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Review Article

REVIEW ON INDIAN REGULATORY REQUIREMENTS OF CLINICAL TRIALS ON COVID VACCINES

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ABSTRACT

COVID-19 is an infectious disease caused by a coronavirus strain that was discovered in December 2019 in Wuhan city, China. Corona viruses are a type of virus that causes common colds, MERS (Middle East Respiratory Syndrome), SARS (Severe Acute Respiratory Syndrome) and other illnesses. After the United States and Brazil, India has risen to third place in the world in terms of the number of COVID-19 cases. To protect humans from the disease, a race among vaccine developers around the world has begun, with hundreds of COVID-19 vaccine candidates in various stages of clinical trials. On January 16, 2021, India's government began offering free COVID-19 vaccinations, and as part of what is anticipated to be the world's largest immunization campaign, it is asking all of its residents to get vaccinated. Four COVID-19 vaccines, out of the eight being tested in various phases of clinical trials in India, were created. The Indian medicines regulator has given its approval. Covishield, the Oxford-AstraZeneca vaccine, and Covaxin, a locally produced vaccine made by Bharat Biotech, are only to be used in cases of extreme urgency. The capability of Indian producers to supply the nation's anticipated future demand for COVID-19 vaccines has been confirmed. The initial immunisation of 30 million healthcare workers can be completed with the help of the staff and cold-chain infrastructure in place prior to the pandemic. The Indian government has acted quickly to increase the nation's capacity for vaccine production and has also created an effective digital system to handle and monitor all facets of vaccine administration.

Keywords: COVID-19, SARS-CoV-2, New Vaccine Introduction, Clinical trials.

1. INTRODUCTION

Pharmaceutical regulations are a collection of legal, administrative and technical measures implemented by governments to ensure the safety, efficacy and quality of medicines, as well as the relevance and accuracy of product data made available to the public. The term 'regulation' includes a variety of texts such as guidelines, recommendations, procedures, policies etc., that have legal bases and authority [1]. The regulations are required for both new and pre-existing products, domestically produced products and those imported from other countries. The primary goal of regulatory agencies is to maintain drug standards at every stage in order to serve the patient population [2].

A Regulated system for medicines must provide access to effective treatments in time for patients, protect patient safety and promote research into new treatments [3]. Regulatory agencies provide strategic, tactical and operational guidance as well as support for working within regulations to accelerate the development and delivery of safe and effective medicines healthcare products to public place. Current Pharmaceutical industry is very organised, systematic and compliant to International regulations. Multiple tragedies like Sulphanilamide elixir, vaccine tragedy and Thalidomide tragedy led to the need for a well-controlled regulatory framework [4].

The following are the various regulatory agencies and organizations throughout the world are:

- World Health Organization (WHO)
- International conference on harmonization (ICH)
- Pan American health organization (PAHO)
- World trade organization (WTO)
- World intellectual property organization (WIPO)

They also play a significant role in applying pharmaceutical regulations in all aspects related to drug

development, registration, production, distribution, marketing, price control and research. They also ensure an increased regulatory implementation in unregulated parts of the world for the safety of the public [5].

Table 1: National Regulatory agencies

Country	Name of Regulatory Authority
India	Central Drug Standard Control Organisation (CDSCO)
USA	Food and Drug Administration (FDA)
Europe	European Medicines Agency (EMA)
UK	Medicines and Health Care Products Regulatory Agency (MHRA)
Australia	Therapeutic Goods Administration (TGA)
Canada	Health Canada
New Zealand	Medicines and Medical Devices Safety Authority (Medsafe)
China	State Food and Drug Administration (SFDA)
Japan	Ministry of Health Labour & Welfare (MHLW)
Switzerland	SWISSMEDIC, Swiss Agency Therapeutic Products

2. COVID - 19

A novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS COV- 2) was detected in December 2019, in Wuhan city, Hubei province, China and ever since it has impacted global public health in an unprecedented way [6]. The severity of disease was made very much high that the World Health Organization (WHO) declared this as a public health emergency of international concern and term this outbreak as a global pandemic about this infectious disease on 31st January 2020 [7].

More than 200 countries have been affected by this epidemic. As on 31st July 2020 1,70,64,064 confirmed cases have been reported across the globe with 2,51,255 new cases added in the last 24 hours. COVID-19 has also cost globally 6,68,073 deaths including US, Brazil and India was very much affected by this virus with 85,79,701 confirmed cases reported from these 3 huge countries with 2,75,935 casualties by the end of 31stJuly 2020 in the reference of World Health Organization situation report, 2020. Due to this pandemic, India has faced enormous medical, socio-economic problems. The report provided by worldometers.info has confirmed that there are 16,63,174 COVID-19 cases on 31st July 2020 which includes 35,980 deaths in India.

In the last 24 hours almost 55000 new cases have been reported in several states in India for example Maharashtra (1,48,454 active cases), Karnataka (69,708 active cases), Andhra Pradesh (69,252 active cases) and Tamil Nadu (57,962 active cases) are some of the Indian hubs where Covid-19 has become very infectious and dangerous disease. There was no vaccine or any specific antiviral drugs available for COVID-19 or COV-2 until the late 2020, many labs have researched and found the vaccines and antivirals for this infectious disease across the world by the late 2020. There were already 26 potential vaccine candidates under clinical evaluation stage and more than 135 vaccine candidates are in pre-clinical stages (WHO, 2020).

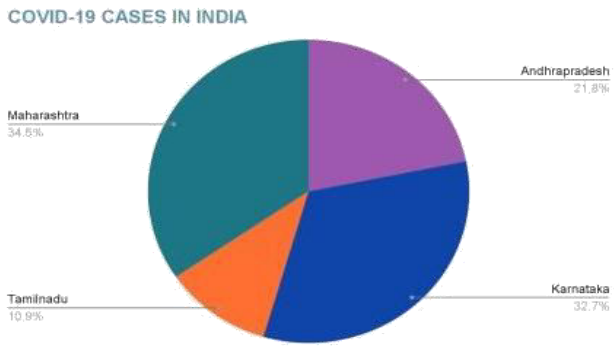

Fig. 1: Covid-19 cases in India

3. INTRODUCTION OF VACCINES

A vaccine is a biological preparation that provides active acquired immunity against a specific infectious or malignant disease [8]. Vaccines have been thoroughly researched and proven to be effective [9]. A vaccine usually contains a substance that resembles the disease-causing microorganism and is often made from the forms of the microbe that have been damaged or destroyed by its surface proteins or its toxins. The substance stimulates the body's immune system to recognize the substance as a threat, destroy it and further identify and destroy all microorganisms associated with the substance with which it may come into existence in the future.

The administration of vaccines is called Vaccination. Vaccination is the most effective way to prevent infectious diseases [10]; widespread immunity from vaccination is largely responsible for the global eradication of smallpox and the containment of diseases such as polio, measles and tetanus in a large part of the world. According to the World Health Organization (WHO) licensed vaccines against 25 different preventable infections are currently available [11].

3.1. Importance of vaccine

- Vaccines are obtained from the manufacturers.
- Transporting and storing the vaccines.
- Maintaining the supply of vaccines.
- Vaccine should be kept at a low temperature.
- Protecting the vaccine from sunlight exposure.
- Maintaining the potency of vaccines.

3.2. Are vaccines effective in containing pandemic?

contain the virus-at least for the time being. They mostly accomplished this by immunising sizable populations and advocating for COVID-appropriate behaviour and vaccinations. Using the tried-and-true method of vaccination, Israel [12], the United Kingdom [13] and the USA [14] have greatly decreased transmission and the ensuing morbidity and mortality. The best example is Israel, where during the large third wave distributed more than 10 million doses in just four months, immunising roughly five million people with two doses of the mRNA vaccine administered 21 days apart. Nearly 88% of those 50 years or older people will receive this vaccinations [13] The USA has administered at least one dose of the COVID-19 vaccine [14] to over 63.4% of its adult population, according to the Centers for Disease Control and Prevention (CDC). More than 68 million people in the UK have received one dose of vaccine, with 28 million receiving both doses [13]. In April 2021, Bhutan, a small nation with an effective healthcare delivery system, was able to immunise 94% of its adult population [15].

4. PRECLINICAL TRIALS ON COVID-19 VACCINES

Clinical trials cannot be carried out without first undergoing preclinical testing. Prior to the drug being tested "*in vivo*" on humans, preclinical studies are designed to evaluate the potential toxicity of new therapeutic drugs using either human cell cultures or animals. Before new vaccines can be tested on humans, preclinical testing is required to demonstrate their safety. Preclinical testing is usually extensive in order to gather enough data to reliably indicate not only the safety of a new vaccine, but also its potential efficacy, toxicity and pharmacokinetic properties. Furthermore, preclinical trials enable scientists to simulate potential drug-target interactions [16].

5. CLINICAL TRIALS ON COVID-19

A clinical trial is the testing and evaluation of an investigational drug, device or procedure to determine its research study with human participants. Before an investigational drug, device or method is approved for use, it must be evaluated in a series of clinical trials. Clinical trials are closely monitored by various regulatory bodies to ensure the safety of all trial participants who consent to participate. These regulatory bodies include the Food and Drug Administration (FDA) in the United States, the European Medicines Agency (EMA) in Europe, and other ministries of health and regulatory bodies around the world. They are all government agencies responsible for issuing rules and regulations in their jurisdiction regarding the conduct of clinical trials. Clinical trials are divided into 4 different phases. Each phase is designed to collect specific information about investigational drug, device, or procedure.

There are many candidates belonging to University of Oxford, non-replicated vital vector vaccine who have completed their phase 1 and 2 trials and in phase 3 trials by the end of 2020. This candidate vaccines have shown a very promising result from preclinical evaluations and have done with their phase 1 and phase 2 trials [17, 18].

The studies which have included WHO International clinical trials registry platform (ICTRP). Clinical trials data set was used buy U.S. National library of medicines, Chinese clinical trials registry and European Union clinical trials register to document or provide detailed or comprehensive information on ongoing trials on Covid19 [19-25]. These studies were very much important for the understanding of clinical trials eco-system on covid-19. India being the primary member of WHO (ICTRP) has its own trials registry known as Clinical trials registry of India or CTRI.

5.1. Clinical development stages/ clinical trial phases on humans

The vaccine development cycle is divided into several stages, including exploratory, preclinical, and clinical

development, manufacturing, quality assurance, and regulatory review and approval control. The article, however, will primarily focus on the stage of clinical development, also known as clinical trial On humans, phases According to the US Food and Drug Administration Certain regulatory approval steps are required by the Food and Drug Administration (FDA) must be followed by the development of a new vaccine a sponsor(s), for example, an investigational new drug application, clinical trials for pre-licensure vaccines, and a Biologics License Application (BLA), manufacturing facility inspection and findings presentation. The clinical trial begins after the drug is submitted for investigational new drug approval. There are three stages of human clinical trials: phase I, phase II, and phase III. All human-subject studies in most countries require formal regulatory approval, ethical clearance, and ethical consideration in accordance with the Helsinki Declaration, which is a statement of ethical principles for medical research involving human subjects [26].

Table 2: Clinical Trials

PHASE -1	PHASE-2	PHASE-3	PHASE-4
First trials in humans These trials usually involve small numbers of participants. **GOALS:** Determine the maximum tolerated dose (the highest dose of a drug or treatment that doesn't cause unacceptable side effects). Check for any potential side effects.	***Aiming at the target*** Designed to see whether the investigational drug, device or procedure works in patients with target disease being studied. Phase 2 trials usually involve a large group of participants. **GOALS:** Designed to confirm the safety data established in the Phase 1 trial.	***Strength in numbers*** Further test the safety of the investigational drug or procedure and how well it works. Phase 3 trials involve hundreds or even many thousands of participants with the target disease being studied. **GOALS** Often, compare the investigational drug or procedure with a placebo (contains no active medicine) or in existing standard treatment in a randomized fashion. Detect less common side effects & determine the benefits of the investigational drug, device or procedure for a particle patient population.	***Welcome to the real world*** Conducted after the regulatory authorities have approved a drug, device or procedure and after it is on the market. Phase 4 trials typically involve a large number of participants. **GOALS** Find out more real-world information about the product. For example, Phase4 trials may evaluate new users of existing therapies or be used to detect side effects that didn't appear during Phase 3 or earlier clinical trials.

5.2. Covid-19 vaccine candidates in clinical trails in India

The COVID-19 vaccine candidates, India is currently producing and testing in clinical settings are among the top goods worldwide. In addition to India's own COVID-19 vaccines, some regional pharmaceutical and biotech firms have collaborated with 8 developers of vaccines based abroad. These partnerships span anything from doing clinical trials to large-scale production of vaccines and distribution of those vaccines [27].

The vaccine candidates undergoing clinical trials in India are:

5.2.1. The Serum Institute of India's by Covishield

A few businesses, including Oxford-AstraZeneca, Codagenix, and Novavax, have struck collaborations with Serum Institute of India (SII), a company in Pune [28]. Covishield is manufactured in accordance with the Drugs Controller General of India's (DCGI) "at-risk manufacturing and stockpiling licence," and for Medical Research in India (ICMR). The ICMR provided funding for the clinical trials of Oxford Astra Zeneca provided the master stock used to develop the Covishield vaccine with the SII. A Phase II/III, observer-blind, randomised, controlled trial was collaboratively carried out by ICMR in the safety of Covishield (produced in India) was compared in 14 centres with healthy adults.

India as opposed to the original Oxford-ChAdOx1 in the fight against COVID-19 illness. All told, the study involved 1600 eligible volunteers who were at least 18 years old. Of these, 400 individuals-who were a member of the immunogenicity cohort-were randomly randomised to receive either Covishield or Oxford-ChAdOx1, in a 3:1 ratio, according to their treatment,

the 1200 participants who remained randomly assigned in a 3:1 ratio to receive, either Covishield or placebo from the safety cohort substitute, respectively. ChAdOx1 administration data on efficacy, immunogenicity, and safety among 23,745 volunteers who were at least 18 years old in two doses each containing 5×10^{10} virus particles. Clinical research conducted outside of India revealed a 70.42% [29] vaccination effectiveness rate.

Table 3: Potential vaccine candidates in India

Company & collaborating agency	*Brand name*	*Vaccine design*	*Storage temperature*
Serum Institute of India (SII), Pune, India (in collaboration with the University of Oxford, UK, and pharma giant AstraZeneca)	Covishield	Non replicating chimpanzee adenovirus vaccine vector (ChAdOx1)	2-8°C
Bharat Biotech Ltd, Hyderabad, India(in collaboration with the National Institute of Virology of ICMR, India)	1.Covaxin ™ 2.Unname d	Inactivated virus vaccine	2-8°C
Cadila Healthcare,/Zydus (supposed by the Department of Biotechnology, Government of India)	ZyCoV-D	Plasmid DNA vaccine	2-8°C
Biological E. Limited, Hyderabad, India 1.(in collaboration with Dynavax Technologies Corporation and Baylor College of Medicine,USA) 2.Home grown	1.RBD219N1 2.Unnamed	Recombinant RBD protein based vaccine, with adjuvant CpG 1018	2-8°C
Dr. Reddy's Laboratories, Hyderabad, India (vaccine developed by Gamaleya National Research Institute of Epidemiology and Microbiology, Moscow, Russia)	Sputnik V	Inactivated human adenovirus Ads and Ad26 with Spike proteins inserts	-18°C
Gennova Biopharmaceuticals Ltd, Pune, India (in collaboration with HDT Biotech Corporation, USA)	HDT-301	mRNA vaccine	2-8°C

** The Russian company has been testing lyophilisation, turning the liquid vaccine into a dry, white mass that can be stored at normal fridge temperatures of 2-8°C*

5.2.2. Covaxin by Bharat Biotech Ltd

One of the two vaccines produced by the firm, Covaxin™, which was developed and manufactured by Bharat Biotech International Limited in partnership with the National Institute of Virology of ICMR, is currently undergoing clinical trials and is being stored under at-risk production and stockpiling licence. An inactivated viral vaccine called Covaxin™ was created in Vero cells. Alhydroxiquim-II (Algel-IMDG) is mixed with the inactivated virus, then chemosorbed an adjuvant to increase immunological response and aluminium hydroxide gel containing imidazoquinoline, a more durable immunity. An agreement for licencing this technology was made with the Kansas-based company

ViroVax. The T-cell response changes when the Imidazoquinoline class of adjuvants (TLR7/8 agonists) is used. Th1, A T-Helper 1 phenotype that lowers the likelihood of immunopathologically induced increased illness and is thought to be safer than Th2 responses against SARS-CoV-2 [30]. India Biotech Limited on November 16, 2020, ICMR started Covaxin™ Phase-III studies with 26,000 volunteers over 25 locations throughout India. The company claims that it is the largest clinical trial for a vaccination for COVID-19. The company has produced data on safety and immunogenicity in a variety of animal species including mice, rats, rabbits and Syrian hamsters. It has also carried out challenge experiments on non-human primates (Rhesus macaques) and hamsters. These data have all been made available by the business that houses India's drug regulatory agency. Clinical investigations in Phase-I and Phase-II were performed on 800 subjects roughly, and the outcomes have shown that the vaccine is secure and offers solid immunity and defence. Since the Phase-III efficacy trial's inception in India with 25,800 volunteers, around 22,500 people have received the vaccine throughout the world. According to the facts currently available, the vaccination is secure.

Bharat Biotech has amassed supplies. Bharat Biotech stopped producing Covaxin early this year due to a lack of consumer demand, despite the fact that the vaccine manufacturer has set up manufacturing to reach an annualised capacity of 1 billion doses.

Covaxin is available from Bharat Biotech in more than 200 million doses in bulk and about 50 million doses in vials that are ready for use. Covaxin production was stopped earlier this year due to a lack of consumer demand, according to sources. The company is also putting together a protocol to increase the testing of children aged 2 to 15 years with its immunisation.

5.2.3. ZyCoV-D by Cadila Healthcare (Zydus Cadila)

The Department of Biotechnology, Government of India, is supporting the production of another domestic COVID-19 vaccine, ZyCoV-D, by Cadila Healthcare, Ahmedabad, based on the new plasmid DNA vaccine technology. Vaccines based on plasmid DNA technology are not approved for use in the general public. Plasmids are used as vectors to deliver the DNA encoding the target antigens directly into the recipient's body. Recombinant plasmid DNA contains the pathogen's antigen sequence engineered into it. The Phase-I trials of this vaccine began on July 13, 2020, with volunteers aged 18-55. ZyCoV-D demonstrated promise in a Phase-I study, and Cadila is currently completing Phase-II trials on over 1000 volunteers across nine sites. This vaccine is given intravenously.

5.2.4. Biological E. Limited's unidentified COVID vaccine

The COVID-19 vaccine (RBD219-N1),developed in partnership with Dynavax Technologies Corporation and Baylor College of Medicine, is currently undergoing a Phase I/II clinical study in India under the direction of Biological E. Limited (BE). The COVID-19 vaccine candidate from BE is built on a traditional vaccine of SARS-CoV-2 Spike RBD, a protein antigen, was adsorbed to Alhydrogel (Alum), an adjuvant, in combination with another Adjuvant, CpG 1018, is approved. The S1 subunit's RBD binds to the host's ACE2 receptor, an enzyme that converts blood pressure enables virus penetration and damages cell membrane. The therapeutic outcome trials are done in the year 2021, February. Phase-I/II of BE clinical trial will evaluate the drug's immunogenicity and safety. Three doses of the vaccination candidate in approximately 360 healthy subjects between the ages of 18 and 65. Each study participant will receive two intramuscular injections (of the same strength), spaced 28 days apart, as part of the vaccination protocol. A locally created, yet undisclosed COVID-19 BE vaccine has additionally received regulatory approval for India's clinical trials. The pharmacological studies' specifics have not yet been made public.

5.2.5. Sputnik V by Dr. Reddy's Laboratories

Gam-COVID-Vac, also known as Sputnik V, is a COVID-19 vaccine created by the Gamaleya National Epidemiology and Microbiology of Moscow, Russia. Sputnik V is a two vector viral infection vaccine based on human adenovirus. Sputnik V employs adenoAd5 and Ad26 [31]. Adenovirus recombinant types 26 and 5 are biotechnology-derived viruses that carry the SARSCoV-2-S cDNA for protein. They are both injected into the deltoid muscle to boost immune responses. The first day involves the Ad26-based vaccine, while the 21st involves the Ad5 vaccine.. The Russian Sputnik V vaccine requires storage at temperatures not higher than 18°C.

The DCGI has given Dr. Reddy's Laboratories in Hyderabad regulatory approval to conduct mid-to-late-

stage human trials for Russia's Sputnik V vaccine in India. The Russian RDIF-Gamaleya Institute has signed contracts with several Indian companies for the large scale production of their Sputnik V vaccine.

5.2.6. mRNA vaccine (still unnamed) by Gennova Biopharmaceuticals Ltd

The mRNA vaccine developed by Pune-based Gennova Biopharmaceuticals Ltd in collaboration with HDT Biotech Corporation, USA, is the most recent COVID-19 vaccine candidate to be granted conditional permission for Phases 1 and 2 of human clinical trials by DCGI.

5.3. Covid-19 vaccination in India

A National Expert Group on Vaccine Administration for COVID-19 (NEGVAC) has been established by the Indian government to offer recommendations. The administration of the COVID-19 vaccine in India from all angles [32]. NEGVAC states that the COVID-19 vaccination will be provided first to frontline employees, healthcare professionals, and people over 50 years of age (with preference given to those over 60), then individuals with related comorbidities who are under 50. The administration has established a committee with representatives from various numerous areas, such as pulmonology, nephrology, and oncology and cardiology to specify the clinical standards by which people are evaluated based on priority should be given to those who have comorbidities for Covid-19 immunisation. A congenital cardiac condition that results in pulmonary arterial hypertension, end-stage kidney disease or cancers like lymphoma, leukaemia, or myeloma has been advised against by a committee. Priority should be given to treating sickle cell anaemia, primary immune deficiency diseases and decompensated liver cirrhosis. The most recent general election electoral roll will be utilised to determine the population that is at least 45 years old. On January 16, 2021, India began administering COVID-19 vaccinations. As of March 4, 2023, India had delivered about 2.2 billion doses of the currently licenced vaccines, including first, second, and precautionary (booster) doses. In India, 95% of the eligible population (12+) has received at least one vaccination, and 88% is fully immunized. For those eligible individuals who have been left off the rolls for whatever reason, there will be a facility for self-registration for vaccination, following providing some kind of identification.

6. CLINICAL CHARACTERISTICS AND INDICATORS OF IN-HOSPITAL MORTALITY AMONG OLDER PATIENTS RECEIVING COVID-19 TREATMENT

6.1. In-hospital complications and treatment

Estimated 10.7% of patients had a qSOFA of 2-3 points upon admission. During hospitalisation, 902 patients (60.1%) acquired respiratory failure, 143 (9.7%) experienced cardiac failure, and 248 (16.7%) experienced renal failure (KDIGO stage 1 acute kidney damage or worse) developed systemic inflammatory response syndrome, and 342 (23.5%) acquired sepsis (SIRS). In addition, 38 patients (2.6%) experienced a relevant bleeding event while they were hospitalised, and 19 an embolic incident (1, 3%).Antiviral medications, antibiotics (such as Azithromycin) and hydroxychloroquine respectively (82.2, 78.7, and 59.1%) were often used. Nearly 80% needed oxygen throughout 6.4% of admissions used mechanical ventilation.

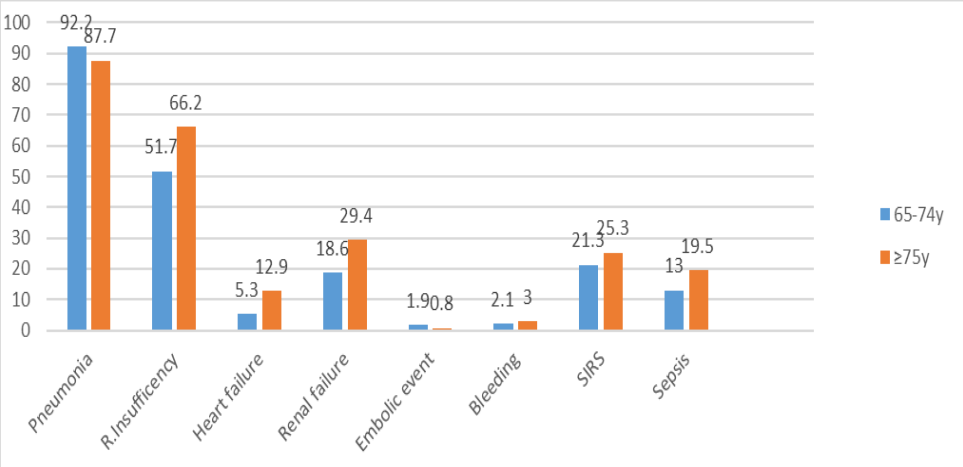

Fig. 2: Graph above shows as: Percentage of in-hospital complications in patients aged 65-74 and ≥75 years *(Xaxis= type of complication; Y axis = percentage (%). *P <0.05)*

6.2. Patients who are at least 75 years old

Compares baseline features, baseline medication, baseline symptoms, in-hospital outcomes, and therapy between patients aged 65-74 and 75 years. In addition to Appendix A1b, S2, More comorbidities were present in patients who were 75 years or older such as dementia, chronic heart disorders, chronic renal disease, hypertension, greater CCI (1.4 vs. 2.0 points). As a result, practically all forms of medication were prevalent at the time of admission to the hospital. Other than dyspnea and exhaustion this is typical. The older age group had a lower prevalence of COVID-19 presenting symptoms (e.g., fever at 82 vs. 74.2%). Clinical indicators such peripheral oxygen saturation below 92% (35.7 vs. 52.0) and they were more frequently abnormal at admission among those employed for qSOFA computation.

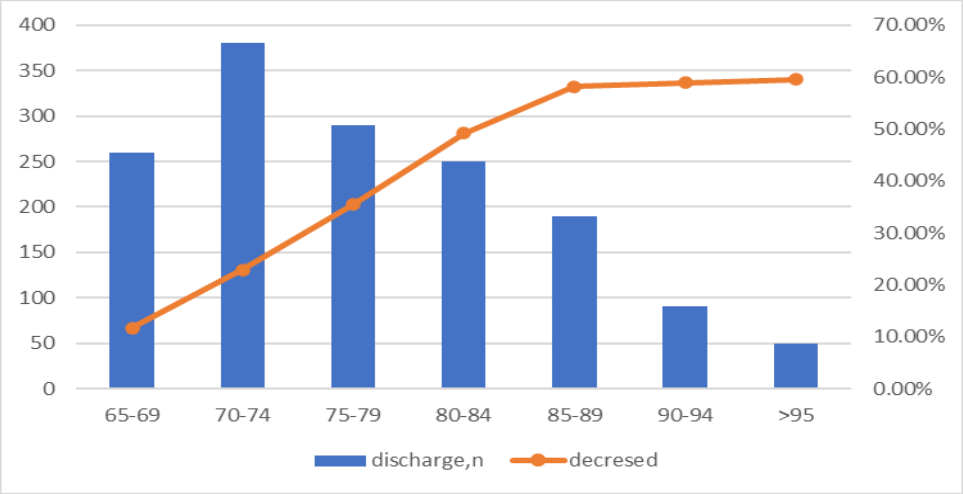

Fig. 3: Graph shows Number of patients aged ≥65 years hospitalised for COVID-19(blue boxes) and percentage of deaths (orange dots) according to age.

6.3. Interim statement on childhood COVID-19 immunisation

Children and teenagers are still vulnerable to SARS-CoV-2. Compared to adults, children and adolescents often experience less severe sickness from the disease. The level of exposure also affects the risk of transmission to and from children as well as the type of virus circulating [33].

Age-disaggregated cases reported to WHO during the initial pandemic phase with the ancestral strain suggest that children under five are most at risk. In 2022, reported COVID-19 cases among children sharply increased at a period when most nations reduced public health and social policies. 18.6% (14,003,497/ 75,463,921) of all recorded cases involved minors. There are 18,605 cases per 100,000 children [34]. By the 24th of July 2022, children under 5 years old and those between 5 and 14 years old showed 2.47 and 10.44%, respectively [35].

Adolescents and young people account for 13.91% of all deaths worldwide, according to World Health Organization (WHO) figures.

Children under the age of five account for 0.11% of fatalities worldwide, compared to 0.089% of the population aged 5-14 [36]. Children and teenagers may experience protracted clinical symptoms (referred to as "long-term" SARS-CoV-2 infection's post-acute sequelae, COVID-19," post COVID-19 condition [37]. However, research into the prevalence and characteristics of these disorders is ongoing they currently seem to occur less frequently than adults. Despite its rarity, syndrome has been shown to occur globally and makes recovering from COVID-19 [38-39]. Pediatric inflammatory multisystem syndrome is the name for this condition. Multi system inflammatory disease and SARS-CoV-2 (PIMS-TS) temporally related in Europe syndrome (MIS-C) in children in North America [40].

Pre-existing disorders are linked to an increased risk of COVID-19 in children. Type 2 diabetes, severe asthma, heart and lung illnesses, seizures, other neurological conditions, and developmental issues (e.g. Down Syndrome) are pre-existing risk factors [41].

6.4. Children and teenagers' contribution to SARS-CoV-2 transmission

COVID-19 outbreaks have been reported in secondary schools, summer camps, and day care facilities. Early research suggests that younger toddlers may be less secondary attack rates, but more infectious than teenagers and adults adults [42]. SARS-CoV-2 is a virus that children who contract it shed in their respiratory tract and in their faeces as well [43].

The age at which SARS-CoV-2 is most or least contagious remains unclear, largely because it is difficult to separate the influences of environmental, biological, host, and virus-related concerns [44]. Children, adolescents, and adults who tested positive for SARS after developing symptoms showed similar quantities of viral RNA shedding in the respiratory tract [45].

Antibodies maintained even after silent infections for 12 months in all age groups. Children under the age of three were discovered to have higher levels of binding antibodies than adults over 18 [46].

7. SAFETY OF COVID-19 VACCINES IN ADOLESCENTS AND CHILDREN

The Global Advisory Committee on Vaccine Safety (GACVS) concluded in October 2021 that the benefits of COVID-19 vaccines outweighed the risks in all age groups. In Phase 2/3 trials, efficacy and immune-genicity were comparable or higher in adolescents than in adults safety and reactogenicity profiles in adolescents were comparable to young adults. No safety signal was identified during the Phase 3 trials in young children aged 6 months to 5 years, but the sample size was too small to detect rare events. Myocarditis/pericarditis occurred more frequently in younger men 16-24 years old and after the second dose of the vaccine than in older adults or children [47].

Although the risk of Thrombosis with Thrombocytopenia Syndrome (TTS) following adenoviral-vector vaccines was lower overall, it was higher in younger adults compared to older adults, but no data on the risk below the age of 18 years are available [48].

8. CONCLUSION

India is in a unique position to produce important generic medications that are both affordable and used throughout the world. India is world's largest manufacturer and worldwide distributor of vaccine. COVID-19 is the unexpected change in the development of vaccines which is one of the most urgent challenges of this generation.

9. REFERENCES

1. Lezotre PL. International cooperation, convergence and harmonization of pharmaceutical regulations: a global perspective. Academic Press; 2013.
2. Nidhi B, Mano K. *Pharmaceutical Medicine and Translation Clinical Research* ,2018 ; 215-231.
3. Breckenridge A, Woods K. *BrMedJournal*, 2005; **331(7520)**:834-836.
4. Sri Harsha Y, Sharmila Reddy V, Nary D, Nagarjunareddy D, Nagabhushanam M, Brahmaiah Bonthagarala V. *International Journal of Pharmaceutical Research and Bio-Science,* 2017; **6(2):**170-177.
5. Mankar SD, Gholap VD, Zende TP, Dighe RS. *International Journal of Institutional Pharmacy and Life Sciences,* 2014; **4(2):**288-300.
6. Nasab FR, Rahim F. *Library Philosophy and Practice,* 2021; **5(1):**1-3.
7. Song P, Karako T. *Bioscience trends,* 2020; **14(1):**1-2.
8. Ghattas M, Dwivedi G, Lavertu M, Alameh MG. *Vaccines (Basel)*, 2021; **9(12)**:1490.
9. Zimmer C. *National library of medicine, New York Times,* 2020.
10. Ulmer JB, Valley U, Rappuoli R. *Nature biotechnology*, 2006; **24(11):**1377-1383.
11. Cserep T. *Poultry diseases,* 2008; **1(6):**66-81.
12. Jee YS, Jee YS. *Journal of exercise rehabilitation*, 2019; **15(3)**:339-340.
13. Fauci AS. *The New England Journal of medicine,* 2012; **366:**454-461.
14. Muhammad MS, Vaccines are the most effective method of protecting the public against infectious diseases. Accessed from: http://196.202.134.58:8080/xmlui/bitstream/handle/123456789/5067/1-%20First%20Page.pdf?sequence=1&isAllowed=y, accessed on 11 September 2012.
15. Perry J, Osman S, Wright J, Richard-Greenblatt M, Buchan SA, Sadarangani M, Bolotin S. *PLoS One*, 2022; **17(4)**:e0266852.
16. Leshem E, Wilder-Smith A. *The Lancet,* 2021; **397(10287)**:1783-1785.
17. Bhatia R, Abraham P. COVID-19 vaccines & pandemic Accessed from: https://coronavirus.data.gov.uk/details/vaccinations, accessed on May 31, 2021.

18. Bhatia R, Abraham P. COVID-19 vaccines & pandemic https://coronavirus.data.gov.uk/details/vaccinations, accessed on May 31, 2021.
19. Dorji T, Tamang ST. *BMJ Glob Health,* 2021; **6:**e005977.
20. Artaud C, Kara L, Launay O. *Malaria Control and Elimination*, 2019:165-76.
21. Jackson LA, Anderson EJ, Rouphael NG, Roberts PC, Makhene M, Coler RN, et al. *New England Journal of Medicine,* 2020; **383(20)**:1920-1931.
22. Graham SP, McLean RK, Spencer AJ, Belij-Rammerstorfer S, Wright D, Ulaszewska M, et al. *NPJ vaccines*, 2020; **5(1)**:69.
23. Aggarwal R, Bhattacharya S, Singh S. *MedRXiv,* 2020 Jun 29:2020-2026.
24. Fragkou PC, Belhadi D, Peiffer-Smadja N, Moschopoulos CD, Lescure FX, Janocha H, et al. *Clinical Microbiology and Infection,* 2020; **26(8)**:988-98.
25. Fidahic M, Nujic D, Runjic R, Civljak M, Markotic F, Makaric ZL, Puljak L. *BMC Med Res Methodol*ogy, 2020; **20(1)**:161.
26. Lythgoe MP, Middleton P. *Trends in pharmacological sciences,* 2020; **41(6)**:363-382.
27. Mehta HB, Ehrhardt S, Moore TJ, Segal JB, Alexander GC. *BMJ open,* 2020; **10(6)**:e039978.
28. Xu P, Xing X, Yu K, Lv Z, Cui H, Shi Y, et al. *Emerging Microbes & Infections*, 2020; **9(1)**:1695-1701.
29. Zhu RF, Gao YL, Robert SH, Gao JP, Yang SG, Zhu CT. *Journal of translational medicine*, 2020; **18**:1-9.
30. Moghadas SM, Vilches TN, Zhang K, Wells CR, Shoukat A, Singer BH, et al. *Clinical Infectious Diseases,* 2021; **73(12)**:2257-2264.
31. Kumar VM, Pandi-Perumal SR, Trakht I, Thyagarajan SP. *npjVaccines,* 2021 Apr 21; **6(1)**:60.
32. Voysey M, Clemens SA, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. *The Lancet,* 2021 Jan 9; **397(10269)**:99-111.
33. Keech C, Albert G, Cho I, Robertson A, Reed P, Neal S, et al. *New England Journal of Medicine,* 2020 Dec 10; **383(24)**:2320-2332.
34. Ella R, Vadrevu KM, Jogdand H, Prasad S, Reddy S, Sarangi V, et al. *The Lancet Infectious Diseases,* 2021 May 1; **21(5)**:637-646.
35. Logunov DY, Dolzhikova IV, Zubkova OV, Tukhvatulin AI, Shcheblyakov DV, Dzharullaeva AS, et al. *The Lancet,* 2020 Sep 26; **396(10255):**887-897.
36. Ghosh PK. *Journal of Medical Sciences,* 2021 Jul 1; **8(3)**:289-296.
37. Geva A, Patel MM, Newhams MM, Young CC, Son MB, Kong M, et al. *E Clinical Medicine,* 2021 Oct 1; 40.
38. Atkins DL, Sasson C, Hsu A, Aziz K, Becker LB, Berg RA, et al. American Academy of Pediatrics, https://www.aap.org/en/pages/2019-novel-coronavirus-covid19infections/children-and-covid-19-state-level-data-report/, Accessed on 2022.
39. Florez H, Singh S , Online dashboard and data analysis approach for assessing COVID-19 case and death data, Accessed from: https://app.powerbi.com/view?r=eyJrIjoiYWRiZWVkNWUtNmM0Ni00MDAwLTljYWMtN2EwNTM3YjQzYmRmIiwidCI6ImY2MTBjMGI3LWJkMjQtNGIzOS04MTBiLTNkYzI4MGFmYjU5MCIsImMiOjh9 , accesed on 8 Jun 2020.
40. Pillai A, Nayak A, Tiwari D, Pillai PK, Pandita A, Sakharkar S, Balasubramanian H, Kabra N. *Vaccines,* 2023 Mar 17; **11(3)**:693.
41. Chaichana U, Man KK, Chen A, Wong IC, George J, Wilson P, Wei L. Definition of Post–COVID-19 Condition Among Published Research Studies, https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1, 3 Apr 2023.
42. Dufort EM, Koumans EH, Chow EJ, Rosenthal EM, Muse A, Rowlands J, et al. *New England Journal of Medicine*, 2020 Jul 23; **383(4):**347-358.
43. Feldstein LR, Tenforde MW, Friedman KG, Newhams M, Rose EB, Dapul H, et al. *JAMA,* 2021 Mar 16; **325(11):**1074-1087.
44. Jiang L, Tang K, Levin M, IrfanO, Morris SK, Wilson K, et al. *Lancet Infect Dis,* 2020 Nov 1; **20(11):**e276-288.
45. Shi Q, Wang Z , Liu J, Wang X , Zhou Q, Li Q , et al. *E Clinical Medicine*, 2021; **41:**101155.
46. Xu W, Li X, Dozier M, He Y, Kirolos A, Lang Z, Mathews C, Siegfried N, Theodoratou E. *Journal of global health,* 2020; **10(2):**021104.
47. Xu Y, Li X, Zhu B, Liang H, Fang C, Gong Y,et al. *Nature medicine*, 2020 Apr; **26(4):**502-505.
48. Madera S, Crawford E, Langelier C, Tran NK, Thornborrow E, Miller S, DeRisi JL. *Scientific reports,* 2021 Feb 4; **11(1):**3044.
49. Rajmil L. *BMJ paediatrics open,* 2020; **4(1):**722.

50. Di Chiara C, Cantarutti A, Costenaro P, DonàD, Bonfante F, Cosma C, et al. *JAMA network open,* 2022 Jul 13; 5(7).
51. Gargano JW, Wallace M, Hadler SC, Langley G, Su JR, Oster ME, et al. Use of mRNA COVID-19 vaccine after reports of myocarditis among vaccine recipients, https://www.who.int/news/item/11-08-2022-interim-statement-on-covid-19-vaccination-for-children#:~:text=Available%20from%3A%20https%3A//www.who.int/news/item/27%2D10%2D2021%2Dgacvs%2Dstatement%2Dmyocarditis%2Dpericarditis%2Dcovid%2D19%2Dmrna%2Dvaccines%2Dupdated, accessed on Oct 2021.
52. Price AM, Olson SM, Newhams MM, Halasa NB, Boom JA, Sahni LC, et al. *New England Journal of Medicine,* 2022 May 19; **386(20):**1899-909.