report also identifies prophylactic antibiotic usage as a driver for selection pressure for AMR although studies have shown that such practices may contribute to lowering of institutional rates of nosocomial infections. It highlights the need to have equitable distribution of resources since most facilities are overly focused on controlling infections by MRSA and VRE. The report identifies that there should be focus on good clinical practices that lead to prevention of colonization with AMR organisms and the focus should not be merely on infection prevention.

The report outlines the following set of activities that need to be undertaken for an optimally functioning IPC:

- Surveillance of health care associated infections
- Outbreak investigation and control
- Policy development, review and compliance monitoring
  - Isolation practices
  - Hand hygiene
  - Sterilization and disinfection of equipment and supplies
  - Housekeeping
  - Laundry
  - Food
- Employee health relevant to infections
- Education of staff, patients and visitors

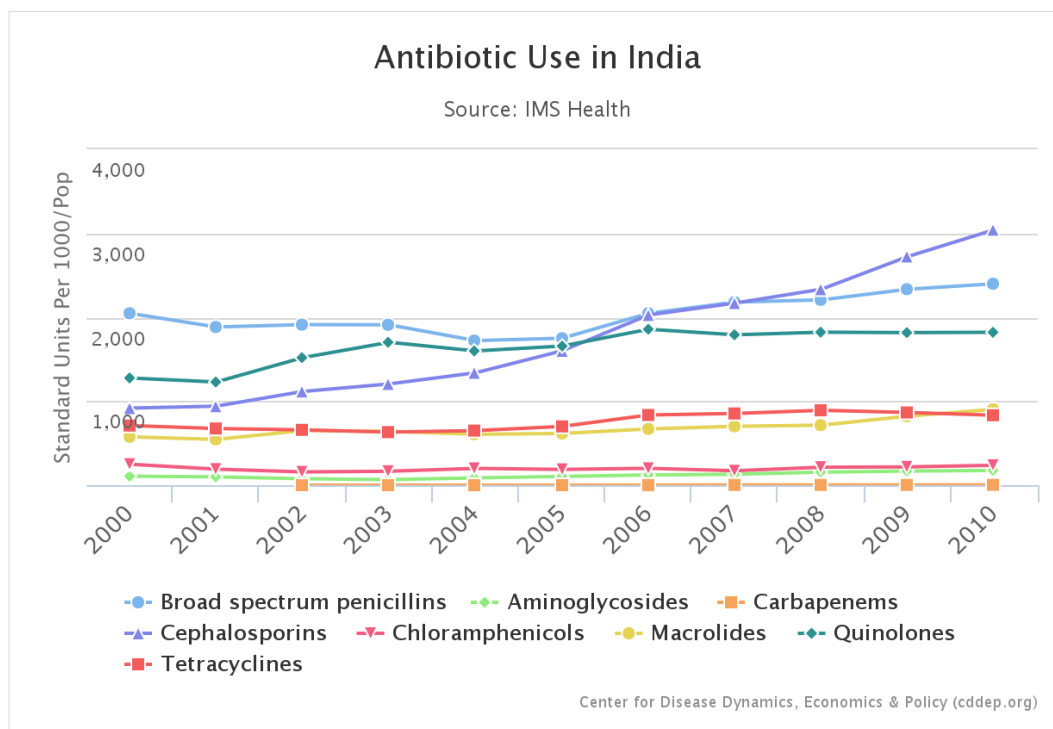
The ICMR guidelines on infection control were released at the international conference in February 2016, which further identified the need to develop IPC standards for each level of health care facility and not just tertiary care centres. It noted the need to establish functional hospital infection control committees (HICCs) to provide leadership to the IPC programmes at the institutional level. The need to integrate IPC programmes, both from the policy-making and implementation angles, was also stressed. Establishing IPC focal experts at the policy-making levels, linking of IPC programmes to AMR surveillance and nosocomial infection surveillance were identified as key policy integrations to drive more successful IPC programmes in India.

### Key messages

- An infection prone environment not only favours more frequent instances of infectious diseases, but also creates a conducive milieu for the spread of genes encoding resistance through transfer of mobile genetic units or plasmids between interacting bacteria.
- Environmental contamination with antibiotic residues either through use in food animals or farms or through industrial effluents, is an emerging concern.
- The AMRSN has outlined a roadmap to scale up the programme to carry out surveillance of hospital-acquired infections and antibiotic use patterns in health care settings.
- Guidelines on IPC in the health care setting have been developed and released by ICMR; extension of the guidelines that are applicable to health care institutions at all levels is being undertaken.
- Developing the *Swachh Bharat Abhiyan* into a cross-cutting programme encouraging espousal of open defaecation free zones, better sanitation and hygiene standards, and awareness of infection prevention at the community level is likely to reduce infection load, thus leading to lesser propensity to consume antibiotics. However, India remains as one of the nations with a very high proportion of bacterial infections, especially in areas with poor water, sanitation and hygiene conditions.

## 2.6 Use of antimicrobials in humans, animals and food

Limited data is available in the public domain on antibiotic sales. Based on available data, trends may be observed as shown in the figure below:

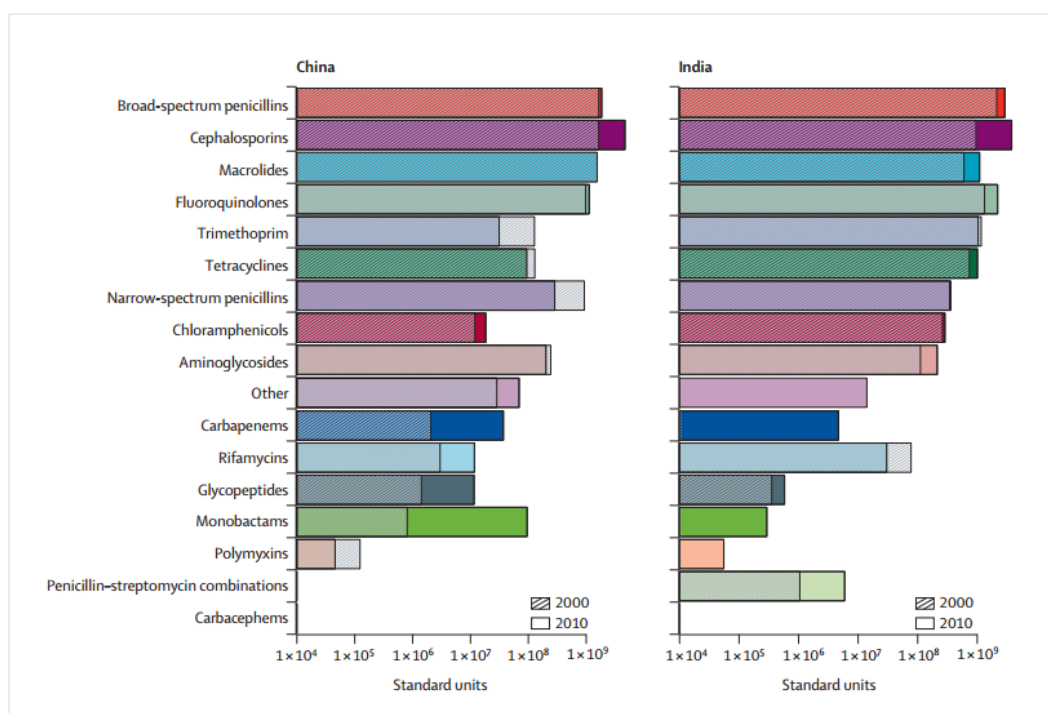


At  $12.9 \times 10^9$  units<sup>2</sup> of antibiotics consumed in 2010, India was the largest consumer of antibiotics for human health. Although the per capita consumption of antibiotics in India (10.7 units per capita) was lower than that seen in many other countries (e.g. 22 units per capita in USA), the overall population and infection load led to higher total consumption. Almost 23% of the increase in the retail antibiotics sale in the BRICS countries was attributable to India (63).

From a study by van Boeckel et al, the consumption of antibiotics in India and China are compared, by class of drugs, in the image on next page (63).

<sup>2</sup> These data are based on sales estimates projected using a proprietary algorithm developed by IMS Health in order to have an approximation of the total volume of sale and consumption of antibiotics. IMS defines the standard unit to be the number of doses sold, each dose being defined as a pill/capsule/ampoule of the drug. More details are available from Van Boeckel et al. (63)





With respect to consumption of antimicrobials in food animals, the global consumption was estimated to be 63,151 ( $\pm 1,560$ ) units in 2010 (27); India accounts for 3% of the global consumption and is the fourth highest in the world, behind China (23%), the United States (13%) and Brazil (9%). The consumption of antimicrobials in the food animals sector in India is expected to double by 2030. Intensive rearing of food animals has contributed to as much as 46% of the increase in the consumption of antimicrobials in Asia.

In India, the highest levels of antimicrobial consumption are seen in the southern coast, Mumbai and Delhi. The total acreage in which animal consumption of antimicrobials is very high ( $>30$  kg/sq. km) in South Asia is expected to be driven by the growth of the poultry industry in India. The expansion of acreage with high animal consumption of antimicrobials is expected to increase by 312% in India by 2030, pushing the Asian surge in animal consumption of antimicrobials (27).

An outpatient based study from New Delhi found that 39% of the patients attending private retail pharmacies and public facilities and 43% of patients visiting private clinics were prescribed at least one antibiotic (64). The study further highlighted the extremely high antibiotic consumption across public sector (43,390 DDDs/1000 patients for all antibiotics),

private retail sector (125,544 DDDs/1000 patients for all antibiotics) and private clinics (81,467 DDDs/1000 patients for all antibiotics).

The absence of stringently framed and implemented regulatory frameworks to limit the use of antimicrobials in livestock and food animals, especially for non-therapeutic purposes, like growth promotions, has been one of the drivers of antibiotic overuse at the community level (3). The National Policy for Containment of Antimicrobial Resistance in India (57) reiterated that antibiotics are widely used in food animals as growth promoters and to prevent and treat infections. Non-therapeutic use is particularly rampant in the absence of regulatory provisions regarding the use of antibiotics in the livestock sector. Except for certain types of seafood (Prevention of Food Adulteration Rules), and poultry intended for export only, there are limited policy provisions restricting the use of antibiotics in raising livestock.

The FSSAI under MoHFW is the main authority for laying down evidence-based standards for articles of food and regulating their manufacture, storage, distribution, sale and import, to ensure availability of safe and wholesome food for human consumption and for matters connected therewith as per the rules specified by Food Safety and Standard Act, 2006 (FSSA, 2006). It is the responsibility of FSSAI to adopt good manufacturing practices, good hygiene practices, hazard analysis and critical control point and such other practices as may be specified by regulation. The various provisions that may have direct or indirect implication for antibiotic growth promoters (AGPs) are:

- The food authority should specify the limits for use of food additives, crop contaminants, pesticide residues, residues of veterinary drugs, heavy metals, processing aids, mycotoxins, antibiotics and pharmacologically active substances and irradiation of food (sec 16 [2][b], FSSA, 2006).
- Section 21 (1) specifies that “No article of food shall contain insecticides or pesticides residues, veterinary drug residues, antibiotic residues, solvent residues, pharmacologically active substances and microbiological counts in excess of such tolerance limit as may be specified by regulations.”
- Section 2.3.2 of the Food Safety and Standards (Contaminants, Toxins and Residues) Regulations, 2011 of FSSA, 2006 specifies the limits for antibiotics and other pharmacologically active substances in sea foods including shrimps, prawns or any other variety of fish and fishery products.

- A more recent directive has been issued in January 2015, by the FSSAI (65) which outlines certain principles that include limiting the use of antibiotics in livestock rearing. It does little besides reiterating the directives of a previous advisory (66) from the Department of Animal Husbandry, Dairying and Fisheries. This document urges a review of the situation of AGPs and discourages the indiscriminate use of antibiotics.
- The National AMR Containment Policy (57) also highlights the need to establish a separate Schedule H1 under the Drugs and Cosmetics Rules, to regulate the sales of antibiotics. The national policy also outlines the proposal for colour-coded tagging antibiotics, and newer molecules (carbapenems, tigecycline, daptomycin, etc.) to eliminate their use outside of tertiary care settings. The Red Line Campaign was also launched at the international conference in February 2016 (67).

These measures to ensure rational use of antibiotics are being further supported by the National Treatment Guidelines for Antimicrobial Use in Infectious Diseases, which were released in February 2016 (68). These shall be revised at fixed intervals, based on the data on AMR gathered through surveillance on a regular basis.

Antibiotic stewardship programmes are a key component of countering the overuse and inappropriate use of antibiotics in the clinical setting. It is a multidisciplinary programme which delivers a package of interventions to improve appropriate use of antibiotics; additionally, there is an element of monitoring and evaluation built into the system to estimate the impact of the programme on improvement in antibiotic prescription practices in the short run and a reduction of resistance levels in index bacteria in the long run (69). The main objectives of running an antibiotic stewardship programme include: reduction of inappropriate use of antibiotics; optimization of drug class selection, dose, route, and duration of treatment to achieve the best possible outcomes for the patients; minimizing adverse effects to drug use and medical costs; and preventing or containing the emergence of antibiotic resistance in index bacterial species.

To establish an effective antibiotic stewardship programme, it is essential to have a multidisciplinary clinical team in place. It is recommended that the core team comprise of a clinical pharmacist, a physician trained in infectious diseases, a clinical microbiologist, an informatics expert, a hospital epidemiologist, and an infection control specialist (70).

ICMR launched the programme on Antimicrobial Stewardship, Prevention of Infection and Control (ASPIC) in 2012 through collaboration between the office of the National Chair of Clinical Pharmacology, ICMR and the Christian Medical College, Vellore.

A national workshop was hosted as a part of a 1-year programme to develop capacity of key stakeholders in Antibiotic Stewardship. The ASPIC workshop trained the participants with the following essential skills (69):

- Skills and understanding required for IPC practice,
- Knowledge and skills required for development and implementation of antimicrobial policy guidelines for rational use of antibiotics to curb AMR, and
- Ability to plan and conduct research projects in antibiotic policy and IPC practice.

The launch of the AMRSN in 2013 coincided with the Chennai Declaration, which sought to identify a roadmap to tackle the challenge of AMR (71). In addition to launching the AMRSN, the ICMR also instituted an evaluation of the antimicrobial stewardship programme (AMSP) practices through an in-depth facility survey in private and government health care institutions (72). The results showed that though there was a very high degree of adherence to the guidelines when it came to dealing health care associated infections (HAIs) or hospital infection control (HIC) measures, compliance was poor with the other aspects of antibiotic stewardship, especially with respect to having a documented stewardship programme, antibiotic prescription guidelines and usage surveillance, and a truly multidisciplinary team.

It was also seen that the stewardship programmes in private institutions were better equipped to deal with emerging crises like AMR or HAI outbreaks, in comparison to the government facilities in the survey. It is suggested that the accreditation mandates, which certain private institutes adhere to on account of financial compulsions, may have a positive impact on the programme.

The evaluation report recommends that government health care facilities also need to seek mandatory accreditations to improve their stewardship programmes. The survey revealed a paucity of implementation strategies, including formulary restrictions and drug rotation policies.

Prescription audits were conducted in very few institutions; efforts in development, dissemination and regularly updated prescription policies were also deficient; absence of

computer-assisted programmes, especially in government facilities, also hampered the work of the stewardship programme.

The ICMR report (72) outlines a set of recommendations based on their extensive survey, which include the following:

- For the standardization of health care (including AMSP practices) in the country, the government must make accreditation of all hospitals and their diagnostic laboratories mandatory.
- Infectious diseases physicians must be available in all health care institutions (HCIs) providing tertiary and secondary health care.
- Clinical pharmacists must be available in all tertiary and secondary HCI for better control and use of therapeutics especially antimicrobials.
- All HCIs must have written documents on AMSP and perform frequent audits to ascertain how well the guidelines are being followed.
- A comprehensive record of HAI must be kept and trends analysed regularly.
- AMR data must be regularly analysed specific to acquisition of infection, site of infection and the pathogen.
- Antimicrobial usage data must be analysed regularly.
- Regular education, easy availability of guidelines and audit of antimicrobial prescription practices and their feedback are essential.
- Major stakeholders, physicians and surgeons must be involved in and even be leaders in all aspects of AMSP, guidelines and audits.
- Continuous research is warranted in all aspects of AMSP to obtain the best programme for local needs.

### *Key messages*

- Acknowledging the need to incorporate basics of antibiotic stewardship and rational use of antibiotics as a curricular component in professional training (in medical and veterinary sectors) is a step toward universalization of stewardship efforts.
- To establish an effective antibiotic stewardship programme, it is essential to have a multidisciplinary team in place.

- ASPIC, a multidisciplinary programme, has been initiated with the objective of capacity building and implementation of the AMSP, including identification of gaps in the knowledge and implementation capacity of AMSP at the institutional level.

## 2.7 Research and innovations

Research and development in the field of developing newer classes of antibiotics has been slow. There has been a definite slowdown in the pipeline for production of effective novel classes of antibiotics globally. It has been proposed that in order to develop truly novel antimicrobial agents, drugs should be developed with three attributes: (i) these drugs should be ones against which there is no demonstrable resistance or cross-resistance with other classes of antimicrobials; (ii) they should have a narrow spectrum of activity to reduce the likelihood of rapid development of resistance; and (iii) they should be developed against agents or conditions which have a direct public health implication (73).

In 2004, in the 15 largest pharmaceutical companies, only 1.6% of the drugs in the development stages were antibiotics, and none of them were from novel classes, nor were they targeted to treat multidrug-resistant agents (74). Despite the obvious need to develop newer classes of drugs to respond to the challenges of emerging AMR, there are few late stage candidates in the process of development (75). Additionally, pharmaceutical agencies have been reluctant to invest in research and development of antibiotics owing to the nature of the market, the current policies on conservation of newer classes of antimicrobials and the nature of antibiotic chemotherapy for infectious diseases.

Antibiotic development has been associated with a positive externality (proper usage of antibiotics would cure infections, obviating the need for antibiotic use over the long term) and a negative externality (emergence of resistance, which renders a drug ineffective or of limited effectiveness), leading to market failures, generating apprehension in the pharmaceutical agencies when it comes to investing in research and development of novel antibiotics (76). Furthermore, if a private entity does succeed in developing an effective novel antibiotic, it is unlikely to be able to reap the financial rewards. Newer drugs, being more effective, would likely be shelved for infrequent use to conserve effectiveness, thus resulting in smaller financial

rewards. Finally, unlike drugs for chronic conditions like diabetes or hypertension, which need to be consumed for long periods of time, antibiotics are taken for shorter duration and if effective, lead to complete cure. This results in higher marketing costs and lower returns on investment.

Overall, the financial incentives for developing new classes of antibiotics seem to be little, especially for private, for-profit entities. An estimate suggests that a risk adjusted net profit value of antibiotics stands at 100, whilst it is 300 for an anti-cancer drug, 720 for a neurological drug and 1150 for a musculoskeletal drug (77). It is expected that with such adverse market forces to contend with, the onus on stimulating research and development of antibiotics and developing tools to combat AMR falls on the governmental agencies. However, there has been limited involvement of the national research councils, both from medical and agriculture sectors, in investments to develop newer classes of antibiotics.

One of the first needs to have a strategic R&D agenda for containment of AMR is to establish a set of needs and then prioritize them in order to understand the most critical gaps in our understanding of the AMR problem and how to contain it. Aside from the need to develop newer classes of antibiotics, especially for Gram negative organisms, which account for a major share of the mortality and morbidity resulting from drug resistant infections, there are three broad areas in which research and innovation needs to be channelled: surveillance, diagnostics and interventions (78).

The challenge of developing gene-based surveillance mechanisms, including the process of resistome analysis, is likely to provide information on the molecular mechanisms of the spread of AMR. Emerging evidence suggests that in countries which have strict control over antibiotic usage, like Denmark, hospitalized patients tend to show fewer resistance genes than compared to countries where more prolific consumption of antibiotics is the norm (79). The need for developing diagnostic aids that help in early diagnosis and antimicrobial susceptibility testing is critical to have targeted therapies and reduce the burden of broad-spectrum drug use, which promotes resistance rates.

The Cadila approach of developing the antibiotic resistance breakers (ARBs) to restore effectiveness of older classes of antibiotics has also emerged as an innovative way around the issue of resistance. ARBs can be known compounds as well as novel molecules which have no or minimal antibacterial activity, but which help in restoring the effectiveness of drugs to

which the microbes would otherwise be resistant. The current consensus seems to be that there is a need to develop ARBs that are likely to salvage key members of each group of antibiotics, especially those that target Gram negative bacteria. Antibiotic classes that are the most in need of ARBs for restoration of their effectiveness include: cephalosporins and carbapenems (which disrupt cell wall synthesis); polymyxins (which disrupt cell membrane synthesis); fluoroquinolones (which disrupt DNA synthesis); tetracyclines and aminoglycosides (which disrupt protein synthesis by inhibiting the 30S ribosomal subunit); and macrolides (which disrupt protein synthesis by inhibiting the 50S ribosomal subunit) (80). Some of the priority, existing compounds which are being tested for being repurposed to be used as ARBs include: ciclopirox, an antifungal; loperamide, an anti-motility drug; berberine, a traditional medicine; curcumin; epigallocatechin-3-gallate; naltrexone and naloxone (80).

There is also emerging evidence to suggest the need to investigate novel sources for the emergence of AMR, such as the role played by the human microbiome, which needs to be evaluated to better understand the micro-level or individual-level dynamics of emergent resistant organisms (81).

The Organization of Pharmaceutical Producers of India (OPPI) has supported the public health measures seeking to limit the overuse and abuse of antibiotics and promote their rational use. They have also supported the launch of the Red Line Campaign to limit the OTC sale of antibiotics and sale of antibiotics against invalid and inappropriate prescriptions.

Access has been identified to be a major limiting factor, especially when it comes to adequate dose and duration of therapy. In case of expensive antibiotics, there is a risk that due to the cost constraints, patients may discontinue taking the medications once symptomatic relief is felt, but the disease is yet to be completely cured. Incomplete therapy has been the bane of drug resistance in several programmatic experiences, especially with respect to tuberculosis control. The policy focus on providing generic medications at low cost or for free, from government hospitals, could be a step in the right direction. By reducing the cost differential of expensive antibiotics, the generic drug movement ensures that patients comply with the prescribed dosage and do not consume an inadequate quantum, thereby precipitating risk of drug resistance. There is also a consequent need to see how the provision of free or low-cost drugs changes prescribing practices in physicians and if there is an increase in the amount of



antibiotics consumed. This, once again, ties in with the identified need to have surveillance of use and indications for use, of antibiotics.

Given the hesitancy in the private pharmaceutical industry to engage in research and innovation to develop newer antimicrobials, innovations are necessary to overcome this barrier. One such endeavour was the Open Source Drug Discovery (OSDD) initiative launched by the Council of Scientific and Industrial Research (CSIR) in 2008, which was tasked to identify new treatment regimens for tuberculosis, malaria, filaria and leishmaniasis. OSDD restructured the method of bringing newer drugs to the market by sharing of resources, risks and rewards by crowdsourcing solutions through a network of online and wet-lab collaborators, through a semantic, web-based, wiki portal constructed with support from Infosys (82). The OSDD has 7600 registered participants from 130 countries, 10 engaged CSIR laboratories, 39 academic institutions and 14 industry partnerships, running 240 projects under 180 principal investigators.

The OSDD has a number of successes to its credit, including the task of re-annotation of whole genome of *Mycobacterium tuberculosis*, a task which should take an estimated 300 person-years, within a mere 4 months (83). The OSDD has also led to the development of a novel molecule, PA-824, completed Phase IIB clinical trials and has progressed to Phase III trials across 50 sites (84, 85). This molecule, in a novel combination regimen (pyrazinamide + moxifloxacin + PA-824) can not only treat drug-resistant tuberculosis, but can also potentially reduce the treatment duration of drug-sensitive tuberculosis from 6 months to 2 months.

Initial research in the field of alternative therapeutic approaches to reduce the quantum of antibiotics consumed in India is limited. Although several promising avenues have been identified, there has been limited investment in developing these through directed research activities (86). Some of the strategies that could be explored include – phage therapy (87, 88); bacteriocin (89–92); killing factors (93–95); non-antibiotic drugs with antibacterial properties (96–99); and quorum quenching (86, 100, 101), among others.

## Key messages

- Emergence of resistance against newer classes of antibiotics often used as a last resort like carbapenems indicates the need to not only curb antibiotic use, but also the need to invest in developing newer drug classes.
- Limited interest from the pharmaceutical industry and other private stakeholders in investing on research and innovation to develop newer groups of antimicrobials with innovative mechanisms of action has resulted in the drying up of the antibiotic pipeline.
- The Open Source Drug Discovery (OSDD) initiative, launched by the Council of Scientific and Industrial Research (CSIR) in 2008, which was tasked to identify new treatment regimens, restructured the method of bringing newer drugs to the market by sharing of resources, risks and rewards by crowdsourcing solutions through a network of online and wet-lab collaborators, via a semantic, web-based, wiki portal.
- There is an absence of a strategic R&D agenda for containment of AMR, which should establish a set of needs, and then prioritize these to address the critical gaps in our understanding of the AMR problem and how to contain it.

## 2.8 Financing of AMR containment efforts

The economic consequences of AMR represent a heavy and growing burden requiring urgent action both at national and global levels. In 2013, the World Economic Forum had warned that AMR is one of the major global health security risks with losses of GDP from AMR ranging from 0.4 to 1.6% (102). At present, the annual cost of antibiotic-resistant infections is already estimated to be between US\$21 million and US\$34 million (103).

The Planning Commission (now NITI Aayog) envisioned that in course of the Twelfth Five-Year Plan, the NCDC would provide leadership to the AMR containment programme, in addition to conducting disease surveillance, meeting the needs of International Health Regulations, improving the implementation of existing programmes, and helping in roll out of programmes which were being expanded to the national level (like the rabies control programme, prevention of hepatitis B programme and containment of AMR). To this end, the

Twelfth Five-Year Plan document outlined a proposal to upgrade the existing NCDC facilities and establish another 27 additional units. For the upgradation of the existing facilities, an amount of INR 288 crores was proposed, whilst an additional INR 855 crores was earmarked for the establishment of 27 new branches of NCDC (104).

The Planning Commission further committed INR 112 crores for the initiation of a national AMR containment programme based on the recommendations of the National Task Force which was constituted by MoHFW in August 2010, under the chairmanship of the Director General of Health Services, to frame the national policy for containment of AMR.

The Planning Commission contended that the activities included under the ambit of the programme would include, among others, the following activities: (i) surveillance of AMR; (ii) surveillance of antimicrobial use; (iii) development and implementation of National Infection Control Guidelines and Standard Treatment Guidelines; (iv) operational research on antimicrobial usage, environmental surveillance and AST methodology; and (v) creating awareness among the health care workers and community about rational use of antibiotics (104). The Planning Commission recognised the gap in the Eleventh Five-Year Plan, when no cognizance was taken of the growing menace of AMR.

### *Key messages*

- Financial outlays for system strengthening for AMR containment by the highest policy-making body of the day in India recognize the AMR issue, with heightened political commitment.
- Follow up action on the implementation side will be the key to sustaining political commitment and effective AMR containment.

## 3. Lessons on AMR – disease control programmes

### 3.1 Tuberculosis

Tuberculosis (TB) is an ancient scourge, which has appeared as a renewed threat with the emergence of multidrug-resistant TB (MDR-TB). WHO estimates that globally, in 2014, 5% of new cases and 20% of previously treated cases were likely to suffer from MDR-TB (105). Resistance surveillance data suggest that almost half a million people developed MDR-TB in 2014, 40% of whom eventually succumbed to it (105). Advanced techniques seem to suggest that MDR-TB in the paediatric population is a bigger problem than previous estimates seemed to suggest (106). The even more worrying trend of extensively drug resistant TB (XDR-TB) has also emerged, with 105 countries reporting cases of XDR-TB in 2014 (105). An estimated 9.7% of cases with MDR-TB are suspected to suffer from XDR-TB (107).

The Indian public health system has mounted a systematic response through the Revised National Tuberculosis Control Programme machinery (RNTCP) in order to identify and deal with MDR-TB cases. Some experts have identified MDR-TB control to be an index case that exhibits the challenges and strategies to overcome them, in the context of resistance containment in a diverse country like India (108). In addition, the response to control MDR-TB has also followed a similar approach to the one being adopted by the GAP-AMR – through devising a set of core strategic objectives. The five priority actions identified by WHO in order to address the global MDR-TB crisis include (107):

1. Prevent the development of drug resistance through high quality treatment of drug-susceptible TB.
  - Prevent MDR-TB as a first priority.
2. Expand rapid testing and detection of drug resistant TB cases.
  - Scale up rapid testing and detection of all MDR-TB cases.
3. Provide immediate access to effective treatment and proper care.
  - Ensure prompt access to appropriate MDR-TB care, including adequate supplies of quality drugs and scaled up country capacity to deliver services.
4. Prevent transmission through infection control.

- Implement appropriate TB infection control measures and quickly enrol diagnosed patients on effective treatment to minimize the risk of disease transmission.
5. Increase political commitment with financing.
- Underpin and sustain the MDR-TB response through high-level political commitment, strong leadership across multiple governmental sectors, ever-broadening partnerships, and adequate financing for care and research.

One of the biggest takeaways from the way drug resistant TB has been dealt with has been the systematic identification of implementation gaps, including testing the intermittent regimen and considering moving to a daily regimen in course of the initiation phase of the treatment of drug-susceptible TB (109). Exercises like the “Out of Step” report developed jointly by Médecins Sans Frontières (MSF) and the Stop TB Partnership, conducted an analysis of policies and interventions related to TB prevention and control in 24 high burden countries; the survey revealed implementation gaps and recommended steps to address them (110). A similar task is underway in several countries that have been tasked to develop the NAP-AMR, aligned to the GAP-AMR, in order to streamline the programmatic approach to contain and prevent the emergence of AMR.

Unlike TB, which has a minimal disease load in the developed countries, AMR has been acknowledged to be a problem in both the clinical as well as community settings. This has therefore been helpful in raising political will internationally to treat AMR as a major public health concern. The decision to discuss the issue of AMR at the United Nations General Assembly in New York in September 2016 reflected the urgency to converge on strategies to combat the emergence of AMR (6).

In line with the End TB Strategy (111) and the Global Plan to End TB (112) which articulated time-based targets against which the progress of TB control would be evaluated, the AMR containment programmes should also develop measurable, defined targets. The NAP-AMR can play a role in this, by outlining targets based on each individual nation’s needs and baseline status. Developing a blueprint for dealing with AMR, along with ensuring a mechanism to obtain sustainable funding and garnering sustained political will to support a long-term commitment, would also prove to be crucial cogs in the public health approach. These will help to combat and contain AMR on a national level, especially in low- and middle-income

countries which have a rapidly expanding market, which may precipitate easy access to antibiotics and their irrational use (108).

One particularly successful development in the response to MDR-TB is the presence of advanced diagnostics, which can not only provide a definite diagnosis, but also help in identifying resistant cases. A three-pronged strategy has proven to be of much use in combating MDR-TB: universal access to diagnostic tools to identify the causative agent and its resistance profile; universal access to necessary first line, second line and reserve drugs to treat drug resistant as well susceptible cases of TB; and potent health care systems that can provide adequate, empathetic care. The diagnostic arsenal of point-of-care resistance mapping has been limited, especially in the context of AMR organisms. This area needs to be strengthened in order to reduce the quantum of broad-spectrum or empirical use of antibiotics, which may result in proliferation of resistant clones.

The TB response has further been characterised by the presence of multiple partnerships. Some key successes include the rolling out of GeneXpert diagnostics to developing countries through innovative financing models used by UNITAID with support from the Bill and Melinda Gates Foundation and the US Government. In the BRICS nations, the primary source of funding to fight TB has been from domestic sources, with critical inputs from the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM). The Global Alliance for TB Drug Development (TB Alliance) has also been successful in developing and deploying fixed-dose combinations of anti-TB drugs for pediatric dosages. There are extensive partnerships in research and development related to TB as well; some examples include the Geneva-based Foundation for Innovative New Diagnostics (FIND), which has played a critical role in co-developing GeneXpert and Line Probe Assays (LPAs). Similar collective action is also being mobilized for AMR containment, and although many of the associations in the Indian context are in their infancy, they are a step in the right direction. Developing cross-sectoral teams that can use their sectoral understanding to address the complex reality of AMR is therefore, an important development in the AMR containment process.

Though both TB and bacterial infections are prone to be aggravated by drug resistance, the drivers and determinants of the two conditions – MDR-TB and AMR bacteria – are fundamentally very different. The fact that the rise of AMR bacteria crosses sectors, to include animal health, animal husbandry, agricultural, industrial, environmental and socioeconomic dimensions makes it an infinitely more complex problem to solve. So, despite the MDR-TB

response and the successful implementation and expansion of the RNTCP that can provide a programmatic guideline, they need to be considered as a part of the larger context of AMR being driven by multifactorial, cross-sectoral issues.

## 3.2 Malaria

The Jim O'Neill report on AMR, commissioned by the Prime Minister of the United Kingdom (113) reflects on the impact of emergence of drug resistance on the progress made in malaria control. The report mentions the difficulty in modelling the impact of resistance and the potential outcomes in malaria owing to the complex epidemiology of the disease. This is particularly true because the issue of resistance affects the disease epidemiology at two levels: at the level of the disease-causing pathogen, *Plasmodium spp.*, which is getting resistant to drugs that were previously successfully used in monotherapy for malaria; the other is at the level of the vector mosquitoes, which have largely become resistant to older pesticides which were extensively used on a global level over the past several decades (113). The report ominously warns that the advances made in the control of diseases over the past several decades may all come undone unless the emerging crisis of drug resistance is tackled effectively.

India has successfully raised a public health response to malaria control, but it all may be unravelled if the emerging resistance problem is not tackled proactively. A recent systematic review suggests that continued use of chloroquine for *Plasmodium falciparum* is likely to become ineffective; additionally, concerns about the emergence of resistance against sulfa-pyrimethamine have been raised. The National Vector Borne Disease Control Programme (NVBDCP), the nodal programme for the control of several vector-borne diseases, has come up with a cohesive response to drug resistant malaria. The NVBDCP has addressed malaria control at two levels: vector control, both through preventive measures that reduce breeding of mosquitoes, as well as undertaking efforts to reduce vector density, especially during the peak transmission seasons; the second level approach is to have a flexible treatment protocol, which addresses the local resistance profiles while advising therapeutic decisions. For example, owing to the high levels of chloroquine resistance in general across the North-Eastern states of India, it is imperative to use artemisinin-based combination therapy (ACT) at the first instance of contact between a patient and the health care system.

This approach to develop locally relevant, standard treatment guidelines (STGs) to deal with patients suffering from bacterial and viral infections reflects a flexible and malleable malaria drug policy, which continually tries to keep abreast of the regional or local realities while providing therapeutic guidelines.

Large-scale studies have shown that there are multiple drivers of malarial drug resistance in *Plasmodium spp.*, specifically, with respect to artemisinin derivatives, which have formed an important part of the drug arsenal against malaria. Some of the most common reasons of such drug resistance include: wide availability in the private sector, issues with drug quality, high frequency of usage in wrong dosages, use of monotherapy and inadequate knowledge about the drugs and their mechanisms.

## Key messages

### TUBERCULOSIS

- Emergent MDR-TB and XDR-TB are sources of concern but a systematic response has been mounted through the RNTCP to identify and treat such cases early.
- To approach the issue of drug resistant tuberculosis management in a structured manner, WHO has devised a set of core, strategic objectives. A similar approach has been adopted by the GAP-AMR to streamline the response to emergent AMR. Continuous scrutiny of the programme implementation through monitoring of key indices to identify implementation gaps and address challenges in a timely manner is needed.
- Tuberculosis control was aided by the development of defined, measurable goals, which were to be achieved in a time-bound manner. This, in addition to indices, helped identify critical implementation limitations and address them.
- There has been development and deployment of advanced diagnostics to identify cases of MDR-TB or XDR-TB. Further, employment of innovative funding strategies has led to rolling out of erstwhile expensive diagnostics which have not only sped up identification of resistant cases, but also has increased diagnostic accuracy for identifying them.



## MALARIA

- Resistance is an issue at two levels: vector resistance to pesticides; and pathogen (*Plasmodium spp*) resistance to anti-malarial drugs. Given the epidemiology of malaria, this makes the situation uniquely complex.
- Identification and tracking of local resistance profiles has been closely done through extensive monitoring and evaluation activities. This has, secondarily, led to the designing of standard treatment guidelines that are locally relevant.
- Making high quality anti-malarial agents available and accessible and ensuring that complete course of medications is consumed by the patients has been a key programmatic challenge.

## COMMON POINTS

- Moving from monotherapy to combined drug regimens has been a core strategy in both malaria and tuberculosis control.
- Aside from this, the other common learning points from these programmes are the deployment of targeted diagnostics through the public health system to identify and deal with resistant cases.

## 4. International & bilateral collaborations on AMR

### 4.1 International collaborations

India has some existing international collaborations in the area of antimicrobial resistance.

#### Australia

A collaboration exists between Australian Pharmaceuticals, Public Health Foundation of India and Organisation of Pharmaceutical Producers of India (OPPI).

#### Japan

There is collaboration between ICMR and National Institutes of Infectious Diseases (NIID) of Japan on development of integrated surveillance programme covering epidemiology and genomic data, initiated in April 2016 on the side-lines of the Asian Health Minister's meeting on AMR.

#### Norway

Indo-Norwegian cooperation (Indo-Norwegian Research effort – INNORES) on AMR between the Indian Council of Medical Research in collaboration and the Research Council of Norway was initiated in October 2014. The Indo-Norwegian Meeting on AMR jointly organized by ICMR and Research Council of Norway was held in October 2016.

#### Sweden

Collaboration between the NCDC and Central Drugs Standard Control Organization (CDSCO) and the Public Health Agency of Sweden with a focus on surveillance, especially data analysis, lab strengthening, quality assurance, antimicrobial stewardship, awareness, infection control and regulations, was initiated in 2009.

## The Netherlands

Collaboration exists between the NCDC, Delhi and Netherlands National Institute for Public Health and the Environment (RIVM) and DSM Anti Infection India Limited, which is a leading manufacturer, exporter and supplier of penicillin-based bulk drugs, was initiated in 2014 and focuses on One Health – human-animal-food and environment. The Indo-Dutch meeting on AMR with a One Health approach was organized in December 2016, which reviewed the collaboration and drafted a roadmap to strengthen the collaboration with an action plan.

## United Kingdom

UK is helping to reduce AMR in Indian hospitals in support of the PM's Global Campaign against AMR. This is being supported by a grant from the Foreign and Commonwealth Office Prosperity Fund, British Society for Antimicrobial Chemotherapy (BSAC) under the UK Foreign and Commonwealth Office Prosperity Fund.

Collaboration between the London School of Hygiene and Tropical Medicine (LSHTM) and Public Health Foundation of India (PHFI) and ICMR on research in AMR was initiated in 2014. The UK India Workshop on New Diagnostics and Therapeutics to Tackle Antimicrobial Resistance was organised in New Delhi in October 2015. Collaboration was undertaken between the Research Council of UK and the National Institute for Health and Care Excellence (NICE) with the Departments of Biotechnology and Health Research to organise the Global AMR Summit in London in 2016 and the high-level meeting on AMR at the United Nations General Assembly in 2016.

## United States of America

The US National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Department of Health and Human Services (DHHS) signed a Letter of Intent, under the Indo-U.S. Vaccine Action Program, on AMR research with the Indian Council of Medical Research (ICMR), Ministry of Health and Family Welfare and the Department of Biotechnology, Ministry of Science and Technology, India in June 2015.

USAID in partnership with Government of India provides technical assistance to strengthen capacity of national entities to prevent the rise of antimicrobial resistance in India, ensuring

veterinary related antimicrobial resistance issues are fully represented in the National Action Plan on AMR. USAID's efforts have focused on incorporating inputs and recommendations from the livestock, poultry, fisheries and aquaculture sectors for surveillance and monitoring of AMR and strengthening of governance related to AMR. In collaboration with WHO, NCDC, ICMR and ICAR, USAID provides technical assistance to scale up infection control assessments, strengthen lab capacity to detect AMR and to assess AMR burden at both the national and state level. USAID also collaborates with the private sector on One Health AMR to promote best practices for industry regulation of antibiotic use in animal feed.

In September 2015, the NCDC and ICMR networks (through the All India Institute of Medical Sciences) each initiated AMR collaboration with the US Centers for Disease Control and Prevention (CDC) through the Global Health Security Agenda (GHSA) platform. These initiatives leverage the existing AMR networks to further strengthen, standardize and expand capacity of the public health and health care systems in India to generate, apply and report accurate AMR data, implement appropriate IPC procedures, enhance antimicrobial stewardship practices, and strengthen routine hospital-based surveillance for HAIs. The specific objectives of the GoI/CDC collaborations are:

- Strengthen health care facility IPC programmes based on gaps identified through standardized assessments
- Implement standardized surveillance of HAIs caused by AMR pathogens
- Understand antimicrobial use practices and promote stewardship to improve rational use
- Enhance laboratory surveillance of priority AMR pathogens using externally quality-assured data
- Improve capacity to respond to outbreaks of AMR infections related to health care delivery

In addition, CDC also partners with the Government of Tamil Nadu on AMR, with a focus on district and sub-district level issues, realities and concerns. The goal of this project is to build capacity of the public health system in Tamil Nadu to prevent and control HAIs and reduce the spread of AMR. The project activities focus on district and sub-district level health care facilities in three pilot districts in Tamil Nadu (Tirunelveli, Coimbatore, and Kancheepuram), with an end goal of scaling these activities to other districts and states in India.

There are collaborations between US CDC, WHO Country Office for India and NCDC and Indian Veterinary Research Institute (IVRI) on AMR under GHSA.

## 4.2 Sub-national collaborations

Sub-national collaborations have started to take form only recently. Kerala became the first state to adopt a comprehensive policy for containing AMR by instituting a state-level programme for antibiotic stewardship (114). The programme is expected to shape up in a phased manner, with the allopathic physicians and pharmacists being the target population in the first phase; in subsequent phases issues of veterinary use of antibiotics and prescription of antibiotics by Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homoeopathy (AYUSH) practitioners and unlicensed health care practitioners will be addressed (115).

### Key messages

- In the recent past there has been a ramping up of interest in AMR on a global scale. This has led to fostering of international networks with key Indian institutions. However, the establishment and expansion of these networks should result in actionable knowledge generation, which is locally relevant and feasible.
- At the sub-national level, most of the efforts to contain AMR have been limited to deploying stewardship programmes by individual institutions. There has not been wide-scale adoption of these issues at the state level except for in Kerala, where a systematic stewardship programme was launched in 2016.
- The core principles aligning the national and international networks should be in line with the strategic objectives of the NAP-AMR and the GAP-AMR so that the activities are directly relevant to the programme for containment of AMR in India.

## 5. Conclusion

Historically, AMR has not received adequate focus and attention in India. However, recent trends clearly illustrate the growing political commitment at the highest levels to have a cogent response in place that can provide the necessary gravitas for nation-wide surveillance and stewardship for containment of AMR. Efforts are also being made to incorporate the One Health approach into these plans.

WHO's framework for National Action Plans is a template that can aid in systematically addressing AMR containment in India and make it comparable to global efforts. On 27 September 2016, MoHFW notified three governance mechanisms – an intersectoral coordination committee, a technical advisory group and a core working group on AMR.

The recent UNGA declaration is an opportunity for the technical leadership in India to leverage the current conducive policy environment.

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## 7. Annex

### Summary of regulatory frameworks

– for manufacture, distribution and sale of drugs and pharmaceuticals for human use in India

Drug development stage	Regulatory framework or authority	Level/agencies	Description/roles
Drug control	Central Drugs Standard Control Organization (CDSCO)	MoHFW	<ul style="list-style-type: none"><li>• Approval of new drugs to be introduced in the country</li><li>• Permission to conduct clinical trials</li><li>• Registration and control on the quality of imported drugs</li><li>• Laying down regulatory measures and amendment of Acts and, Rules</li><li>• Laying down standards for drugs, cosmetics, diagnostics and devices, and updating Indian Pharmacopoeia</li><li>• Approval of licenses as the Central Licensing Authority</li><li>• Approving authority for manufacture of drugs</li></ul>
	State Drug Controller	State governments	<ul style="list-style-type: none"><li>• Licensing of manufacturing establishments and sales premises</li><li>• Carrying out inspections of licensed premises for ensuring compliance to conditions of licenses</li><li>• Drawing samples for testing and monitoring the quality of drugs and cosmetics moving in the State</li><li>• Taking appropriate actions like suspension/cancellation of licenses, surveillance over sale of spurious/adulterated drugs</li><li>• Instituting legal action, wherever needed, as provided in the Act and Rules</li></ul>

Drug development stage	Regulatory framework or authority	Level/agencies	Description/roles
			<ul style="list-style-type: none"> <li>Monitoring objectionable advertisements pertaining to drugs</li> </ul>
	National Pharmaceutical Pricing Authority	Ministry of Chemicals & Fertilizers, Department of Pharmaceuticals	<ul style="list-style-type: none"> <li>Monitoring of prices by fixing and revising prices of bulk drugs</li> </ul>
Import of drugs	Drugs and Cosmetics Act Schedule Y (Rules 122A, 122B, 122D, 122DA, 122DAA and 122E) of the Drugs and Cosmetics Rules, 1945	MoHFW	<ul style="list-style-type: none"> <li>Requirement for standards of quality for imported drugs</li> <li>Defines misbranded, adulterated and spurious drugs</li> <li>Rules for prohibition of import of drugs and cosmetics</li> </ul>
Drug manufacture	Schedule M of Drugs and Cosmetics Rule, 1945	MoHFW	<ul style="list-style-type: none"> <li>Requirements of appropriate methodology, systems and procedures, manufacturing premises</li> <li>Documentation and maintenance for inspection and reference</li> </ul>
	Schedule U (Rules 74, 74A, 74-B, 78 and 78A) of Drugs and Cosmetics Rule, 1945	MoHFW	<ul style="list-style-type: none"> <li>Requirements of <ul style="list-style-type: none"> <li>Particulars to be shown in manufacturing records</li> <li>Records of raw materials</li> <li>Particulars to be recorded in the analytical records</li> </ul> </li> </ul>

Drug development stage	Regulatory framework or authority	Level/agencies	Description/roles
Drug quality	The Indian Patent and Design Act, 1970 and as amended (2005)	Department of Industrial Policy and Promotion (Ministry of Commerce and Industry)	<ul style="list-style-type: none"> <li>Provides patent protection for processes (1970) as well as products (2005 amendment)</li> </ul>
	Factories Act 1948	Department of Industrial Policy and Promotion (Ministry of Commerce and Industry)	<ul style="list-style-type: none"> <li>Provides for mandatory structural, manpower and procedural requirements for manufacturing units including those in the pharmaceutical sector</li> </ul>
	Schedule M of Drugs and Cosmetics Rule, 1945	MoHFW	<ul style="list-style-type: none"> <li>Requirements of appropriate methodology, systems and procedures, manufacturing premises</li> <li>Documentation and maintenance for inspection and reference</li> </ul>
	Schedule P of the Drugs and Cosmetics Rules, 1945 [Rule 96]	MoHFW	<ul style="list-style-type: none"> <li>Lays down rules for life period of drugs</li> </ul>
Drug combination	Rule 122 (E) (c) of the Drugs & Cosmetics Rules; principal notification under Section 26-A of the Drugs and Cosmetics Act, 1940	MoHFW	<ul style="list-style-type: none"> <li>Rules for prohibiting manufacture, sale and distribution of certain fixed dose combinations (FDCs), which do not have any therapeutic justification or are likely to involve risk to humans</li> </ul>

Drug development stage	Regulatory framework or authority	Level/agencies	Description/roles
	Schedule-Y of the Drugs & Cosmetics Rules Notification of Licensing Authority under section 21(b) i.e. DCGI (India)	MoHFW	<ul style="list-style-type: none"> <li>Provision for examination of whether FDC is rational or irrational; power of examination of an FDC with the licensing authority</li> </ul>
Drug distribution	Drugs and Cosmetics Act, 1940	MoHFW	
Drug pricing	Drugs (Prices Control) Order 1995 (DPCO), under the Essential Commodities Act (ECA)	NPPA (Ministry of Chemicals and Fertilizers)	<ul style="list-style-type: none"> <li>Outlines classification of price-controlled products and methods of price fixation and revision of bulk drugs</li> </ul>
		Department of Revenue (Ministry of Finance)	<ul style="list-style-type: none"> <li>Fixes customs duty and taxes</li> </ul>
	Industries (Development and Regulation) Act, 1951	Department of Industrial Policy and Promotion (Ministry of Commerce and Industry)	<ul style="list-style-type: none"> <li>Secures equitable distribution and availability at fair prices of any article or class of articles relatable to any scheduled industry for regulating the supply and distribution thereof and trade and commerce therein</li> <li>Authorizes the Centre to control the prices of essential items</li> </ul>
Marketing authorization	Drugs and Cosmetics Act (DCA) and its subordinate legislation, the Drugs and Cosmetics Rules (DCR)	MoHFW, Department of Biotechnology and Ministry of	



Drug development stage	Regulatory framework or authority	Level/agencies	Description/roles
		Environment Forest and Climate Change	
Advertising to the general public on drugs	Drug & Magic Remedies (Objectionable Advertisement) Act	MoHFW	<ul style="list-style-type: none"> <li>Provides list of ailments for which no advertising is permitted</li> <li>Prohibits misleading advertisements, which, directly or indirectly, give false impressions regarding the true character of the drug, make false claims, or are otherwise false or misleading in any particular respect</li> </ul>
Retail sale of drugs	Schedule H and Schedule X of Drugs and Cosmetics Act, 1940	MoHFW	<ul style="list-style-type: none"> <li>Requirements for dispensing drugs under Schedule H and Schedule X</li> <li>Mandatory requirements for labelling</li> </ul>
Counterfeit drugs	Drugs and Cosmetics Act, 1940 as amended (2008)		<ul style="list-style-type: none"> <li>Punishments for the manufacture and sale of sub-standard drugs</li> </ul>
	Trade and Merchandise Marks Act, 1958		<ul style="list-style-type: none"> <li>Prevention of the use of fraudulent marks on merchandise that include drugs and antibiotics and their counterfeit versions</li> </ul>

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