

# Pivotal role of Pharmacovigilance Programme of India in containment of antimicrobial resistance in India

Vijit Agrawal<sup>1,2</sup>, Tarani Prakash Shrivastava<sup>1,2</sup>, Pramod Kumar Adusumilli<sup>1</sup>, Kalaiselvan Vivekanandan<sup>1</sup>, Prasad Thota<sup>1</sup>, Shashi Bhushan<sup>1</sup>

<sup>1</sup>National Coordination Centre, Pharmacovigilance Programme of India, Indian Pharmacopoeia Commission, MoHFW, GoI, Ghaziabad, Uttar Pradesh, <sup>2</sup>Research Scholar, School of Pharmaceutical Sciences, Delhi Pharmaceutical Sciences and Research University, Government of NCT, New Delhi, India

## Abstract

Misuse of antimicrobials has become one of the grave concerns of public health. In last two decades, this has been largely contributing in the emergence of antimicrobial resistance (AMR) among all the pathogens. A 2013 report of Centres for Disease Control and Prevention, USA figured that at least 2 million people get an antibiotic-resistant infection every year and as many as 23,000 people lost their life. A multi-country survey in Southeast Asia region conducted by World Health Organization (WHO) in 2015, identified several gaps in knowledge and awareness about the optimal use of antimicrobials and AMR. Following this, the Ministry of Health and Family Welfare (MoHFW), Government of India, developed National Action Plan in the year 2017 to combat AMR. Pharmacovigilance Programme of India (PvPI) being a flagship programme of MoHFW holds the responsibility of ensuring safety of medicines used by India population and has recently identified AMR as one of the strategic priorities. This article intends to provide insights of the recent attempts and deliberate efforts made by PvPI in the containment of AMR in India and it also intends to sensitize healthcare fraternity on restricting AMR in public interest.

**Keywords:** Adverse drug reaction, antimicrobial resistance, antibiotics, evidence-based medicine, Indian Council of Medical Research, National Health Programmes, pharmacovigilance, Pharmacovigilance Programme of India

**Address for correspondence:** Dr. Prasad Thota, National Coordination Centre, Pharmacovigilance Programme of India, Indian Pharmacopoeia Commission, MoHFW, GoI, Sector-23, Raj Nagar, Ghaziabad - 201 002, Uttar Pradesh, India.  
E-mail: prasad.thota187@gmail.com

## INTRODUCTION

Accepting the 1945 Nobel Prize in Physiology or Medicine, Alexander Fleming raised this concern that irrational practices in the use of antibiotics will eventually lead to the emergence of antimicrobial resistance (AMR) someday.<sup>[1]</sup> A few years later the term AMR surfaced around the world when the discovery of several antibiotics against penicillin-resistant

bacteria has started in the 1960s. However, this has followed a golden era of the development of antibiotics/antimicrobials which shifted the diseases burden from infectious to noncommunicable diseases in at least the developed countries. By the 1980s, development of new antibiotics drastically reduced while the antimicrobial-resistant bacteria became predominant in hospitals.<sup>[2]</sup>

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## CONSEQUENCES OF ANTIMICROBIAL RESISTANCE

Resistance in pathogens against antimicrobials/antibiotics develops naturally over the time. However, misuse or overuse of these agents accelerates the AMR. Inappropriate handling of antibiotics in humans or animals for example using antibiotics in simple cough and cold, over-the-counter (OTC) use without professional guidance and use as growth promoters in animals or to prevent diseases in healthy animals triggers generation of antimicrobial-resistant microbes that are present everywhere including people, food, animals, soil, water, and air.<sup>[3]</sup>

In the last two decades, the AMR has pronounced radically and represents an emerging patient safety concern for present health-care systems around the world. AMR besides threatening the prevention and treatment of increasing range of infections also has laden the governments with increased cost of therapy for treating resistant infections.<sup>[4]</sup> World Health Organization (WHO) estimated that extensively drug-resistant tuberculosis (XDR-TB) in which the bacterium is resistant to at least 4 of the core anti-TB drugs was detected in 105 countries until 2016 and about 10% of the worldwide pool of multidrug-resistant TB patients are already converted into XDR-TB patient every year. Further to this, WHO also reported that AMR has already started to complicate the fight against HIV and malaria.<sup>[5]</sup> To map the AMR research landscape, Department for Biotechnology (DBT), Government of India (GoI), published a report in November 2017 on a targeted study which was conducted by DBT in strategic partnership with Research Councils United Kingdom across India. This report summarized the current AMR situation in India and identified factors such as high consumption of broad-spectrum antibiotics, injudicious use of antibiotic fixed-dose combinations, self-medication, varying knowledge among health-care providers/consumers on the problem of AMR, and lack of Continuing Medical Education (CME) on this problem.<sup>[6]</sup>

## CONTAINMENT OF ANTIMICROBIAL RESISTANCE

Raised concerns on AMR invited a chain of debate among the global health forums and the WHO in 2015 drafted global action plan for combating against this serious public health concern.<sup>[7]</sup>

To embark upon the issue of AMR, India has regarded a due concern and a “National Program on Containment of Antimicrobial Resistance” was launched under the

12<sup>th</sup> five-year plan (2012–2017) of GoI. This national program highlighted its activities as surveillance for containment of AMR in various geographical regions, development and implementation of national infection control guidelines, training and capacity building of professionals in relevant sectors, promotion for rationale prescribing/use of antibiotics, and development of National Repository of Bacterial strains/cultures.<sup>[8,9]</sup> To prevent indiscriminate use of high-end antibiotics, the Indian drug regulatory authority, the Central Drugs Standard Control Organization (CDSCO) has implemented Schedule H<sub>1</sub> in India. Came in effect from March, 2014, this schedule covers 24 antibiotics (falling under the third and fourth generations) available which were sold OTC in India. The drugs covered under schedule H<sub>1</sub> are now restricted for sale on a prescription by a health-care professional only, on providing a valid prescription.<sup>[10]</sup> However, designing and implementing comprehensive surveillance systems that are practical and cost-effective and interlink with the national health-care system is a challenge.<sup>[11]</sup> To overcome these challenges the National Regulatory Authority (NRA) i.e. Central Drugs Standards Control Organization (CDSCO) has taken several stringent steps and policy measures such as; executive orders and regulatory actions directing pharmaceutical supply chain (retailers, chemists, and drug makers) on the sale of antimicrobials restricted under schedule H and H<sub>1</sub> of Drugs and Cosmetics Rules, 1945. Regulatory actions including issuance of notices and advisory to all concerned stakeholders such as the Medical Council of India, the Dental Council of India, the Indian Nursing Council, the Pharmacy Council of India, and the Indian Medical Association (IMA) on the rational use of antibiotics and on limiting/containing AMR have also played a crucial role in sensitizing the health-care professionals.<sup>[12]</sup> To create a nation-wide system for medicines safety reporting/monitoring and to support the CDSCO in the decision-making process on the use of medicine, Pharmacovigilance Programme of India (PvPI) was operationalized in July, 2010, by the Ministry of Health and Family Welfare (MoHFW), GoI with a mission to reduce the risks associated with the use of medicines in Indian population. The AIIMS, New Delhi, was established as the National Coordinating Center for PvPI. Later on, MoHFW, GoI on April 15, 2011, recasted this program and shifted the National Coordination Centre (NCC) from AIIMS, New Delhi, to Indian Pharmacopoeia Commission (IPC), Ghaziabad. NCC-PvPI collects, collates, and evaluates spontaneous reports of ADRs due to use of medicines, vaccines, medical devices, and herbal products from all health-care professionals and consumers/patients; besides this, NCC-PvPI also holds the responsibility of continuously updating and sensitizing stakeholders on the issues relating

to the safety and efficacy of drugs.<sup>[13]</sup> As the AMR not only affects efficacy but also the safety of antibiotics, PvPI has taken several initiatives to curb the menace of AMR in India, and the present article intends to endow with various initiatives taken by PvPI in the containment of AMR in the country.

### **ROLE OF PHARMACOVIGILANCE PROGRAMME OF INDIA**

PvPI is a flagship program under the aegis of MoHFW; GoI is working with the sole conviction to identify, monitor, prevent adverse drug reactions (ADR) associated with medications prescribed in India, and to promote patient safety. The main objective of the PvPI is to identify signals and to minimize the risk associated with the use of medications in the public of India.<sup>[13,14]</sup> At present, 250 ADR monitoring centers (AMCs) are working under the umbrella of PvPI to monitor and report ADRs to NCC-PvPI. The program is steered from IPC, Ghaziabad. These AMCs cover government and private teaching hospitals, corporate hospitals, specialized hospitals, government general hospitals, TB and HIV treatment center etc.<sup>[15]</sup>

Capacity building, strengthening legislation, and stakeholder coordination/cooperation are the crucial force behind the development of pharmacovigilance. NCC-PvPI, IPC is the apex body for creating awareness, and strengthening the pharmacovigilance has taken many steps. One such landmark achievement is the commencement of Skill Development Program on “Basics and Regulatory Aspects of Pharmacovigilance” to enhance the skills of the workforce engaged in pharmaceutical industry and to effectively meet quality standards.<sup>[16]</sup>

PvPI works closely with AMCs, Indian Council of Medical Research, IMA and has harnessed their potential in creating awareness on reporting of ADRs and prudent use of antibiotics. Now, with the advent of a more difficult problem of AMR as a patient safety concern, the NCC has taken pledge to sensitize all the stakeholders in this regard. Following initiatives have been taken by NCC-PvPI to prevent the occurrence of AMR in Indian population.

#### **Inclusion of an appendix on antimicrobial resistance in the National Formulary of India**

National Formulary of India is a reference document published by IPC for the health-care professionals which provides the standards/statutory provisions/requirements based on the Drugs and Cosmetic Act 1940 and Rules 1945.

PvPI provides regular updates to IPC regarding the emergent situation on AMR in the country which is reported by the 250

AMCs under PvPI. The collated data showed the emergency to include an appendix in NFI which has its outreach to the maximum health-care professionals. Adopting the policy as per the National Strategic Plan to contain AMR, the recent edition (5<sup>th</sup> edition) of NFI-2016 has included an appendix stating the mechanisms involved in AMR and conveys the strategies to prevent AMR in health-care settings. As this reference document has a widespread acceptance among health-care professionals, the appendix dedicated to address the AMR may be of great value in the containment of resistance to the antimicrobial agents.<sup>[17]</sup>

#### **Expanding the scope of pharmacovigilance to monitor antimicrobial resistance**

The problem of antimicrobial resistance invites standardization of the guidelines, in considering antibiotic usage, curbing the use of antibiotics by prohibiting them to be sold as OTC medications, forbidding or limiting the usage of antibiotics as growth promoters in livestock. Considering the currently existing practices, the National Health Policy-2017 advocated to enhance the scope of current Pharmacovigilance practices to include prescription audits and evaluation of antibiotic usage in hospitals and community.<sup>[18]</sup>

There exists a network of 250 AMCs under the umbrella of PvPI, which utilizes Vigiflow® (web-based Individual Case Safety Report [ICSR] management system) for reporting ADRs and drug-related problems. The ICSRs received at NCC-PvPI are collated, analyzed and submitted to NRA for necessary action(s)/intervention(s). PvPI also regularly publishes various resource materials for updating the stakeholders (physicians, pharmacists, nurses, etc) regarding the drug safety information. A study of PvPI database on pattern of ADRs occurred due to OTC usage of drugs identified that more than 40% of the ADRs were associated with the inappropriate use of antibiotics which were used without prescription. This study was published in the PvPI newsletter (Vol. 6, Issue. 16, 2016) which helps to enhance the awareness about the consequence related to the misuse of antibiotics.<sup>[19]</sup> Based on such data, PvPI recently updated the modules of trainings such as CME, advance level trainings, and the skill development program to include AMR as a part of the training and the dedicated technical sessions on the menace of AMR, and pharmacovigilance during outbreaks was made as essential components. These advancements in the training courses shall contribute in the containment of AMR and to manage other drug-related problems.

#### **Research-based pharmacovigilance to address antimicrobial resistance**

In order to strengthen the understanding of antibiotic

resistance and promoting rational use of antimicrobials NCC-PvPI, IPC has recently collaborated with the Department of Microbiology, Nizam Institute of Medical Sciences, Hyderabad, and National Institute for Research in Tuberculosis, Chennai. PvPI has directed its efforts in promoting patient safety through focused pharmacovigilance of antimicrobials and recommended health-care professionals to practice evidence-based medicine.<sup>[20]</sup>

The collaborating centers will initiate research in pharmacovigilance in accordance with their core area of competence to address the gaps and needs that may be fulfilled by the respective institution. These institutions are at the pinnacle of their expertise. These institutes are provided with the data received by the PvPI so that they can inoculate the basic predicament behind AMR and help in its containment. The collaborations of PvPI in this regard will be highly beneficial in generating the database on the ADRs associated with the misuse of antimicrobial agents and to address AMR effectively.

#### Pharmacovigilance in Public Health Programs

National Health Programmes including Revised National TB Control Program, Antiretroviral Therapy under National AIDS Control Organization, Adverse Event Following Immunization, and National Vector Borne Disease Control Program have been collaborated with PvPI. The ADR reports are being submitted by these programs, and PvPI in collaboration with the WHO country office India provides technical support to these programs with a periodic analysis of received ADRs so that better health outcomes can be achieved in Indian population. The major goal of integrating the pharmacovigilance in public health programs is to identify the cause of resistance to the medicines used in the program, e.g., antitubercular medicines.<sup>[16,21]</sup>

This targeted approach will not only address the patterns of ADRs but also it will identify the trends of resistance to antimicrobials in local communities across the country. Further, this also will enable the HCPs to understand the crisis of educating the patients in rural and urban areas on AMR.

#### Collaboration of Pharmacovigilance Programme of India with National Accreditation Board for Hospitals and Health-care Providers accredited Hospitals

Hospitals are a critical component of the AMR problem in the country. The combination of highly susceptible patients, intensive and prolonged antimicrobial use, and cross-infection has resulted into an higher prevalence

rate of infections majorly acquired due to highly resistant bacteria pathogens. Hospitals are also the eventual site of treatment for many patients with severe infections due to resistant pathogens acquired in the community. To achieve the objectives as per the established infection control programs, it is sought that AMR is managed effectively based on current best practices and all the hospitals have easy access to such programs. Establishment of effective hospital therapeutics committees with the responsibility for overseeing antimicrobial use in hospitals will provide a great support in developing and regularly updating guidelines for usage of antimicrobials in treatment and prophylaxis. Keeping this in view, IPC signed a Memorandum of Understanding (MoU) with the National Accreditation Board for Hospitals and Healthcare Providers (NABH) on January 10, 2017. The objective of this MoU between IPC and NABH is to promote monitoring and reporting of ADRs by NABH-accredited hospitals to PvPI. To train the NABH-accredited hospitals staff on pharmacovigilance, PvPI has imitated series of workshop-cum-training program which is being organized throughout the country.<sup>[22]</sup> These trainings provide a platform for the participants from NABH-accredited hospitals to not only understand the system and procedures involved in ADR-reporting but also the modules are being updated so as to cover AMR as one of the topics for enhancing awareness to curtail the consequences of AMR.

#### Outreach of Pharmacovigilance Programme of India to rural masses

Patient-related factors are major drivers of inappropriate antimicrobial use and therefore contribute to the increasing prevalence of AMR. In particular, the perception of patients that most episodes of suspected infection require antimicrobial therapy notably influences the prescribing practices of providers. The direct-to-consumer marketing by the pharmaceutical industry increasingly influences patient expectations and behavior. Patients commonly misunderstand the pharmacological actions of antimicrobial agents. Experience suggests that many people do not know the difference between antimicrobials and other classes of drugs and thus are not able to understand the issues of resistance uniquely related to antimicrobials. Catering to public health safety at microlevel and for optimization of drug safety by evidence-based research, PvPI has recently extended its coverage to district-level hospitals. In the first phase of this expansion, seven new district-level AMCs were set up in eastern Uttar Pradesh during the year 2017. The primary objectives of covering district-level hospitals include raising awareness level for safe drug use among rural masses, widening the health-care professionals' base for PV activity which will not only provide public access



to ADR-reporting but will also help generate better PV network connectivity. Awareness campaigns and workshops at microlevel will be helpful to cover menace of AMR.<sup>[23]</sup> These campaigns shall be helpful for the HCPs as well as for the consumers for better adherence with the antimicrobial therapy and limit the inappropriate usage of antibiotics.

## CONCLUSION

The intent of present work is to sensitize and aware the readers, including health-care professionals from all disciplines-medical, pharmacy, nursing about the rational use of antibiotics, so as to curb the menace of AMR in public interest. The main functions of PvPI to eradicate AMR are to educate, train, and motivate all stakeholders in rational and appropriate usage of antibiotics. PvPI through its continuous efforts such as recommendation for regulatory intervention, training, social awareness, and educational approach is striving hard to curb the menace of AMR. To combat AMR, we must strengthen pharmacovigilance activities at national, regional, and district levels to safeguard public health. It is need of the hour to educate both health-care and non-health-care professionals for the rational use of antimicrobials in our country.

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## Conflicts of interest

There are no conflicts of interest.

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