Table with legends

Table 1: Chronological development of Pharmacovigilance Program in India and abroad

Year	Event(s)/Activities	References
1888	• **Major Laurie,** a Surgeon of Hyderabad Medical School, performed a study on 40,000 patients to check the cardiac side effects of anaesthetic agent **chloroform** and confirmed that it is **safe** • Laurie's study disproof the report of Glasgow Committee about lack of safety of chloroform as compare to ether	[12]
1937	• Improperly prepared **sulfanilamide elixir containing Di-ethylene glycol** used for the treatment of streptococcal infections. • It caused mass poisoning in the US in **1937.** • Due to this >100 people died. • Therefore, American Congress approved Food Drug and Cosmetic Act in **1938** to ensure safety of the drug before marketing	[13, 14]
1950	• Report of aplastic anemia as ADR after chloramphenicol use	[15]
1957-1962	• **Thalidomide** launched in **1957** and marketed in 46 countries for morning sickness and nausea. • Use of thalidomide results in a severe birth defect called **phocomaelia**. • Then, it was discontinued in **1962 a**fter reporting **several cases of phocomaelia (20,000 cases)**	[16, 17]
1963	• Decided to take rapid action on ADRs in 16th World Health Assembly • Kefauver- Harris amendment was approved • It is meant for the requirement of sufficient data of safety and efficacy of drugs before testing in humans.	[15]
1964	• UK starts the **"YELLOW CARDS"** system • This card is a specific form to compile a spontaneous report of drug toxicity	[18]
1968	• The Thalidomide tragedy was the milestone in the origin of Pharmacovigilance. • Formation of WHO Programme for International Drug Monitoring (IDM). • 10 countries took part in this program at its infancy • WHO programme for International Drug Monitoring (IDM) is now coordinated with the Uppsala Monitoring Centre (UMC) in Uppsala, Sweden (UMC also known as IMC) • UMC uses VigiBase software to record the ADRs. • The programme has expanded to more than 86 countries.	[19]
1975	• First PubMed indexed case series on ADRs of 338 patients were reported and	[20]

	admitted to the general medical ward due to ADRs	
1983	• A formal ADR monitoring system was established by Dr. Molly Thomas at Christian Medical College, Vellore, India to spread knowledge about ADRs and its reporting	[21]
1986	• India proposed ADR monitoring system comprising of 12 regional centre with population sizes of approximately 50 million each	[22]
1989	• **6 regional centers** were set up under the aegis of Drug Controller General of India • **ICMR** started **12 centers** as Multicenter project to strengthen the PV in India by improving the ADRs reporting	[15, 23]
1992	• A task force project on ADRs was initiated by ICMR and identified the gaps in ADRs reporting mechanism • In **1992** The European Society of Pharmacovigilance **(ESOP)** was introduced	**[9, 21, 24]**
1996	• Start of Clinical trials in India	[15]
1997	• India joined WHO Adverse Drug Monitoring Reactions (ADRs) programme based in Uppsala, Sweden. • 6 more centers were set up in the country including AIIMS, KEM etc.	[21, 25]
1998	• Establishment of 'Society for Pharmacovigilance, India' in Aligarh, Uttar Pradesh • Initiation of Pharmacovigilance in India	[15, 21, 26]
2002	• Establishment of 67th National Pharmacovigilance Center in India	[15]
2005	• On **January 1, 2005** National Pharmacovigilance Programme of India (NPVP) sponsored by WHO and World Bank was started. • NPVP was started with 2 zonal, 5 regional and 24 peripheral centers • On **January 20, 2005,** Schedule Y was amended to ensure the effective compliance of PV by pharmaceutical industries. • Starting of structured clinical trials activities.	**[3, 15]** **.**
2010	• On **July 14, 2010,** Government of India initiated Pharmacovigilance Programme of India (PVPI) with AIIMS, New Delhi as the National Coordination Centre (NCC). • Total 22 ADR monitoring centers were established including AIIMS, New Delhi	[27, 28]
2011	• On **April 15, 2011**, Indian Pharmacopoeia Commission (IPC), Ghaziabad, Uttar Pradesh was designated as NCC under the aegis of Drug Controller General of India	[29]
2012	• On December 10, 2012, IPC launched Haemovigilance Programme of India (HVPI) in collaboration with National Institute of Biologics (NIB), Noida. • The main objective of HVPI is to monitor and record ADRs associated with blood transfusion and blood products administration. • NIB developed "Haemo-Vigil" software to collect ADRs from 90 Medical institutes in the country enrolled under this program	[30]
2013	• Starting of a toll-free helpline number for ADRs reporting	[31]

	• Revised National Tuberculosis Control Program (RNTCP) linked with PvPI to monitor and report ADRs associated with anti-TB drugs.	
2014	• National AIDS Control Organization (NACO) linked with PvPI to monitor and report ADRs associated with anti-retroviral drugs. • In **May 2014**, NCC received about 3,537 Individual Case Safety Reports (ICSRs) and 1,948 Adverse Events Following Immunization (AEFI) from AMCs. • UMC, Sweden has also given access to VigiFlow to **7 more AMCs**. • VigiFlow is functional in total **97 AMCs** but 82 centers have used VigiFlow to submit ADR's report.	[15, 31]
2015	• Launched 'Materiovigilance Program of India (MVPI)' and development of a separate specific to monitor the safety of medical devices • WHO launched VigiAccess web application where anyone can obtain information about ADRs available at UMC and to encourage for the reporting of ADRs of medicinal products	[19, 32]
2016	• Drugs and Cosmetic Act 1940 made mandatory to have Pharmacovigilance cells in the organizations of manufacturers and importers • 123countries joined the WHO PIDM programme	[28, 33]
2017	• On **January 10, 2017**, IPC signed MoU with the National Accreditation Board for Hospitals and Healthcare (NABH) to encourage monitoring and reporting of ADRs by NABH-accredited hospitals Commencement of **skills development program** in whole country on 'Basics and Regulatory Aspects of Pharmacovigilance' • On **October 30, 2017**, WHO established its first WHO Collaborating Centre for Pharmacovigilance Public Health Programs and Regulatory Services in India at National Coordinating Center, IPC, Ghaziabad • Launched National Strategic Plan to strengthen the PV in India • Pharmacovigilance guidelines was launched for the stakeholders	[21, 34, 35]
2018	• 250 AMCs established to monitor serious ADRs • Report of contamination of N-nitrosodimethylamine (NMDA) which is a known carcinogen in formulation containing valsartan.	[17, 36]
2019	• IPC identified 22 more AMCs and 13 medical device monitoring centers (MDMCs) with aim to improve the quality and quantity of ADRs and SAEs data • IPC collaborated with Centre for Cellular and Molecular Biology (CCMB) Hyderabad, Institute of Microbial Technology (IMTech), Chandigarh, Punjab University for further strengthen the PvPI • SCTIMST, Thiruvananthapuram designated as the collaborating centre under Materiovigilance Programme of India (MvPI) • Report of contamination of known carcinogen N-nitrosodimethylamine (NMDA) in Zantac brand containing ranitidine.	[17, 37, 38]
2020	• Setting up to 300 AMCs focusing NE regions by 2020.	[39]

	• Plan to utilize artificial intelligence (AI) to analyze ADRs data at IPC, Ghaziabad under PvPI	

Table 2: Studies conducted on ADRs monitoring and reporting in urban and rural areas of India

Study Area	Place of study	No. of Patients involved/ HCPs	Suspected ADR reported	Reported by	Reporting mechanism/ method	Remarks	References
Urban	Tertiary care hospital, Pt. J.N.M. Medical College, Raipur (Chhattisgarh)	532,514	232 ICSRs	Doctors, Nurses, Patients	Spontaneous reporting	▪ ADRs occurs due to Polypharmacy ▪ Under-reporting observed due to unawareness about ADRs reporting, poor literacy and high workload of HCPs	[59]
Urban	Rajiv Gandhi Institute of Medical Sciences (RIMS) General hospital at Kadapa district, Andhra Pradesh, India	Not mentioned	254	Physician, Nurses, PharmD students, Clinical Pharmacists	Suspected ADR reporting form filling (Spontaneous reporting)	▪ Under-reporting due to lack of aptitude of HCPs, time constraint, non-accessibility of ADR reporting forms, lack of incentives ▪ ADRs occurrence can be reduce by proper examination of patient history and monitoring by HCPs	[60]
Urban	Tertiary care teaching hospital from north India	Not mentioned	2,586	HCPs	Suspected ADR reporting form filling (Spontaneous reporting)	▪ ADRs occur due to antimicrobials	[61]
Urban	Dhanalakshmi Srinivasan Medical College and Hospital (DSMCH), Perambalur (Tamil Nadu)	101 (including HCPs)	Not mentioned	Not mentioned	Questionnaire based interview	▪ Deficiency of actual ADR reporting practices among HCPs	[62]

Urban	North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences, Mawdiangdiang, Shillong, Meghalaya	119	106	HCPs	Suspected ADR reporting form filling (Spontaneous reporting)	▪ Active monitoring is important for early detection, assessment and prevention of ADRs	[63]
Urban	Govt. Medical College, Vadodara, Gujarat	101 (including PG students)	Not mentioned	Not mentioned	Questionnaire based interview	▪ PG students have good attitude toward ADRs reporting but lacks knowledge and poor practice of ADRs reporting	[48]
Urban	Hakeem Abdul Hameed (HAH) Centenary Hospital, Jamia Hamdard, New Delhi, India	220	26	HCPs	Suspected ADR reporting form filling (Spontaneous reporting)	▪ Lack of information about prescribed drugs and their associated side effects ▪ Assessment of ADRs is important to ensure safety of the drugs	[64]
Urban Slum	Mehrauli, Khanpur, and Tigri, Primary Health Centers (PHCs),South Delhi, India	316	224	HCPs	Suspected ADR reporting form filling (Spontaneous reporting)	▪ Diabetes mellitus (DM) influences the incidence of ADR	[65]
Urban	ART centre GMC Jammu, India Under National AIDS Control Organization (NACO), Jammu	106	119	HCPs	Suspected ADR reporting form filling (Spontaneous reporting)	▪ Suggested the importance of collaboration of NACO with PvPI to enhance drug safety	[66]
Urban	Pharmacology Department and Chest Medicine Department of a tertiary care hospital, Kolkata, India	296	312	HCPs	Suspected ADR reporting form filling (Spontaneous reporting)	▪ Stressed upon the regular monitoring of ADR to decrease the development of resistance and morbidity among patients with ADRs	[67]
Urban	Postgraduate Institute of Medical Education and Research, Chandigarh	174	152	Doctors, Nurses	Suspected ADR reporting form filling (Spontaneous reporting)	▪ Study suggested that cancer chemotherapy is often associated with ADRs even in monotherapy	[68]
Urban	Tertiary care hospital, Pt. B.D. Sharma PGIMS,	235	181	HCPs	spontaneous/ solicited monitoring	▪ Potential ADRs associated with drugs used in the treatment of gynaecological disorders	[69]

	Rohtak (Haryana)					should be considered before prescribing	
Urban	Department of Dermatology and Venereology, Government Medical College, Trivandrum, Kerala, India	901	28	HCPs	Suspected ADR reporting form filling (Spontaneous reporting)	▪ Study showed the lower ADR cases associated multidrug therapy (MDT)	[70]
Urban	Mahatma Gandhi Memorial Hospital,Warangal, Telangana, India	201	3370	HCPs including Clinical Pharmacists	Questionnaire based	▪ Suggested to provide educational training to HCPs identify and report ADRs. ▪ Proposed to recruit clinical pharmacists in every specialty division to solve the under-reporting problem	[71]
Urban	Private hospitals/clinics of Bhubaneswar and Cuttack, Odisha	124 Doctors	Not mentioned	HCPs	Semi-structured Questionnaire	▪ Good attitude among private health care Practitioners toward PvPI but adequate awareness required ▪ Easy availability of suspected ADR form at the site of reporting and optimum educational interventions through media can increase the reporting	[46]
Urban	Department of Neurology of Dr. Ram Manohar Lohia Hospital, New Delhi	30	30	HCPs	Preformed Questionnaire interview	▪ Study suggested about spreading awareness of ADR reporting directly to the Government through Toll-free number (18001803024), ADR application, emails and social media.	[72]
Urban	Departments of Radiotherapy and Hemato-Oncology, AIIMS Rishikesh	500	665	HCPs	Suspected ADR reporting form filling (Spontaneous reporting)	▪ Data were collected from patients and existing medical records. ▪ Safety data regarding use of anticancer drugs are required to alert the doctors at its recurrence	[73]
Urban	Cancer radiotherapy Department, Maulana Azad Medical College and Lok Nayak hospital, New Delhi,	101	Not mentioned	HCPs	Suspected ADR reporting form filling (Spontaneous reporting)	▪ About 95% patients experience ADRs associated with the use of anticancer drugs	[74]

Urban	Dharmapuri and Krishnagiri districts in Tamil Nadu	264 HCPs	Not mentioned	HCPs	Questionnaire based	▪ Demonstrated a lack of knowledge and awareness of PV and ADRs reporting among HCPs ▪ Suggested to establish a ADR monitoring centre near to Dharmapuri and Krishnagiri area	[75]
Urban	HNB Base & Teaching Hospital, Pauri Garhwal, Uttarakhand	>100	111	HCPs	Suspected ADR reporting form filling (Spontaneous reporting)	▪ Cutaneous ADRs (CADRs) occurred due to the drugs prescribed by the physician therefore it is important to make aware the physician about early detection of CADRs. ▪ Study indicated that physician should be encouraged to report ADRs.	[76]
Urban	Department of Pharmacology, Pt. BDS. PGIMS, Rohtak	859	600	Clinical Pharmacologists	Suspected ADR reporting form filling (Spontaneous reporting)	▪ Early detection and prevention of ADR is important to generate signal and to help the regulatory bodies to make policy decision ▪ Urged to conduct awareness program on risk factors and in-depth knowledge about ADRs	[77]
Urban and Rural	SRM Medical College and Research Centre, Tamil Nadu, India	250	09	HCPs	Suspected ADR reporting form filling (Spontaneous reporting)	▪ Lack of awareness about process of ADEs reporting, consumer-based reporting and benefits of ADEs reporting. ▪ Educational interventions useful to increase awareness about ADR reporting and its importance among patients	[78]
Urban and Rural	Department of Pediatrics, SMGS Hospital, Jammu	104	Not mentioned	HCPs	Suspected ADR reporting form filling (Spontaneous reporting)	▪ Urged to conduct rigid ADR monitoring and reporting in pediatric patients ▪ Suggested to organize awareness programme to encourage spontaneous reporting	[79]

Urban and Rural	Tertiary care teaching hospital, Pramukhswami Medical College (PSMC), Gujarat	150	Not mentioned	Pharmacologists	Questionnaire based study	▪ Non-awareness about ADR reporting center ▪ Educational intervention is important for awareness about ADRs reporting	[52]
Urban and Rural	Department of Pharmacology, Pramukhswami Medical College (PSMC), Gujarat (tertiary-care rural hospital)	150	Not mentioned	HCPs	Questionnaire based (In regional language i.e. Gujrati)	▪ Educational interventions are important to make aware the patients about ADR reporting and its importance	[52]
Rural	Shree Krishna Hospital (SKH) rural tertiary care teaching hospital attached to Pramukhswami Medical College(PSMC), Karamsad	600	18	Physicians and Investigators	Structured and pre-tested format or proforma	▪ Demonstrated the importance of PV in ADR reporting	[80]
Rural	Adichunchanagiri Institute of Medical Sciences (AIMS), B G Nagar, Mandya, Karnatka	94 Nurses	Not mentioned	Nurses	Questionnaire based	▪ Findings pointed out toward under-reporting due to lack of proper knowledge about ADR reporting procedure. ▪ Most of the nurses have good knowledge and attitude toward PV and the importance of ADR reporting. ▪ Study also suggested that there should be awareness program like training and continuous medical education (CME) to improve knowledge about PV and ADRs reporting procedures.	[81]
Rural	Department of Pharmacology and Department of Dermatology MSDS Medical College, Fatehgarh	7692	23	Doctors, residents, interns and students	Suspected ADR reporting form filling (Spontaneous reporting)	▪ Signified the PV activities in increasing ADR reporting effectively	[82]
Rural	Department of Pharmacology,	Not mentioned	30	HCPs	Suspected ADR	▪ Indicated for early detection and regular	[83]

	Kamineni Institute of Medical Sciences, Narketpally, Nalgonda, INDIA				reporting form filling (Spontaneous reporting), yellow adverse drug reactions forms, through physicians and patient records	monitoring of ADRs associated with prescribed drugs to reduce mortality, morbidity and cost of the treatment ▪ Under-reporting is the main challenge and ADR reporting can be enhance by making aware the HCPs about it	
Rural	Swami Ramanand Teerth Rural Government Medical College, Ambajogai, Maharashtra	51	31	HCPs	Suspected ADR reporting form filling (Spontaneous reporting)	▪ Suggested to document the ADRs associated with anti-snake venom	[84]
Rural	Pravara Rural Hospital, Loni	40	Not mentioned	HCPs	Suspected ADR reporting form filling (Spontaneous reporting)	▪ Results indicated the under-reporting problem and suggested to encourage the HCPs about ADR reporting importance	[57]
Rural	Doctors in rural area of Thane and Raigad districts, Maharashtra, India	143 Doctors	Not required	HCPs	Questionnaire based	▪ Results suggested that continued educational interventions are the important tools to improve awareness about PV in rural areas	[54]
Rural	Department of Pharmacology, Kamineni Institute of Medical Sciences, Narketpally, Nalgonda, INDIA	Not mentioned	175	HCPs	Yellow forms dropped in the red ADR boxes in all wards	▪ Awareness is important to educate the HCPs about rational use of polypharmacy to reduce ADR.	[85]

Table 3: Comparison of ADR reporting related parameters in urban and rural areas

Parameters of Comparison	URBAN AREAS	RURAL AREAS
Reporting mechanism	There are systematic methods of reporting.	There are no systematic methods of reporting
Awareness about ADRs & its reporting	Most of the people are aware about the ADR reporting and its importance	Majority is unaware about ADR reporting and its significance.

Role of Patients	Patient can directly report ADR to NCC-PvPI	Patients do not know that they can directly report to NCC-PvPI
Role of People	People are getting education about pharmacovigilance	Lack of knowledge of pharmacovigilance
Role of HCPs	HCPs are more trained in PV and active in ADR reporting	Most of the HCPs are unaware and those who are aware are not active in ADR reporting.
Resources for PV programme	The resources are adequate as well as prominent	There are lack of adequate resources in rural areas

Table 4: Challenges and possible approaches to solve the issues of PV in rural areas of India

Challenges	Possible Approaches
Lack of awareness among common people and healthcare professionals (HCPs)	Organization of training and awareness program about PvPI by trained professionals
Lack of robust PV database	Easy accessibility of PV database
Inadequate training of healthcare professionals	Appointment of Pharmacologist as PV officer at district and tehsil level
Gap in reporting mechanism	Display of ADR reporting toll free number at every primary health care centre (PHC) and gram panchayat
Inadequate healthcare professionals in remote areas	Appointment of trained clinical pharmacist at village level for ADR collection and reporting
Self-medication by patient	Proper guidance for self-medication
Communication gap between people and HCPs	Establishment of effective communication through toll free number, android App, text and voice messages in local languages using phone
Inadequate facilities	Utilization of existing of PHC
Under-reporting	Use of reporting form, electronic medical record, feedback system, telecommunication, collaboration to enhance ADR reporting
Inadequate warning on label of drug insert	Prior intimation of warning of possible side effects

by HCPs

Use of Health ID Card, prepared under National Digital Health Mission, to extract patients details including ADRs

Use of artificial intelligence (AI)

Easy and simplified ADR reporting mechanism