EIGHTH ISSUE
JUNE 2020

PHARMACOALERT

NEWSLETTER

Drug Safety Alert, New Drug Marketed, Drug Interactions And Banned Drugs

Contents

- A Glance at the Race to Develop Antibody Drugs for COVID-19
- Repurposed Antibody drugs in COVID-19
- Vaccine : The Final Hope in fight against Novel Coronavirus
- Promising Vaccine candidates in clinical evaluation
- Impact of Pharmacovigilance on Public programmes
- New Drugs Approved

PUBLISHED MONTHLY BY
DEPARTMENT OF PHARMACOLOGY
DR RAM MANOHAR LOHIA INSTITUTE
OF MEDICAL SCIENCES
LUCKNOW

From The Desk of Editorial Team

The department of Pharmacology, Dr. RMLIMS, Lucknow, is pleased to present the June issue of our newsletter.

We have tried to put together articles which have aroused serious interest like- Use of monoclonal antibodies in COVID-19 which has been dealt in the article A Glance at the race to develop antibody drugs for COVID -19. Also an effort has been made to tabulate the already approved monoclonal antibodies which have been repurposed to be used in COVID -19 and have been touted to have some beneficial effect.

A dedicated feature article on the current status of vaccine development against novel Coronavirus has also been incorporated. We have also tried to share the relevant information including the expected route of administration and the number of dose regarding the promising vaccine candidates in clinical trials

It took ardours effort to bring them together with the amount of ever changing scenario and lack of authentic evidences, still we have tried to put together and tabulate them. It may be possible by the time this newsletter reaches you some new therapies may have come or some old drugs again repurposed to be used thus please ignore any anomalies as with every second ticking, we have new information.

Our article on Impact of Pharmacovigilance on Public Health Programmes is also of great importance in present times as it may hold the key to safe and rational use of drugs among masses in future and may be a great tool for tackling pandemics like Covid-19 in future.

We are thankful to our readers for constantly sharing their thoughts and feedback. We are overwhelmed by the numerous mails we receive not only from our colleagues but our fellow pharmacologists from other institutes and colleges too. We hope to receive your love and attention for our forthcoming issues too.

The pandemic has pushed us into maintaining good hand hygiene, use of mask, proper sanitation, social distancing, but the challenge is also to remain connected via the internet and isolate COVID-19 thus we shall continue sharing our newsletter in soft copy through your email.

With the same hope and resolution Stay Safe and Hope we soon emerge victorious against this unseen enemy of mankind.

A GLANCE AT THE RACE TO DEVELOP ANTIBODY DRUG AGAINST NOVEL CORONA VIRUS

The coronavirus disease 2019 (COVID-19) pandemic has created a worldwide crisis and there is an urgent search for prevention and treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection. Immense attention on the development of vaccines, new antiviral agents, monoclonal antibodies and convalescent plasma infusions has been on focus worldwide. Neutralizing monoclonal antibodies are a key component of protective immunity for most viral diseases and in regards to SARS-CoV-2, it has the potential for both therapeutic and prophylactic applications, and can help to guide vaccine design and development. The main target of SARS-CoV-2 neutralizing monoclonal antibodies is the surface spike glycoprotein that mediates viral entry into host cells. Essentially all monoclonal antibodies of interest target this protein. Viral infection is mediated by the interaction between the viral spike and the angiotensin-converting enzyme 2 (ACE 2) receptor found on numerous cell types, but neutralizing monoclonal antibodies block this event.

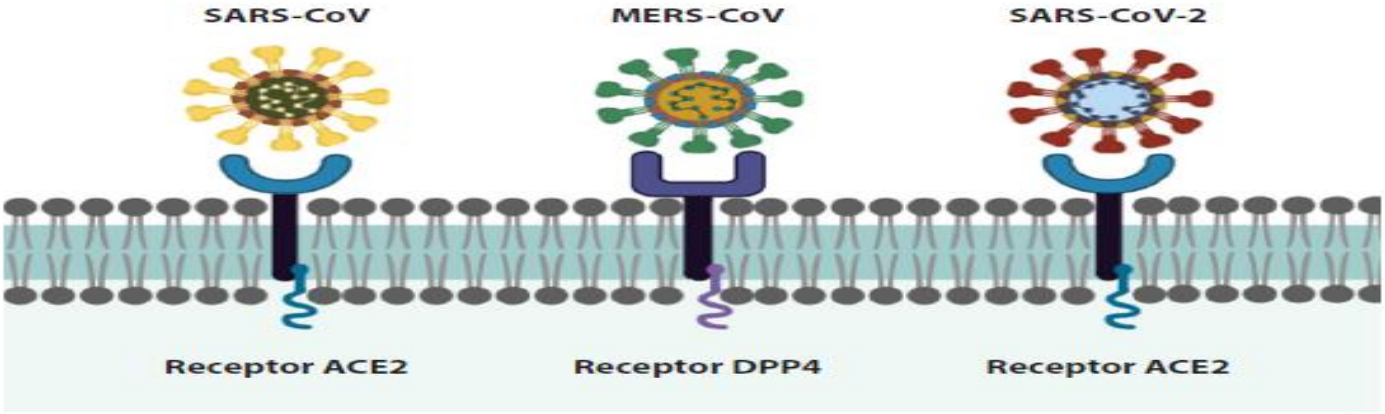


Figure 1: Graphical Representation of SARS CoV, MERS CoV and SARS CoV 2 and its cellular receptor Credit: B.Shanmugaraj et al. APJIAI,2020

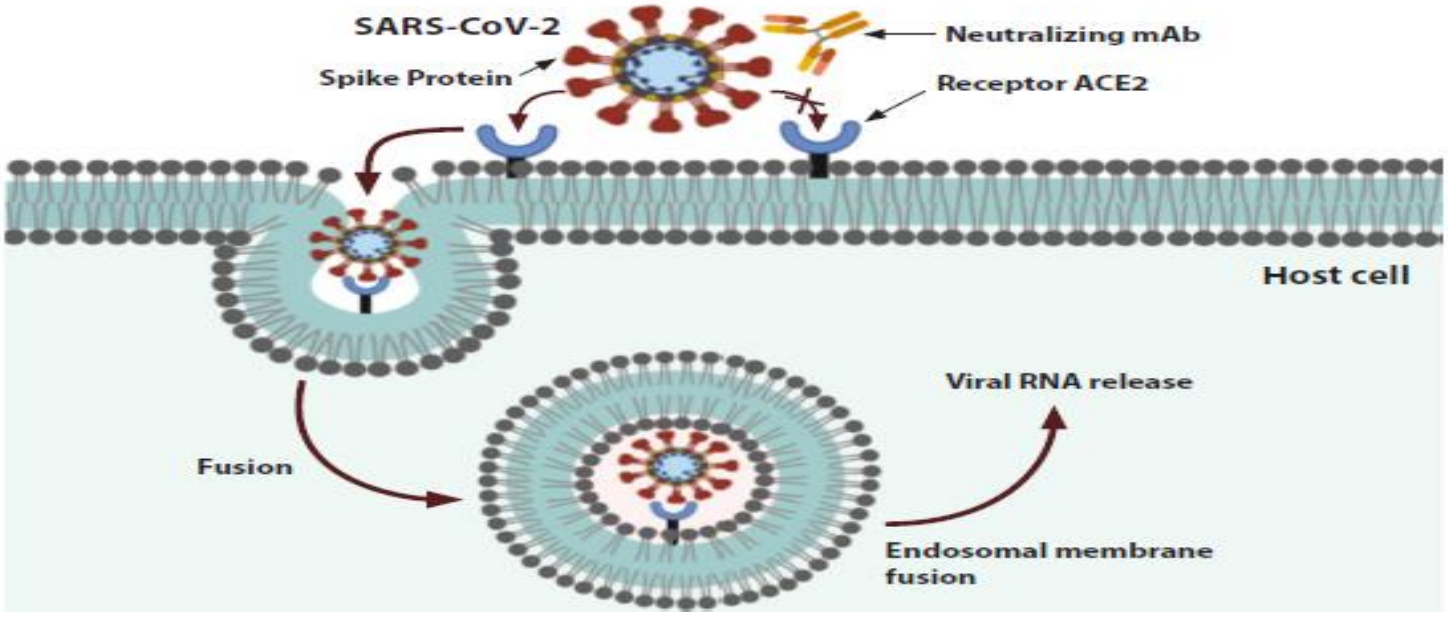
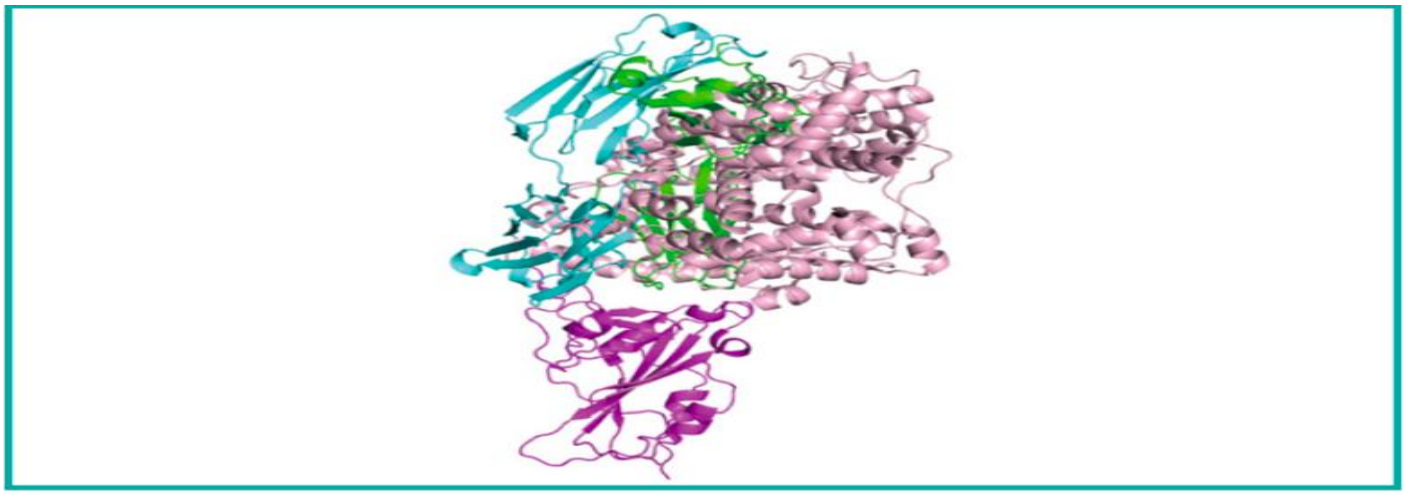


Figure 2: Schematic representation of SARS CoV-2 neutralization mechanism Credit: B.Shanmugaraj et al. APJIAI,2020

Treatment of COVID-19 With Monoclonal Antibodies

Several SARS-CoV-2 monoclonal antibodies have entered clinical trials. Therapeutic trials will include treatment of patients with SARS-CoV-2 infection, with varying degrees of illness, to block disease progression. Given the long half-life of most monoclonal antibodies (approximately 3 weeks for IgG1), a single infusion should be sufficient. Most patients with SARS-CoV-2 infection (in the absence of advanced age or comorbidities) will recover without treatment, albeit at variable rates, emphasizing the need to study monoclonal antibodies in patients most likely to benefit from early monoclonal antibody therapy.There's been other impressive recent progress towards the development of monoclonal antibody therapies for COVID-19.



Antibody Binding to SARS-CoV-2. Structural illustration of B38 antibody (cyan, green) attached to receptor-binding domain of the coronavirus SARS-CoV-2 (magenta). B38 blocks SARS-CoV-2 from binding to the ACE2 receptor (light pink) of a human cell. Credit: Y. Wu et a. Science, 2020

Monoclonal Antibodies directed specifically against SARS-COV-2

MONOCLONAL ANTIBODY	DEVELOPER	RATIONALE	CLINICAL TRIAL
JS016 LY-CoV555	Eli Lilly	JS016, LY-CoV555 binds to the spike protein receptor in SARS-CoV-2 & can block viruses from binding to the ACE 2 host cell surface receptor	Phase 1 trial to evaluate COVID19 patients
REGN-COV2	Regeneron	The dual antibodies attach non competitively to RBD of SARS COV-2	Phase 1 trial to prevent and treat COVID19 patients
S309	Biotech	S309 has neutralising action & effector functioning against SARS COV-2 but doesn't compete with the viral binding site.	Fast track development towards clinical trial
TY027	Tychan (Singapore)	TY027 specifically target SARS COV-2	Phase 1 trial to evaluate COVID19 patients
B38 & H4	Yan Wu, Capital MedicalUniversity, (Beijing)	Binds to the Receptor Binding Domain (RBD) of SARS-COV-2	The first two adaptive Phase 1/2/3 studies are evaluating REGN-COV2 in Covid-19 patients

Limitations

A potential limitation of monoclonal antibodies for treatment of COVID-19 is the unknown bioavailability of passively infused IgG in tissues affected by the disease, especially the lungs, which serve as a key target of SARS-CoV-2 infection.

Another important consideration is the effect of viral diversity leading to emergence of resistant viral mutations under selective pressure of monoclonal antibody treatment. However, researchers claim that a combination of 2 monoclonal antibodies targeting different sites on the spike protein reduces the risk of virus mutating to become resistant to a single antibody.

There is also some concern for immune enhancement of COVID-19 because vaccine-associated enhanced disease has been observed in animal models of SARS-CoV and for other animal coronaviruses. Categories of possible disease enhancement may include antibody-mediated enhancement of viral entry and replication in target cells

Challenges

The monoclonal antibodies are highly expensive and would not be affordable to the world population on the scale that would be needed against the coronavirus. To decrease the cost of human monoclonal antibodies, there should be either an improved industrial efficiency or a discovery of an extremely potent human monoclonal antibody. Neutralizing antibodies have an important role in the protection or recovery from many viral infections. They prove to be cost effective alternative.

Conclusion

An effective vaccine is a necessary solution to the COVID-19 pandemic. Monoclonal antibodies provide an alternative avenue for the prevention of COVID-19. Passive infusion of monoclonal antibodies as pre-exposure or post-exposure prophylaxis might offer immediate protection from infection that could last weeks or months.

Newer technologies that modify the Fc region of the antibody to extend the half-life of monoclonal antibodies can provide potentially protective levels for months, depending on the monoclonal antibody concentrations required. Even if a vaccine is available, the weeks of time required to generate an effective immune response emphasizes the benefits of passive immunity in a variety of circumstances including health care settings, households, and facilities where outbreaks have been common and devastating. In addition, older individuals and those with underlying co morbid conditions might not mount a robust protective response after vaccination, and so monoclonal antibodies may be required to provide protection.

In addition, a drug that reliably prevented progression of COVID-19 would greatly reduce the uncertainty associated with SARS-CoV-2 infection and give physicians a therapeutic tool they must have for their patients. Establishing the therapeutic or prophylactic efficacy of monoclonal antibodies would be a major advance in the control of the COVID-19 pandemic.

References

1) https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-therapeutics-tracker (updated 19 June 2020)
2) Pinto, D., Park, Y., Beltramello, M. *et al.* Cross-neutralization of SARS-CoV-2 by a human monoclonal SARS-CoV antibody. *Nature*(2020).
3) https://investor.regeneron.com/news-releases/news-release-details/regeneron-begins-first-clinical-trials-anti-viral-antibody. (updated 11 June 2020)
4) Wu Yan et al. A noncompeting pair of human neutralizing antibodies block COVID-19 virus binding to its receptor ACE2,*Science* 12June2020:Vol. 368, Issue 6496, pp. 1274-1278

Do you Know ?

The recently approved and repurposed Monoclonal Antibody drugs Itolizumab are manufactured by the Indian biotechnology giant Biocon

Greatest irony is the chief (Executive Chairperson) of the Biocon Ms Kiran Majumdar Shaw has tested COVID -19 positive on 18/8/2020.

Best wishes for her speedy recovery

Repurposed Antibody Drugs In COVID-19

MONOCLONAL ANTIBODY	RATIONALE	CLINICAL TRIAL STATUS
Levilimab (BCD-089)	Targets IL-6 receptor	Phase 3 trial evaluating Covid 19 patients
Pamrevlumab	Targets connective tissue growth factor (CTGF). By preventing the activity of CTGF, could reverse the pulmonary oedema in COVD -19 pneumonia patients	Phase 2/3 trial to assess blood oxygenation level in COVID-19 patients
Mavrilimumab	Targets granulocyte-macrophage colony stimulating facto (GM-CSF) alpha receptor	Phase 2/3 trial in Covid patient with severe pneumonia
Otilimab	Anti-GM-CSF antibody. A potential candidate for COVID-19 treatment in patients who experience cytokine release syndrome.	Phase 2 OSCAR trial of 800 participants with COVID-1
Gimsilumab	Targets the pro-inflammatory cytokine (GM-CSF) which may be associated with acute respiratory distress syndrome in COVID-19 patients	BREATHE trial ,270 patients with COVID-19 with ARDS or lung injury
Leronlimab	CCR5 antagonist. Enhance immune response in patients experiencing cytokine release syndrome from respiratory distress syndrome caused by Covid 19	Phase 2b/3 trial evaluating mild to moderate COVID 19 patients
Tocilizumab	Interleukin-6 (IL-6) receptor antagonist	Phase 3 trial(COVACTA) in severe COVID 19 patients
Itolizumab	Anti-CD6 IgG1 monoclonal antibody approved for psoriasis. Its approved for emergency use in India for the treatment of cytokine release syndrome in moderate to severe acute respiratory distress syndrome (ARDS) due to COVID-19	Pilot study has not shown decreased mortality in COVID-19 patients
Sarilumab	IL -6 receptor antagonist	Phase 2/3 trial 0f 400 COVID 19 patients
Canakinumab	Targets interleukin (IL)-1β	Phase 3 CAN-COVID trial
Ravulizumab	C5 complement inhibitor, It lowers cytokine and chemokine levels in viral pneumonia.	Phase 3 global study of 270 patients with COVID-19 hospitalized with severe pneumonia

Vaccine: The Final Hope In Fight Against Novel Corona Virus

With confirmed COVID-19 cases worldwide continuing to grow, scientists are pushing forward with efforts to develop vaccines and treatments to slow the pandemic and lessen the disease's damage. Researchers worldwide are working around the clock to find a vaccine against SARS-CoV-2, the virus causing the COVID-19 pandemic. Experts estimate that a fast-tracked vaccine development process could speed a successful candidate to market, if the process goes smoothly from conception to market availability.

*To date, just one coronavirus vaccine **Sputnik V** has been approved. Earlier known as Gam-COVID-Vac and developed by the Gamaleya Research Institute in Moscow; was approved by the Ministry of Health of the Russian Federation on 11 August 2020.* Though many experts are doubtful about the vaccine's safety and efficacy given the fact it has not yet entered Phase 3 clinical trials, but general population is quite hopeful too.

The pandemic has created unprecedented public/private partnerships too in many countries. Operation Warp Speed (OWS) is a collaboration of several US federal government departments including Health and Human Services and its sub agencies, Agriculture, Energy and Veterans Affairs and the private sector. Within OWS, the US National Institutes of Health (NIH) has partnered with more than 18 biopharmaceutical companies to accelerate development of drug and vaccine candidates for COVID-19 (ACTIV). The COVID-19 Prevention Trials Network (COVPN) has also been established, which combines clinical trial networks funded by the National Institute of Allergy and Infectious Diseases (NIAID): the HIV Vaccine Trials Network (HVTN), HIV Prevention Trials Network (HPTN), Infectious Diseases Clinical Research Consortium (IDCRC), and the AIDS Clinical Trials Group.

The US government has chosen three vaccine candidates to fund for Phase 3 trials under Operation Warp Speed: **Moderna's mRNA-1273, The University of Oxford and AstraZeneca's AZD1222, and Pfizer and BioNTech's BNT162**. Members of ACTIV have suggested developing *safe controlled human infection models* (CHIMs) for human trials could take 1-2 years. A sponsor would need to provide data from placebo-controlled trials indicating their vaccine is at least 50% effective against COVID-19 in order to be authorized for use, according to FDA guidance issued and effective from 30 June 2020.

Meanwhile researchers at Sinopharm and the Wuhan Institute of Virology under the Chinese Academy of Sciences are developing an **inactivated COVID-19 vaccine candidate**. They have initiated a randomized, double-blind, placebo parallel-controlled Phase 1/2 clinical trial (ChiCTR2000031809) of healthy individuals starting at 6 years old.The vaccine has shown a "strong neutralizing antibody response" in Phase 1/2 trials, according to a release from China National Biotec Group. A Phase 3 trial is underway conducted in the United Arab Emirates.

Another important vaccine hope is the **CoronaVac** (formerly PiCoVacc), a formalin-inactivated and alum-adjuvanted candidate. Results from animal studies showed "partial or complete protection in macaques" exposed to SARS-CoV-2, according to a paper published by researchers in the journal Science. A Phase 1/2 trial enrolled 743 healthy volunteers (18-59 years old) who received two different dosages of the vaccine or placebo. There were 143 participants in Phase 1 (NCT04352608) and 600 participants in Phase 2 (NCT04383574).Results from the Phase 1/2 trials published in the pre-print server medRxiv indicate the vaccine has good safety and immunogenicity, with 92.4% of participants receiving the 3 µg dose on a 0-14 day schedule and 97.4% of individuals receiving the dose on a 0-28 day schedule achieving seroconversion.

Sinovac the developer said a Phase 3 trial in collaboration with Instituto Butantan in Brazil is underway, and the company plans to enrol around 9,000 patients in the healthcare industry.

Status of Vaccine in India: Bharat Biotech, an Indian biotechnology company, is partnering with the National Institute of Virology to develop an inactivated vaccine candidate for COVID-19 called **Covaxin**. A Phase 1/2 trial of about 1,100 healthy participants is underway after approval by the Drug Controller General of India. Early results in the first 50 people who received the vaccine candidate appear to be "encouraging," according to a comment from the trial's principal investigator. The Indian Council of Medical Research has reported this candidate has entered Phase 2 trials. In addition to Covaxin, Bharat Biotech is working on two other vaccine candidates: one with the University of Wisconsin–Madison and FluGen, and the other with Thomas Jefferson University.

Promising Vaccines Candidates in Clinical Evaluation

Sl no	Covid 19 Vaccine Developer /Company	Vaccine platform	Type of candidate vaccine	Number of doses	Timing of doses	Route of Administration
1	University of Oxford/AstraZeneca	Non-Replicating Viral Vector	ChAdOx1-S	1		IM
2	Sinovac	Inactivated	Inactivated	2	0, 14 days	IM
3	Wuhan Institute of Biological Products/Sinopharm and Beijing Institute of Biological Products/Sinopharm	Inactivated	Inactivated	2	0,14 or 0,21 days	IM
4	Moderna/NIAID 2	RNA	LNP-encapsulated mRNA	2	0, 28 days	IM
5	BioNTech/Fosun Pharma/Pfizer	RNA	3 LNP-mRNAs	2	0, 28 days	IM
6	CanSino Biological Inc./Beijing Institute of Biotechnology	Non-Replicating Viral Vector	Adenovirus Type 5 Vector	1		IM
7	Anhui Zhifei Longcom Biopharmaceutical/Institute of Microbiology, Chinese Academy of Sciences	Sciences Protein Subunit	Adjuvanted recombinant protein (RBD-Dimer)	2 or 3	0,28 or 0,28,56 days	IM
8	Institute of Medical Biology, Chinese Academy of Medical Sciences	Inactivated	Inactivated	2	0, 28 days	IM
9	Inovio Pharmaceuticals/ International Vaccine Institute	DNA	DNA plasmid vaccine with electroporation	2	0, 28 days	ID
10	Osaka University/ AnGes/ Takara Bio	DNA	DNA plasmid vaccine + Adjuvant	2	0, 14 days	IM
11	Cadila Healthcare Limited	DNA	DNA plasmid vaccine	3	0, 28, 56 days	ID
12	Genexine Consortium	DNA	DNA Vaccine (GX-19)	2	0, 28 days	IM
13	Bharat Biotech	Inactivated	Whole-Virion Inactivated	2	0, 14 days	IM
14	Janssen Pharmaceutical Companies	Non-Replicating Viral Vector	Ad26COVS1	2	0, 56 days	IM
15	Novavax	Protein Subunit	Full length recombinant SARS CoV2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M	2 0, 21 days IM	0, 21 days	IM

*WHO Draft Landscape of COVID-19 Candidate Vaccines

IMPACT OF PHARMACOVIGILANCE ON PUBLIC HEALTH PROGRAMMES

The **Public Health Programmes (PHPs)** involve the direct administration of medicines to large populations and communities for the prophylaxis, treatment and/or eradication of diseases. Large number of patients receives the drugs in a systematic manner in these programmes which generates the possibility of adverse drug reactions which should be reported, at the same time, there is an opportunity to develop systems for generating valid and valuable data that will assist in decision making. **PHPs and Pharmacovigilance (Pv)** can derive mutual benefits from each other; Pv and adverse drug reactions monitoring in PHPs can detect rare adverse events and risk factors in patients and can have a tremendous positive impact on the implementation and success of these programmes.

Health requirements and the use of medicines in different countries vary considerably for many reasons, including different burdens of disease, economic, ethnic, cultural and dietary factors, and the level of development of a system for the regulation of medicines. Decisions concerning the effectiveness and safety of a product need to be considered in each country's specific context. Vigilance regarding both safety and effectiveness of medicines must become a priority area within public health.

The pharmacovigilance system adopted may be comprehensive, or may be restricted to a specific medicine or programme. It is envisaged that whatever system is used, it will undoubtedly help in the early detection and prompt management of adverse reactions, but will also assist in achieving the goals of the programme. The pharmacovigilance training given should result in a better understanding of the medicine being used in the PHP, better compliance by health workers with prescribing guidelines and better adherence of patients to dosing regimens. During last few years **Pharmacovigilance Programme of India (PvPI) has collaborated with several national health programmes** in order to develop safety database of medicines in India.

In 2017, **World Health Organization recognized IPC- PvPI as a WHO- Collaborating Centre for Pharmacovigilance in Public Health Programs and Regulatory Services**. The PvPI assists WHO**:**

- To develop relevant tools and guidelines for enhancing pharmacovigilance practice in Low and Middle-Income Countries in Asia and beyond.
- Contribute to capacity building of WHO member states to establish high-quality pharmacovigilance systems
- Provides scientific support to countries for pharmacovigilance in public health programmes.

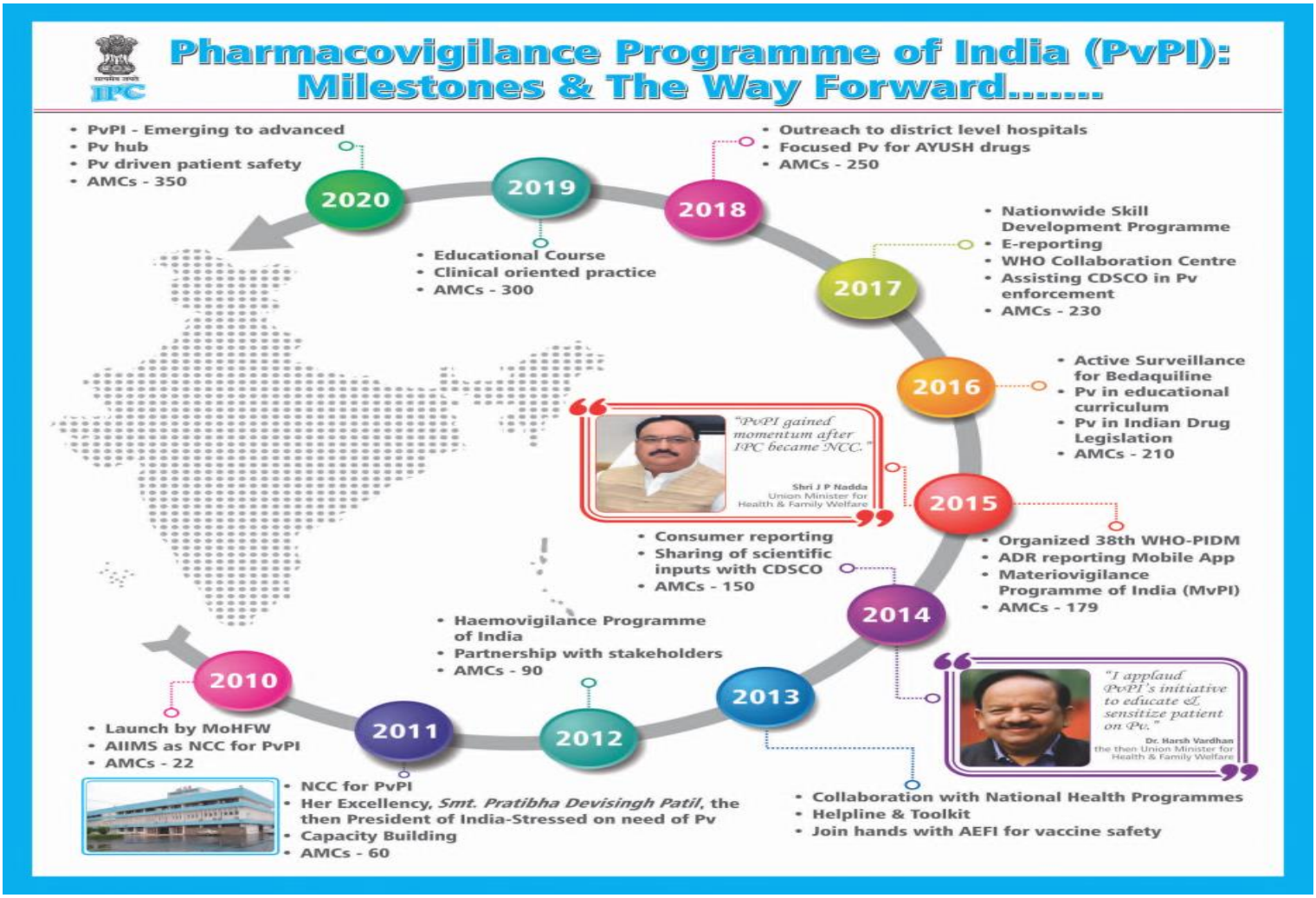
COLLABORATION OF PHARMACOVIGILANCE PROGRAMME OF INDIA (PvPI) WITH PUBLIC HEALTH PROGRAMMES

YEAR	COLLABORATION OF PvPI WITH PUBLIC HEALTH PROGRAMMES
2013-14	• Revised National Tuberculosis Control Programme (RNTCP) now, National Tuberculosis Elimination Programme (NTEP)- Pharmacovigilance of Anti-tubercular drugs • AEFI Secretariat (UIP) - Pharmacovigilance of Vaccines
2014-15	• National AIDS Control Programme (NACO) - Pharmacovigilance of Anti-Retroviral Drugs
2015-16	• Cohort Event Monitoring of Anti-tubercular drug - Surveillance of Bedaquiline at 6 AMCs under PvPI
2016-17	• National Vector – Borne Disease Control Programme - Pv of Kala-azar drugs
2017-18	• World Health Organization- South East Asia Regional Office (WHO-SEARO) WHO Collaborating Centre for Pharmacovigilance in Public Health Programmes & Regulatory services

The Quality Assurance and Safety of Medicines team of the World Health Organization (WHO) aims to assure the safety of medicines by ensuring reliable and timely exchange of information on drug safety issues, promoting pharmacovigilance activities throughout the Organization and encouraging participation in the **WHO Programme for International Drug Monitoring.**

The national centres collaborate in the WHO Programme for International Drug Monitoring, to collect reports of suspected adverse drug reactions (ADRs) and after review, send them to the Uppsala Monitoring Centre, Sweden for entry into the WHO database. This is the largest database of ADR reports in the world and is a prime resource for generating signals of previously unrecognized ADRs and for the safety of medicines. This database would have added value if it included reports about medicines used in public health programmes and could also be a valuable resource for the programmes themselves.

The **integration of pharmacovigilance is crucial for the success of public health programmes** using medicines. It is important that active pharmacovigilance is undertaken by all PHPs that use medicines because no medicine is without adverse consequences although these vary in severity and frequency. The collaboration and communication between pharmacovigilance systems and PHPs at both the national and international levels is important to ensure full integration which will strengthen dedicated national programmes and optimize the use of health resources.



References:

1.https://www.who.int/medicines/areas/quality_safety/safety_efficacy/Pharmacovigilance_B.pdf?ua=1 last accessed on 28.06.2020
2. https://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmpubhealth/en/ last accessed on 28.06.2020
3. http://www.ipc.gov.in/PvPI/pv_home.html last accessed on 28.06.2020

New Drugs Approved in June

Sl no	Name of the Drug	Mechanism of action	Indication	Date of Approval
1	Inebilizumab-cdon	The precise mechanism by which inebilizumab-cdon exerts its therapeutic effects in NMOSD is unknown but is presumed to involve binding to CD19, a cell surface antigen presents on pre-B and mature B lymphocytes. Following cell surface binding to B lymphocytes, inebilizumab-cdon results in antibody-dependent cellular cytolysis.	To treat neuromyelitis optica spectrum disorder (NMSOD)	11/6/2020
2	Lurbinectedin	Lurbinectedin is a DNA alkylating agent. It covalently binds to guanine residues in the DNA minor groove, forming adducts that bend the DNA helix towards the major groove. This process triggers a cascade of events that affect the activity of transcription factors and impairs DNA repair pathways, ultimately leading to double-strand DNA breaks and eventual cell death. Additional mechanism(s) of action include inhibition of RNA-polymerase-II activity, inactivation of Ewing Sarcoma Oncoprotein (EWS-FL11) via nuclear redistribution, and the inhibition of human monocyte activity and macrophage infiltration into tumor tissue.	To treat metastatic small cell lung cancer	15/6/2020
3	Triheptanoin	Triheptanoin is a medium-chain triglyceride consisting of three odd-chain 7-carbon length fatty acids (heptanoate) that provide a source of calories and fatty acids to bypass the long-chain FAOD enzyme deficiencies for energy production and replacement.	To treat molecularly long-chain fatty acid oxidation disorders	30/06/2020