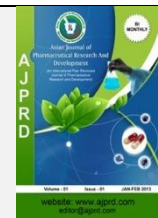


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Review Article

The World of Vaccines: Phases of Clinical Trials and Current Status of COVID-19 Vaccines

Navya Pabbathi¹, Haritha Pasupulati², Soni Gaddam¹, Satyanarayana SV Padi^{1,*}¹Department of Pharmacy Practice, Care College of Pharmacy, Hanamkonda, Telangana, India²Department of Pharmacy Practice, Bharat School of Pharmacy, Hyderabad, Telangana, India

ABSTRACT

The world of vaccines has transformed vaccination by saving millions of lives which otherwise would have killed many people and a hurdle for sustainable development world-wide. Indeed, the coronavirus disease 2019 (COVID-19) pandemic is a public health emergency and an important milestone that revealed how vaccines are really turning point for live changing across the world. Owing to extensive human efforts, vaccines for COVID-19 are discovered and developed and approved globally in less than a year, which is the first time in the history of the world of vaccines. Furthermore, one of the strategic goals of WHO's 'The Immunization Agenda 2030' (IA2030) is the clinical development and approval of 500 new vaccines by 2030. Discovery of immunogens that elicit immune responses is a key step or process by which vaccine candidates have been optimized for further preclinical and clinical trials. Clinical evaluation is carried out in Phases (1-3) and is a sequential approach of establishing safety and efficacy in humans. Regulatory requirements for vaccine approval and licensure to bulk manufacturing are another hurdle. Further, post-marketing safety studies and post-marketing surveillance (Phase 4) are essential to collect the real-world data on safety and effectiveness of the approved vaccines. This review work provides a brief outline on timeline of development of traditional and COVID-19 vaccines and summarizes all the six stages of the vaccine development. Furthermore, current status of COVID-19 vaccines is discussed in view of future approvals.

Keywords: Clinical trials, Clinical evaluation, COVID-19, IA2030, Immunobridging, Seamless design, Vaccine for COVID-19**ARTICLE INFO:** Received 15 Feb 2023; Review Complete 28 April 2023; Accepted 27 May 2023; Available online 15 June 2023**Cite this article as:**

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*Address for Correspondence:

Satyanarayana SV Padi, Professor & HOD, Department of Pharmacy Practice, Care College of Pharmacy, Oglapur (V), Damara (M), Hanamkonda, Telangana, 506006, India

INTRODUCTION

A world without vaccines is unimaginable since many important breakthroughs happened in the history of medicine, such as the first randomized clinical trial conducted by James Lind in 1947, the discovery of the first vaccine against smallpox by Edward Jenner in 1796, the first effective vaccine against polio by Jonas Salk in 1953, development of oral polio vaccine by Albert Sabin in 1961, and so on.^{1,2} The first-time human efforts had beaten a human disease was due to the vaccine development and global vaccination programs that successfully and completely eradicated smallpox by 1980.^{2,3} It is estimated that about 300 million people died of smallpox in the 20th

century alone and at least half a billion people were killed in the last hundred years of its existence.⁴ In fact, the infections and their complications that are now vaccine-preventable, such as polio, diphtheria, pertussis, tetanus, measles, mumps, rubella, and hepatitis B would have been destructive factors for ubiquitous sustainable development and become a global burden if the world is without vaccines.

The World of Vaccines

The world of vaccines has seen tremendous growth in research and development and approvals of a large number of vaccines during 1950-1990, termed the golden era of vaccines that transformed pediatric vaccination. An estimated 3.5-5 million lives of children were saved across

the world every year due to vaccinations, which reduced the global infant mortality rate from 65 per 1,000 live births in 1990 to 29 in 2018.⁵ Epidemiologically, an estimated more than 50 million deaths can be averted through immunizations between 2021 and 2030.⁶ Indeed, regulatory agencies, such as the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the Center for Drug Standards and Control Organization (CDSCO) of India have approved vaccines for 29 known variants of pathogens.

During the past decade, outbreaks, epidemics, and pandemics had posed a serious threat to public health and made millions of people's lives at risk of death. In that prevailing emergency situation of not having approved antiviral drugs and vaccines, only a few repurposed drugs had shown limited benefit. In 2012, The World Health Organization (WHO) endorsed the Global Vaccine Action Plan (GVAP) with an aim to extend the benefits of vaccination to all by 2020.⁷ Moreover, 'The Immunization Agenda 2030' (IA2030) of the WHO has been initiated to achieve 90% coverage for essential vaccines in children and adolescents, to reduce the rate of vaccine missing out by 50%, and the clinical development and approval of 500 novel vaccines in the low and middle-income countries (LMICs) for the next ten years.^{8,9} In line with this, 17 and 25 vaccines are introduced in 2020 and 2021, respectively. These new vaccine approvals and introductions are not limited to dengue, malaria, Ebola virus disease, and respiratory syncytial virus but future introductions might be extended to several vaccine candidates against influenza and tuberculosis as well as neutralizing antibodies and therapeutic vaccines for Alzheimer's disease and cancer.⁹⁻¹¹

In late 2020, the entire world was eagerly waiting for an effective vaccine that has been developed and clinically evaluated by scientifically proven and validated methodologies to be approved. This unprecedented time realized people the facts that hygiene approaches of wearing masks, applying hand sanitizers, and social distancing were only temporarily avoiding spread of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and only a vaccine might protect and end the lockdown.^{9,12} Prospectively, the COVID-19 pandemic is a great and unique example of how vaccines, vaccinations, and immunizations are really game-changers that can improve lives across the world.

DEVELOPMENT AND CLINICAL EVALUATION OF VACCINES

There is a great global demand for vaccines to prevent the spread of infectious diseases, to protect and save lives, and to promote universal equality in health in line with strategic goals of the IA2030. However, preclinical and clinical evaluation is prototypical for the assessment of the safety, efficacy, and effectiveness of vaccines.^{8,9,12} A typical timeline of a standard vaccine development takes 5 to 15 years due to extensive clinical evaluation, delays in regulatory approval processes, and time for bulk manufacture and distribution.^{9,13-15} The typical development of a vaccine occurs in six stages, viz. (1) Exploratory/Discovery stage, (2) Preclinical stage, (3) Clinical development stage (Phases 1-3), (4) Regulatory

review, licensure, and approval stage, (5) Manufacturing stage, and (6) Post-licensure stage (Phase 4).^{9,13-18} The stages and timeline of traditional and accelerated COVID-19 vaccine development and approval are outlined in Table 1 and 2, respectively.

1. EXPLORATORY/DISCOVERY STAGE

In general, this stage necessitates extensive basic and applied research that takes about 2-5 years for the completion and discovery of appropriate antigens (immunogens). This is a typical investigation stage that involves the exploration of basic research and scientists adopt multidisciplinary approaches to conduct research and disseminate knowledge gained to discover the antigens. It involves the application of current research methodologies and technologies in life sciences and informatics with extensive use of genomics, proteomics, and bioengineering techniques (DNA cloning), such as next-generation sequencing, whole genome sequencing of several microbes and immunogens.^{10,11,19} This exploratory research occurs *in vitro* and *in vivo* experimental animals, such as rats, mice, hamsters, ferrets, guinea pigs, rabbits, sheep, and non-human primates, such as rhesus macaques, cynomolgus macaques, baboons, monkeys, etc.^{9,20} Recently, basic research has made exemplary breakthroughs in the advanced understanding of several known pathogens for which no vaccine is available, identifying immunological vaccine candidates for age-related neurodegenerative disorders, such as Alzheimer's disease, multiple sclerosis, and help in developing preventive and therapeutic vaccines for malignant cancers and chronic disorders, such as hypertension and dyslipidemia.^{9-11,21} Most of the basic research is funded by government and pharmaceutical/biotechnology companies that construct scientific consortiums and committees on vaccine development to provide access to genomic libraries, unconditional dissemination of knowledge, and incentives to university-based researchers to stimulate the development of possible vaccine candidates (Table 1, 2). Successful research leads to technology transfer ensuing progress from basic research to the product-development stages.^{19,22}

2. PRE-CLINICAL STAGE/DECIDING STAGE

Pre-clinical stage precedes clinical evaluation that uses both *in vitro* (tissue culture, cell culture system, cell lines) and *in vivo* (experimental animals) studies to investigate the safety and immunogenic potential of several antigens of a pathogen in order to decide the best immunogen suitable for a vaccine candidate. These antigens include viruses/bacteria, weakened virus/bacteria, weakened bacterial toxins, or other substances derived from pathogens, neuroinflammatory targets in Alzheimer's disease, or immune checkpoints in cancers, which will help or stop the disease.^{10,11,23} Once the protective antigens of a specific pathogen are identified and isolated, the methods of delivery of immunogen(s) (vector systems, mRNA, protein subunits, recombinant proteins), pre-formulation, and development and immunologic evaluation of new adjuvant systems are studied depending on the nature of pathogen.^{15,16,24} These studies recommend preliminary doses and methods for the safe administration of vaccine candidates for clinical evaluation and research. This stage is a very critical and deciding phase for excluding

vaccine candidates that are either toxic or do not induce required immune responses. The safe and promising vaccine candidates that can activate the immune system in the preclinical studies progress to Phase 1 clinical development (Table 1, 2).

During emergencies due to outbreaks (Ebola, Zika virus) and pandemics (Swine flu, COVID-19), the development and critical evaluation of vaccine candidates may be atypical and mostly accelerated on priority basis. Past knowledge gained from the experience of several viral outbreaks and the application of present genome sequencing and platform technologies had made it possible to understand the entire genome of several pathogens, including Ebola, SARS-CoV-2 that accelerated discovery and development as well as target-based delivery of drugs and vaccines.^{9,17-19} As in this case, a national government may unite government agencies, international public health units, university research units, academia, nonprofit organizations, and biotechnological and pharmaceutical companies to develop a harmonized strategy for coordinating, maneuvering, prioritizing, and speeding the development of the most promising treatments and vaccines. In addition, the government and non-government organizations may make investments in research and development that energize building manufacturing capacity at their own risk, giving industries confidence that they can invest aggressively in clinical development and allowing faster distribution of a realized and effective vaccine.^{17,20,25,26} Owing to these efforts, several vaccine candidates have already been evaluated in humans, effective vaccines approved within a year, and hundreds of vaccine candidates are undergoing clinical evaluation in humans (Table 2, 3).

3. CLINICAL DEVELOPMENT: Clinical Trials of Vaccines

THE PRE-LICENSURE PROCESS

The early steps of clinical development are often time-consuming as the sponsor of the vaccine development should obtain a license to manufacture, cold chain distribution, and preparation of pilot lots for evaluation purposes in the preclinical stage followed by Phase 1 testing in humans. The next step is to constitute an Institutional Ethics Committee, Biohazard and Safety Committee, members of the clinical trial team who are experts in clinical trial design, and an Institutional Review Board (IRB) representing an establishment, such as clinical research units and hospitals where the clinical evaluation is going to be conducted. The protocols for clinical trials are prepared by the clinical trial team and must be approved by the IRB before submitting an investigational new drug (IND) application to the regulatory body for initiating clinical trials.^{27,28}

Regulatory bodies carefully study complete IND application with respect to adherence to good manufacturing procedures (technology and procedures), good laboratory procedures (quality control and assurance), good documentation procedures (deviations and proof of evidence), and good clinical procedures (ethical safeguarding of humans) in clinical trials. Importantly, clinical trial results will be evaluated by regulators based on all these good practices as well as good trial design during the regulatory decision-making process for approval. The application should

provide details of 1) the description, composition, source, and manufacturing process of the vaccine candidate, 2) quality control tests and the methods used to assess the safety, purity, and potency of the vaccine candidate, 3) summarized results of all laboratory and preclinical testing, particularly animal studies, 4) description of clinical trial design and methodology, and 5) names and qualifications of members of the clinical trial team.²⁵⁻²⁷

A good trial design should focus on methods to minimize bias and errors (type-I and type-II), such as sample size, randomization procedures, selection of participants based on the risk of infection, cohorts or subsets of participants, diagnostic procedures, biological sample collection (nasal, blood, feces), bioassay methods, validation of analytical procedures, quantification and detection limits (low and high), and blinding/masking/concealment, appropriate controls (placebo or active) for comparison, follow-up, collection and monitoring of safety data, and statistical procedures, etc. It is equally important to select valid and appropriate primary and secondary endpoints of outcome to evaluate the safety, reactogenicity, immunogenicity, and efficacy of vaccine candidates as well as criteria for the interim and final analysis of clinical trial data.^{9,29,30}

The FDA reviews the IND application to determine preliminary vaccine safety and efficacy for translating such information in human subjects considering unwarranted exposure and risks during a waiting period of 30 days.²⁵⁻²⁸ During the recent pandemic, regulatory agencies, FDA and EMA, accelerated the review of IND applications for the first human trials of COVID-19-vaccine candidates in a time period ranging from less than a week to 20 days, instead of the typical 30 days.¹⁶⁻¹⁹ Once IND is approved and permitted to conduct studies in humans, Phase 1 of the clinical development stage is initiated under the supervision of the FDA.

PHASE 1/DOSE ESCALATING STUDIES

Objective: Phase 1 clinical trials assess safety/tolerability to identify side effects (SEs) and adverse drug reactions (ADRs), dose, dosing, method of administration, reactogenicity, and immunogenicity to estimate the efficacy of vaccine candidates.

Study design: It is usually an open-label and non-randomized trial. However, it is also possible to conduct parallel and randomized trials with a placebo, an approved vaccine, or an effective vaccine candidate employed as a comparator against a special disease. These studies are often single or double-blinded to minimize bias. It is mandatory to evaluate all the formulations (a lot to lot) and if any change in the original safe formulation during a new Phase 1 trial.

Subject number: It involves 20 to 100 healthy volunteers excluding children, women of any stage, older adults, those who are with co-morbidities, immunocompromised conditions, and individuals with a risk of infection.

Study population: Phase 1 studies are 'First-in-Man' studies that involve small groups of healthy immunocompetent naïve adults who are at low risk of acquiring a vaccine-relevant infection and also called Phase 1a trials. Similar to earlier studies, Phase 1b trials are conducted in different geographies, ages, or population

groups that closely match the target population to evaluate differences in dose, vaccine schedule, route of administration, safety/tolerability, or reactogenicity.^{9,20,31,32}

Study site: In general, the Phase 1 study site is located within or area near tertiary care hospital. It may be conducted at one or multiple centers and one or more countries in case of outbreaks and pandemics. Subjects are closely observed daily for monitoring reactogenicity (SEs and ADRs) after immunization. In particular, live attenuated and toxoid vaccines and sometimes killed vaccines cause possible shedding of infectious agents, feces-oral transmission, transmission to contacts (rare), and a possible reversion to a virulent form and cause disease that requires closely monitored clinical settings and continuous evaluation for any clinical signs of infection.^{33,34} The extent, route, and duration of shedding vary with the type and route of administration of a vaccine. Importantly, older adults, high-risk individuals, and immunocompromised subjects are excluded in Phase 1 trials to prevent exposure to such vaccines and evade suspected indirect infection for a specific period of time.^{34,35}

Outcome:

Phase 1a involves gradual single-dose ascending (dose escalation) to determine the maximum tolerated dose (MTD) based on the results from the safety/tolerability and reactogenicity evaluation. Phase 1b involves evaluating the same endpoints (outcome measures) in cohort subgroups (target population with similar demographic and/or disease characteristics) at one or more dose levels to determine the recommended dose for the Phase 2 trial.^{31,32,36}

In a typical or accelerated vaccine development process, safety/tolerability, reactogenicity, and immunogenicity are done by evaluating the quantity and quality of humoral and cellular immune responses in participants with different booster doses and schedules 2 – 3 months after Phase 1/2 or 1/2a clinical trial.³⁷⁻⁴¹ These studies determine dose-dependent adverse reactions (solicited and unsolicited) with increasing doses and investigate about nature of the vaccine candidate to the extent of inducing immune responses in healthy participants. These trials also focus on studying different doses, vaccination schedules, and preliminary assessments of immunogenicity for expansion to a larger and more targeted population.^{20,29}

The primary outcome measures focus on reactogenicity that includes safety indexes and the occurrence of localized adverse reactions, such as pain, redness, or swelling at the site(s) of injection, and systemic adverse reactions, including fever, fatigue, headache, muscle pain, fatigue, chills, joint pain, nausea and vomiting, feeling unwell or general discomfort, swollen lymph nodes are observed when the shot was given and daily for a duration of 7 days post-vaccination.^{42,43} Endpoints for evaluation of immunogenicity and preliminary efficacy vary from one infection to another infection or disease. In the case of the HPV vaccine, the endpoints are pathologic regression of colposcopic biopsy evaluation, peripheral blood mononuclear cells, and cytokine levels over the 15-week interval.^{29,39,44}

The secondary outcome measures include safety indexes and occurrences of adverse events (AEs), serious adverse events

(SAEs), and adverse events of special interest (AESIs) laboratory measures, such as complete blood profile and function tests of kidney and liver are done 0-28 days, within 6 months post-vaccination.^{30,32} In addition, immunogenicity indexes of humoral and cellular immune immunity, specific cellular immune responses, seroconversion, CD4+, and CD8+ T-cell responses, kinetics of serum cytokine levels, C-reactive protein, and vaccine-induced genes signatures, seropositivity rates using various available methods, and geometric mean titer (GMT), fold concentration (GMC) and increase (GMI) in neutralizing antibody responses are also measured on day 0, 7, 14, 28, and at 6-month post-vaccination.³⁰⁻³² Additionally, consistency and persistence analyses, dose-response and time-dose-response relationships of specific antibodies (cellular and humoral immunity), the relationship between the appearance time of specific antibodies against microbe (bacteria or virus) and the vaccination dose are done among study groups at time points of 0, day 7, 14, 28, month 3 and 6 post-vaccination.⁴⁵ Besides, AEs leading to withdrawal, AESIs, and deaths up to 21 days after each vaccination are also observed as well as potential cases of hypersensitivity, vaccine-associated enhanced disease (VAED), and potential immune-mediated diseases (pIMDs) are monitored throughout the study period. If special populations are involved, pregnancies and patients with co-morbidities and immunocompromised conditions are monitored for 6 months after the vaccine dose. Special biostatistical analyses are done according to the intention to treat (ITT), with additional per-protocol (PP) analyses for immunogenicity outcomes.^{29,46,47} Irrespective of whether a participant drop or not during a clinical trial, ITT includes all randomized participants in the analysis. On the contrary, in a PP analysis, biostatisticians analyze the data from those who strictly adhered to the study protocol and completed the trial.

Considering formulation and manufacturing aspects of vaccine candidates, the critical step is to complete the definition of the vaccine product and vaccine production process before the initiation of Phase 2 dose-ranging studies, which generally take a year or longer. Vaccine product definition includes methods of synthesis, bioprocess steps, number of components, and stability of the formulation. Stability and assays of raw material as well as immunologic and any other assays must be established and validated to support dose-ranging studies in the Phase 2 trial. Parallel to the progression of Phase 1, a regulatory plan for the production process and product submissions of vaccine candidates must be written for approval to initiate Phase 2.^{16,20,40}

Indeed, several vaccine candidates appear to be safe and induce protective immune responses in animals fail in human studies in Phase 1. The high failure rate of vaccine candidates in Phase 1 is attributable to various reasons including a) not having an advanced understanding of the biology of immunogen and immune responses for protection, b) lack of validated animal models to predict immune responses of vaccine candidates in humans, c) complexity and unpredictability of human immune system responses to immunogens since it is accounted for safety, immunogenicity, and efficacy, d) influence of confounders, such as age, health, nutritional status, chronic illness,

immunocompromised conditions, and host genetic variations, e) unpredictability of the impact of multiple components, such as excipients, preservatives, adjuvants, stabilizers, and pH regulators in a vaccine.^{26,48} It is reported that the probability of successful progress from Phase 1 to Phase 2 was 38.2-66.3% and the probability of successful approval by the FDA for a vaccine candidate in Phase 1 was 7.1 (1 out of 14) to 16.2% (1 out of 6).^{49,50} This phase generally takes 1-2 years (Table 1). In an accelerated clinical development, Phase 1 trials can be completed in one to three months, allowing for two doses of a vaccine with an interval of three to four weeks.^{9,51} Intriguingly, Phase 1 trials for COVID-19 vaccine candidates were completed in a month's time due to seamless, combined, and concurrent trial design (Phase 1/2).^{9,16-19,52} In such a scenario, additional assessment of safety endpoints is continued through Phase 2 and 3 studies (Table 2).

PHASE 2

Objective: Phase 2 clinical trials are done to validate formulation and method of administration, establish safety

and reactogenicity profile, assess dose-dependent and time-dependent responses (dose ranging/dose-finding), find long-term persistence of immune response, demonstrate schedule of immunization and immunogenicity, and efficacy in hundreds of participants.

Study design: It is usually randomized, parallel, double-blind, well-controlled studies with a placebo, an approved vaccine, or an effective vaccine candidate employed as a comparator against a special disease. Often, Phase 2 studies can employ adaptive strategies to drop poorly performing vaccine candidates when 'Proof-of-Efficacy' is not established. This approach is more appropriate for Phase 2 trials than Phase 3 trials.

Subject number: It involves 100 to 3000 healthy volunteers of diverse demographic characteristics, such as age, gender, children, and women of any stage, older adults, those who are with co-morbidities, immunocompromised conditions, and individuals with risk of infection and underlying medical condition.

Table 1: Stages and timeline of traditional vaccine development and approval (Adapted from Ref. 9)

Standard vaccine development and approval (5 to 15 Years)					
Discovery/ exploratory (2 – 5 Years)	Pre-clinical (1 – 2 Years)	Clinical development (5 – 10 Years)			Phase 4 (2 – 5 Years)
		Phase 1 (1 – 2 Years)	Phase 2 (2 – 3 Years)	Phase 3 (2 – 4 Years)	
Preliminary <i>in vitro</i> and <i>in vivo</i> (animals) studies and Development of platform technologies & microbial genome databases initiated by national/regional funding, Academia, WHO initiation, NGOs	Identification of microbes, target proteins, vectors; Platform technology, Analysis of genomic data; safety and immunogenicity studies in animals, Selection of endpoints; Development and validation of immunity assays and vaccine process; Translation research; Pre-formulation studies; IND application	Safety, purity, reactogenicity, immunogenicity, dose escalation, age de-escalation, dose escalation mode of administration, selection of needle size, selection of dose for Phase 2	Safety, immunogenicity; Proof of concept, Proof of efficacy; primary and secondary outcomes; Additional cohorts, special population studies	Efficacy trial, Pivotal trials, First booster dose trial; Application for approval; Regulatory Review; Marketing Approval; Manufacturing license; Technology transfer; Bulk manufacturing	Effectiveness trials; Post-licensure safety & monitoring studies; Second/third/ fourth booster (homologous or heterologous) dose trials; Superiority, non-inferiority trials; Additional cohorts, special population studies; Annual vaccination trials after EMA-MAA, FDA-BLA, CDSCO-NDA approval

BLA, Biologic License Application; CDSCO: Central Drugs Standard Control Organization; EMA: European Medicines Agency; FDA: Food and Drug Administration; IND: Investigational New Drug; MAA: Marketing Authorization Application; NDA: New Drug Application

Study population: Phase 2 studies are exploratory clinical trials that involve relatively larger groups of healthy adults who are at no, low, or high risk of acquiring a vaccine-relevant infection and are also called Phase 2a trials. Similar to earlier studies, Phase 2b trials are conducted in different geographies, ages, or population groups that closely match with the target population to evaluate differences in dose, dosing, vaccine schedule, route of administration, safety/tolerability, or reactogenicity. In situations where preclinical animal studies of certain vaccine targets are not predictive of efficacy in humans, such as Human immunodeficiency virus/acquired immunodeficiency

syndrome (HIV/AIDS), tuberculosis (TB), and malaria, Phase 2b studies are done. Such studies, also called 'Proof-of-Concept' or 'Proof-of-Efficacy' employs adaptive clinical trial designs to gain confidence of efficacy in a large number of subjects with a subset of diverse demographic and host characteristics.^{16,20,26}

In Phase 2 studies, vaccine candidates for children start with adult volunteers and gradually step down the age of the test subjects until they reach their target age referred to as age de-escalation or step-down approach. Generally, these studies are performed in both male and female populations aged 9-25 years.⁵³ Younger children are physically

immature and have a rapid phase of growth and development, which are predisposed and vulnerable to AEs of medications. The age de-escalation procedure protects pediatric participants from the unknown risk of participating

in a trial with a new vaccine. This procedure also gives special exclusion criteria by protecting young children from uncertainties of novel interventions, morbidities, and hospitalizations.

Table 2: Stages and timeline of accelerated COVID-19 vaccine development and approval (Adapted from Ref. 9)

COVID-19 vaccine development and approval (Less than a year)				
Exploratory & Pre-clinical (1 week – 2 months)	Clinical development (8 – 10 months)			Phase 4 (2 months – 2 years)
	Phase 1 (1 – 3 months)	Phase 2 (1 – 3 months)	Phase 3 (1 – 6 months)	
	Seamless Phase 1/2 trial		Seamless Phase 2/3 trial	
Exploration of microbial databases along with current genomics, proteomics utilized for pre-clinical research; Funding from government, NGOs, WHO, pharmaceutical, biotechnological companies during public health emergencies; preformulation, IND application	Seamless, immunobridging Phase 1, 1b/2, 1/2a, or 1/2b study; Safety, purity, reactogenicity, immunogenicity, dose escalation, mode of administration, selection of needle size; Interim review/cycles of rolling review of Phase 1, selection of dose, initiation of Phase 2; Global bulk manufacturing initiation	Positive interim data of Phase 1/2 or 1b/2a used for seamless, immunobridging Phase 2b or 2/3 study Involve large number of participants, additional cohorts, special population studies Rapid review of Proof of efficacy; primary and secondary outcomes; Interim review/cycles of rolling review of Phase 2, selection of dose, initiation of Phase 3	Efficacy trial; Involve large number of participants, additional cohorts, special population studies; Primary and secondary endpoints met; Positive efficacy; Application for special approval; Regulatory Review; Manufacturing license; Technology transfer; Bulk manufacturing	Involve large number of participants, additional cohorts, special population studies; First/second/third/ fourth booster (homologous or heterologous) dose trials; Post-licensure safety studies and monitoring
			FDA fast-track review; EUA	FDA-BLA
			CDSCO fast-track review; EUA	CDSCO-NDA approval
			EMA rolling review; CMA	EMA-MAA

BLA, Biologic License Application; CDSCO: Central Drugs Standard Control Organization; EMA: European Medicines Agency; FDA: Food and Drug Administration; IND: Investigational New Drug; MAA: Marketing Authorization Application; NDA: New Drug Application

Owing to this, vaccine trials are initiated in adults as the frontline of any uncertain intervention rather than in children. Importantly, risks of AEs associated with a new vaccine are presumed to be greater in children than that in adults.^{54,55} It is difficult to assume the safety of such vaccines in children without establishing safety/tolerability in adult participants. In such criteria, infants and children starting from 2 months to 18 years of age are randomly divided into various sets of age-dose cohorts.⁵⁶⁻⁵⁸ Importantly, this phase considers a diverse sample of adults (≥ 18 years old) and includes a subset of participants with pre-existing medical conditions, immunocompromised, and those with a potentially increased risk for severe disease. Of particular note, young women are not encouraged to participate in clinical trials owing to miscarriages, complications associated with the termination of pregnancies, premature births, and stillbirths, but not infrequent outcomes of pregnancies.⁵⁹ In general, vaccines are not recommended in pregnancy due to an increase in rates of poor pregnancy outcomes in vaccinated pregnant women over those who are not vaccinated.⁶⁰ Clinical trials exclude pregnant women from participation for two reasons, first when there is no scope of benefit to the pregnant woman, and second, a risk of harm to the offspring is not

known or possibly not established in advance. In general, participants with severe chronic illness, those suffering from or at risk of hepatitis B virus, hepatitis C virus, human immunodeficiency virus, or tuberculosis infection, and those with recent organ transplants are excluded.⁶¹

Study site: Phase 2 clinical trials are usually conducted in community-based study sites where controlled trials are feasible. The study area and sites may differ depending on the type of vaccine candidate being studied. Mostly, the target population is young adults and adolescents, therefore the sources of the study population are colleges, universities, and their surrounding communities. This study conducts at 3 - 4 centers and different countries to selectively target geographical areas and people who are at risk of specified diseases of interest.

Outcome: The primary and secondary endpoints of efficacy and immune response to vaccine candidates in Phase 2a are typically the same as that of Phase 1 trials. However, these studies provide additional safety/tolerability data on frequent SEs, examine dose-dependent safety, reactogenicity, and immune responses, and provide initial information on efficacy i.e., the ability of vaccine candidate to generate an immune response. Vaccine efficacy is a

measure of vaccine effects defined as the proportionate reduction of the incidence of specific infection in vaccinated participants compared to controls.⁶² Importantly, Phase 2b dose-ranging studies are conducted in adults (≥ 18 years old) and include a subset of participants with pre-existing medical conditions, immunocompromised, and those with a potentially increased risk for severe disease. Further, this phase is intended to generate reliable data to establish proposed doses, schedule of immunizations, and method of delivery (route of administration, needle size, and storage conditions).^{29,37-39}

In these studies, seamless adaptive design is possible to combine different phases of trials in the same participant, and booster vaccination is done 1 or 2 years after the first dose (prime) to the Phase 2 participants.^{63,64} A booster either heterologous or homologous is administered to eligible participants at 1, 3, 6, 9, or 12 months after priming depending on the nature of the infection, age of participants, population (pediatric, geriatric) at risk, and target efficacy of vaccine.⁶⁵⁻⁶⁷ In the accelerated process, safety/tolerability, reactogenicity, and immunogenicity are done by evaluating the humoral and cellular immune responses to vaccine candidates at baseline and after each vaccination until 1 year after the booster was assessed. In such cases, prime-booster regimens are given 4-6 weeks apart in Phase 2/3 trials.^{16,20,68,69}

A typical Phase 2 clinical trial for evaluating the safety, immune responses, and dose-ranging of the efficacy of a vaccine candidate takes 2-3 years. In an accelerated approach during healthcare emergencies, Phase 2 studies can be completed in two to four months which allows longer follow-up for better assessment of safety and immunogenicity of vaccine candidates. This timeline is further shortened to one to three months when Phase 1 and Phase 2 trials are combined. A full-fledged Phase 2 study may be conducted based on dose-finding Phase 1/2 interim results in order to get more information on dose-dependent and time-dependant immunogenicity (humoral and cell-mediated immunity) responses and longevity of protection.^{20,61} Moreover, Phase 2b studies provide 'Proof-of-Efficacy' in a larger diverse population that prepares significant resources for the development of process and analytical procedures as well as scale-up lot and establishing production units for bulk manufacturing of successful vaccine candidates. It is reported that the probability of successful progress from Phase 2 to Phase 3 was 32.9-38.3% and the probability of successful approval by the FDA for a vaccine candidate in Phase 2 was 10.0 (1 out of 10) to 24.4% (1 out of 4).^{49,50} This phase generally takes 2-3 years (Table 1). In accelerated clinical development, Phase 2 trials can be completed in two to three months, allowing for two doses of a vaccine with an interval of three to four weeks.^{9,20,51} In such a scenario, additional assessment of safety endpoints is continued through Phase 3 studies. It is highly recommended to complete Phase 1 and 2 trials during inter-epidemic periods to prioritize and accelerate the final analysis of safety, immunogenicity, characteristics of the immune response, and 'Proof-of-Efficacy' that would guide study design and improve the quality of Phase 3 studies (Table 2).²⁹

PHASE 3

Objective: Phase 3 trials are conducted to evaluate and confirm short-term and long-term safety, immunogenicity, efficacy, most common side effects, schedule of vaccination, and the effect of the final formulation of a vaccine candidate in tens of thousands of participants and that is essential for registration and approval of a vaccine.

Study design: Randomized clinical trials, referred to as "gold standard", where the participants are randomly allocated to receive either the investigational or the control vaccine. An intervention Phase 3 trial is a prospective, randomized, double/triple/quadruple blinded, parallel, and controlled to minimize bias for the duration of the study. Quadruple blinding is generally followed in which participant, care provider, investigator, and outcomes assessor are masked about subject and vaccine allocation.^{70,71} Since the primary purpose of this study is prevention, parallel designs are employed to compare the safety and efficacy of vaccines with respect to standard care or approved vaccines for the same infectious disease. In accelerated and priority trials, a cross-over design is adopted to evaluate the efficacy of a booster dose of vaccine in comparison to previous exposure to the same vaccine. In the case of pediatrics and infection due to multi variants of a virus, giving doses of different vaccines or a single shot of multiple vaccines on the same day is possible if safety and efficacy data is well established. In view of this, several vaccines ranging from 2 to 5 are given as single shot or different doses on the same day to assess the safety and immunogenicity of heterologous vaccine regimen to participants 3, 6 months, 1, or 2 years after the first vaccination.⁷²⁻⁷⁴

Subject number: The study involves 10,000 - 50,000 healthy participants and/or participants with clinically controlled diseases of both genders and of different age groups, races, and ethnic groups.

Study population: Phase 3 studies are large-scale clinical trials and consider the fact that sample size is based on disease incidence, low dropout rates, well-defined clinical endpoints related to future label claims, and organized data management to the highest standards. A high incidence means that a smaller number of subjects are required to estimate vaccine safety, most common side effects, immunogenicity, and efficacy in comparison to the numbers needed if disease incidence is low.

Study site: Phase 3 clinical trials is a multicentre study conducted at 3-5 different sites and different countries to selectively target areas and people who are at high risk of contracting a specific disease.

Outcome: The primary objective of Phase 3 is to evaluate the short-term and long-term safety, immunogenicity, and efficacy of the vaccine in comparison to a placebo in infected patients.^{20,71} The primary and secondary endpoints are the same as the previous phases of the vaccine but vary from disease to disease. In general, the incidence of adverse events up to 7 - 14 days after immunization is the primary safety outcome, the number of symptomatic or asymptomatic infection cases after the second dose of the vaccine is the primary efficacy endpoint, and prevention of

disease severity is the major secondary efficacy endpoint.⁷⁵ In the case of HPV vaccines, the primary composite endpoint is cervical intraepithelial neoplasia grade 2 or 3, adenocarcinoma *in situ*, or cervical cancer related to HPV-16 or HPV-18.⁷⁴ Observational vaccine studies are non-randomized and open (not blinded), which are generally conducted after approval, may be conducted as 'field' trials for future target populations after emergency use authorization, and are critically evaluated even before approval in emergency and pandemic situations.^{76,77} Various vaccine effects that are widely used for evaluation are a) vaccine efficacy, direct vaccine effectiveness, total vaccine effects, indirect vaccine effectiveness, total vaccine effectiveness, and overall population-level vaccine effectiveness.^{29,62}

The design of a clinical study is important in analyzing safety and efficacy data wherein a superiority trial design is used when an effective vaccine for the disease is not available whereas a non-inferiority trial design is used to compare with an existing effective vaccine. The reduction in incidence rates and relative risk of disease with the new vaccine is compared with a placebo (superiority) or existing vaccine (non-inferiority).^{29,30} Further, Phase 2b/3 or 3 randomized controlled trials are important in assessing long-term protection (safety and efficacy) and the need for booster dose by analyzing subsets/cohorts of subjects for a longer duration.^{16,40,78} Phase 2b and 3 studies are also conducted to evaluate the efficacy of homologous or heterologous booster dose. A growing body of evidence support that heterologous vaccination (different prime-boost vaccine regimen) induces stronger humoral and cell-mediated immune responses and improves immunogenicity than homologous vaccination (same prime-boost vaccine regimen).⁷⁹⁻⁸² Moreover, heterologous vaccination involves the use of vaccines from different sources, and different platforms, allowing patients to benefit from the advantages of each vaccine regimen and increasing the flexibility of vaccine management. Pivotal clinical trials provide the major evidence of efficacy in the target population that allow approval and support licensure. Vaccine efficacy is calculated using the diagnosis of the first occurrence of mild to moderate infection with onset at least 14 days after the booster vaccination. The secondary endpoints of solicited local and systemic AEs are observed for 7 days after vaccination, unsolicited AEs within 28 days after vaccination, SAEs, medically attended adverse events (MAAE), and AESI throughout the study, as well as the first occurrence of asymptomatic, severe-critical infection, and that requires medical intervention at least 14 days after booster vaccination.^{20,67,75,83} As per the need of the study and efficacy of the vaccine, special analyses of ITT, modified ITT, full analysis set (FAS), per-protocol first-dose (PPFD), and PP are done.^{70,84}

Parallel to Phase 3 clinical evaluation, validation of research and manufacturing units, scale-up and manufacturing of consistency lots, quantification using validated assays, and establishing consistency and real-time stability of formulation are mandatory to support adequate shelf-life claims and labeling. It is reported that the probability of successful progress from Phase 3 to approval was 61.1-74.3% and the probability of successful approval by the

FDA for a vaccine candidate in Phase 3 was 100%.^{49,50} This phase generally takes 2-4 years (Table 1). In an accelerated clinical development, Phase 3 trials should be conducted in areas with a high risk of infection and can be completed in three to six months such that early assessment of safety and efficacy can be established (Table 2). In addition, participants are followed-up for two years or more to evaluate long-term safety and efficacy.^{9,16,20,29}

4. REGULATORY REVIEW, LICENSURE, AND APPROVAL

The manufacturer and the originator of the vaccine can submit an application to the national regulatory authority to license and market the product. Most countries have the same regulatory agency for the approval process for drugs and vaccines. The FDA in the US, the EMA in Europe, and the CDSCO in India are some of the regulatory agencies responsible for regulating vaccines in their country or territory. Based on interim and final data analysis, if proof of safety and efficacy are established during clinical trials, a biologic license application (BLA) is made to the Center for Biologics Evaluation and Research (CBER) of the USFDA, a centralized marketing authorization application (MAA) in Europe, or new drug application (NDA) in India is applied for approval.^{85,86} In general, this application for vaccine approval is a comprehensive document that includes a) detailed information on the manufacturing procedures, source of immunogen, type, standardization, purity, analytical testing methods, and process controls for the product, b) results of all quality control tests, including purity and stability tests, performed on a specified number of lots before, during, and after manufacturing, c) systematically summarized safety, immunogenicity, and efficacy results of the vaccine in a multicenter and multinational clinical study, d) dose, dosing, mode of administration, needle size, and e) proposed labeling, including precautions, warnings, stability and storing temperature.^{24,26,85,86}

Vaccine approval for licensure and marketing is based on 1) a review of all the clinical data for evidence indicating that the vaccine product is safe, tolerable, immunogenic, and effective for its proposed use; 2) a review of the manufacturer's labeling of the product, including administration and storage requirements for its safe and effective use, 3) review of the manufacturer's summarized protocols for manufacturing and quality control testing of several vaccine lots to establish the consistency of process and product, 4) inspection of the manufacturer's vaccine production facilities, and 5) quality assurance testing by the regulatory agency on vaccine samples received from the manufacturer. In addition, a successful approval of a vaccine includes a satisfactory review of records, study sites, site visits, previous compliance history, and appraisals in accordance with current good manufacturing practices, good laboratory practices, good clinical practices, good pharmacovigilance practices, and good documentation practices.^{85,86}

As a part of the successful review of the approval application, manufacturers should include a plan for active follow-up of participants for safety, revisits, and hospitalizations, and any SAEs to generate a database of

information and to assess benefit-risk analysis to support vaccine safety, efficacy, and real-world effectiveness after approval. This step takes 2-4 years for a satisfactory review of regulatory documents, including Phase 3, and a successful approval process (Table 1). Owing to these many systematic approaches, absolutely, almost all the vaccine candidates that reach Phase 3 will get successful approval for marketing.^{9,49,50}

In situations of public health emergencies, several regulatory agencies, including FDA, EMA, and CDSCO may facilitate and authorize the repurposing of certain drugs and the use of newer vaccines through an Emergency Use Authorization (EUA). Under conditions of unavailability of appropriate methods of diagnosis, treatment, or prevention or when there are no adequate, approved, and alternatives available for the management of serious or life-threatening diseases, regulatory agencies authorize the emergency use of unapproved medical products, unapproved uses of approved medical products, or vaccine candidates with proven clinical safety and efficacy in a larger number of participants within a short time in the seamless expedited clinical trials.⁸⁷⁻⁹⁰ Such remarkable authorization for vaccine use is based on strong scientific evidence of safety and immunogenicity that is expected to protect humans and/or prevent disease even though the proof of the efficacy and effectiveness of the vaccine is not well established. The application for EUA consists of all the safety/tolerability, immunogenicity, and efficacy data of vaccine candidates generated from seamless expedited Phase 1, 2, and 3 studies. It also includes a plan to follow up with participants of Phase 3 clinical study for at least 2 months after the full vaccination (prime-booster) regimen (Table 2). Due to emergency conditions of approval, a large number of participants should be enrolled in the Phase 3 study so that the safety database for SAEs and AESIs can be generated from more than 3,000 participants, who would be followed for at least one month after completion of the full vaccination regimen. In addition to this, from a safety perspective to continue emergency authorization and for anticipated marketing licensure in the near future, manufacturers and/or sponsor should continue their clinical trials to obtain additional safety and efficacy as well as effectiveness information.^{9,87-90} Once granted permission, such authorized vaccines for emergency use are widely distributed and promoted for massive and marathon vaccination without scope for branding, marketing, and commercialization.⁸⁷⁻⁹⁰

5. MANUFACTURING STAGE

Large-scale vaccine manufacturing is done immediately after efficacy trials (Phase 3) when the regulatory licensure process is undergoing due to a high amount of investment (Table 1, 2). There are four types of licensures for the manufacturing of biological products, namely short supply, divided, shared, and contract. Short supply is a rare procedure wherein a licensed manufacturer obtains source materials from an unlicensed facility when in short supply. In the case of divided manufacturing, two licensed manufacturers upon agreement and arrangement produce the same biologic product together, only one will have a vaccine product license, and the same is mentioned in the labeling. In shared manufacturing, two or more manufacturers contribute to the production of a vaccine wherein each

manufacturer requires to hold licenses for both vaccine and establishment. Though there is no need to conduct all the steps in the manufacture of the vaccine product, however, both the manufacturing units must provide data that demonstrate the safety, potency, and effectiveness of the vaccine product. In a contract license, upon arrangement, only one manufacturer holds a license while the other performs one or more steps that would not be considered "significant" to warrant a license. Essentially, unlicensed units should be under the direct supervision and control of the licensed manufacturer for quality control, assurance, and validation.^{91,92}

The manufacturing units should follow current good manufacturing practices to demonstrate quality control and validation of product components, types of equipment, manufacturing site, containers, packing and labeling materials, records, and reports, data entry, and expertise of personnel.^{93,94} Vaccine candidates are generally manufactured in lots for clinical trials to establish vaccine safety and efficacy whereas bulk manufacturing is anticipated only when successful completion and establishing safety and efficacy in Phase 3 trials for final licensing and distribution.^{91,92} There are numerous challenges in the life cycle of vaccine production that include industry-institute partnerships, financial support, capacity building, workforce development, process development, lead time, intellectual property, technology transfer, and local vaccine production.⁹³⁻⁹⁶ Moreover, regulatory review and approval of licensure for manufacturing units for large-scale vaccines is mandatory and the review process involves the same as that of units involved in vaccine production in lots. Indeed, this stage is of paramount importance to the WHO to initiate massive vaccine manufacturing and distribution to several low- and middle-income developing nations (LMICs) as a part of national as well as global pediatric vaccination.^{9,93,96}

6. POST-LICENSURE STAGE

PHASE 4- POST LICENSURE EVALUATION OF SAFETY AND EFFECTIVENESS

Phase 4 studies are conducted after licensure to collect additional information on the safety, immunogenicity, and effectiveness of vaccines to meet regulatory commitments, post-authorization, or post-marketing objectives (Table 1, 2). Indeed, evaluation of post-licensure short-term as well as long-term safety, efficacy, and effectiveness of vaccines is highly essential to inform regulatory agencies, policymakers, and other stakeholders and to sustain public confidence in the national immunization programs during normalcy, epidemic, and pandemic situations.⁹⁷⁻⁹⁹

Objective: The purpose of these studies is to monitor the performance of a vaccine in a large target population in a real-world situation for the detection of long-term adverse reactions (risk) and to evaluate and assure long-term effectiveness (benefit). These studies include immunobridging studies, persistence studies, and post-authorization safety studies (Nealon). The objectives of Phase 4 trials may also include the assessment of the influence of any host factor (age, gender, pregnant, non-pregnant), history of infection status (presence or absence),

and co-morbid condition on the vaccine immune response.⁹⁷⁻¹⁰⁰

Study design: Non-randomized, open-label (unblinded), parallel or concurrent, longitudinal clinical trials in which participants involve voluntarily in vaccination programs and followed up immediately after the first dose (prime) and long-term up to two years after receiving the second and/or third dose (booster). Effectiveness studies are pragmatic clinical trials that examine interventions in real-world practice, with more heterogeneous (patient and healthy) populations, less-standardized protocols, and delivery in regular clinical settings. Phase 4 studies are either non-randomized clinical trials or observational studies (cross-sectional, case-control, cohort, ecological) in which blinding is not a stringent criterion.¹⁰¹ Since the primary purpose of this study is to assess long-term safety and protection, parallel designs with a full dosing regimen of an existing vaccine or a historical control are employed to compare the safety and effectiveness of the new vaccine for the same infectious disease.¹⁰⁰⁻¹⁰² Moreover, the safety and efficacy of newer vaccines may also be studied in special populations who were excluded in the previous phases of vaccine clinical trials.^{100,103} In accelerated and priority trials, a Phase 4 study is planned with a cross-over design to evaluate the efficacy of a homologous or heterologous booster dose of vaccine in comparison to previous exposure to the same vaccine and participants are followed up for at least 2 years with an intermittent assessment of the risk of infection and protection from disease after the full (prime-booster) vaccine regimen.^{101,104} It is reported that waning of immune responses after immunization leads to reduced protection against infection and hospitalization, particularly among older adults and patients with immunocompromised conditions. Therefore, it is quintessential to conduct a randomized, parallel, double-blind (participant, care provider), placebo or active comparator-controlled intervention trial to evaluate the safety and efficacy of a third or fourth dose of vaccine (homologous or heterologous booster) that might provide enhanced immunity and extended protection against infection of concern.^{99,102,104-106}

Subject number: The study involves more than 100,000 heterogeneous populations with few to no exclusion criteria. However, each subset or cohort may have less number of participants ranging from 20 or more which is based on the prevalence of disease or co-morbidity condition(s).

Study population: Phase 4 studies are large populations and multiyear follow-up clinical trials considering the fact that sample size is based on disease incidence and assessment of long-term risks and benefits. Mostly, healthy participants and/or participants with clinically controlled diseases of both genders and of different age groups, races, and ethnic groups. It may include participants who had or never had prior infection, pediatrics, women, pregnant and lactating mothers, elderly, patients with immunocompromised conditions such as chronic illness patients, TB, HIV/AIDS, autoimmune disorders, those with co-morbidities that require medical attention, and those undergone transplantation recently.^{99,101,104,107}

Study site: Phase 4 clinical trials is a multicentre study conducted at 3-5 different sites and different countries to

selectively target areas and people who are at high risk of contracting a specific disease.

Outcome:

The efficacy of a vaccine is evaluated in a placebo or standard controlled Phase 2/3 or 3 clinical trials and is based on how much percent of vaccine recipients developed the 'outcome of interest' i.e. infectious disease compared with placebo or standard recipients developed the same outcome. The vaccine efficacy assessed in clinical trials is related to specific outcomes in typical and ideal clinical research settings by following a standardized protocol. Moreover, clinical trials include a wide range of participants selected after exclusion criteria that cannot be a perfect representation of the whole population. Moreover, vaccine efficacy under ideal and controlled conditions does not always translate to effectiveness and an efficacy trial unrealistically overestimates the benefit (protection from infection) of a vaccine in practice.^{101,102,107,108} However, vaccine effectiveness is a true measure of how well vaccines work to protect and truly benefit real populations in real-time in the real world. Therefore, vaccine effectiveness in real-world studies includes a large and heterogeneous population who received a full vaccine regimen and followed up for long-term risk-benefit evaluation in more real-life conditions.

The primary outcome measures are a percentage of participants achieving seroconversion (detection of microbe-specific functional antibodies) within one week after vaccination and the minimal protective neutralizing antibody titer (MPNAT) specific to the infection which indicates the minimum level of neutralizing antibodies that is required to protect the vaccinated participant from infection at least 2 years.^{98,102} The secondary outcome measures include an assessment of the functional antibody levels, and CD4+ and CD8+ T-cell responses at predefined time points, a relative change in neutralizing antibody levels from pre-vaccine to post-vaccine time frame, the number of breakthrough infections, the safety of the vaccine (local and systemic reactions to the vaccination), and any AE, treatment-emergent AEs, and SAEs from the vaccines within the 2 year observation period will be compared between groups.^{98,102,109} In addition, untoward medical incidents, including abnormal laboratory findings and vital signs will also be recorded as AEs. In the case of randomized controlled trials testing the safety and efficacy of a third dose, the primary and secondary endpoints are the same as the previous phases of the vaccine but vary from disease to disease.

PHASE 4 - VACCINE SAFETY MONITORING

Post-licensure detection, identification, assessment, management, and monitoring of vaccine safety and effectiveness is highly significant due to the timeline and sample size of pre-licensure Phases 1 - 3 may not allow detecting and estimating rare reactions, delayed reactions, or reactions among special populations.^{97,110} Surveillance is paramount important to monitoring important characteristics of vaccination, safety, and effectiveness of a vaccine in any population. These characteristics of vaccination include 1) vaccine coverage and estimation of vaccination rates achieved the targeted group, 2) effectiveness of a vaccine in

preventing the disease, 3) influence of confounder and comorbidities on safety and efficacy of a vaccine, 4) identification of information bias due to misclassification of exposure and outcome, 5) the frequency and attributes of vaccine-related AEs, 6) influence of concurrent vaccinations on safety and effectiveness, 7) requirement and estimation of large sample size for addressing vaccine-related rare AEs, 8) safety in special population who are excluded in pre-licensure clinical trials, 9) safety of the childhood vaccination schedule, 10) causality assessment of association of vaccine with AEs, 11) measuring reporting rates of AEs after vaccination, 12) planning timeline and expedited reporting of safety and efficacy of new vaccines, 13) recognition of new infectious disease complications, 14) assessment of safety and efficacy of vaccine against variants of pathogens, 15) need for new and/or additional safety monitoring studies, 16) consideration and improvement in study design for other safety studies in real-world settings, 17) initiation and strengthening of pharmacovigilance practices and pharmacoepidemiology studies, 18) scope for public health vaccination policies, experts scientific advice, and regulatory decision making based on evidence based practices, 19) recognition and futuristic goals of vaccination that require public health attention, and 20) recognizing need of new vaccine research and development opportunities and priorities.^{97,99,102,104,110-112} Owing to these many implications and new avenues for research and development, Phase 4 clinical trials are also referred to as “post-marketing surveillance”, “post-authorization surveillance”, and “post-authorization safety” studies.¹¹¹

Post-authorization vaccine safety monitoring is a government responsibility collectively shared primarily by the national regulatory agency and the departments of public health and family welfare in association with healthcare systems, university academic health centers, and private sector partners. Notably in the US, FDA and the US Centers for Disease Control and Prevention (CDC) this association will use several vaccine safety monitoring systems, such as Vaccine Adverse Event Reporting System (VAERS), the Vaccine Safety Datalink (VSD), the CDC Clinical Immunization Safety Assessment Project, the Biologics Effectiveness and Safety (BEST) Initiative, and Medicare claims data to monitor vaccines in the post-authorization period.^{97,110,111} The Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) in Canada, the yellow card system in the UK, and the blue card scheme in Australia have a long history of ADR monitoring. The government of India has initiated the Adverse Events Following Immunization (AEFI) surveillance program and the Pharmacovigilance Program of India (PvPI) under the guidance of CDSO has started ADR monitoring centers for collecting and generating a large database of suspected ADR across the country.^{113,114} This stage takes about 2-5 years for generating effectiveness from the real-world data (Table 1, 2).

Indeed, several vaccines, such as influenza vaccines and quadrivalent conjugated meningococcal vaccine (MCV4), were reported to be associated with the incidence of

Guillain-Barré syndrome (GBS) following spontaneous reports to the US VAERS and the Korea Adverse Event Reporting System (KAERS) that raised serious concerns.¹¹⁵⁻

¹¹⁷ GBS is a rare, immune-mediated neurologic disorder of the peripheral nervous system that is characterized by ascending weakness and paralysis.¹ Initial surveillance findings suggested that the Ad26.COV2.S (Janssen), COVID-19 vaccine signals, and trends were associated with the risk of GBS. Recently, it has been estimated that the overall incidence of GBS following SARS-CoV-2 vaccination was 1.42 per million doses. An ongoing surveillance data from the Vaccine Safety Datalink reported incidence rate of confirmed GBS after mRNA vaccines was 1.3 per 100 000 person-years.¹¹⁸⁻¹²⁰

CURRENT STATUS OF COVID-19 VACCINES DEVELOPMENT AND APPROVAL

There are 50 vaccines approved by at least one country and have been authorized, licensed, permitted after emergency use authorization, or made available for use without a clinical trial conducted in that country by a national, regional, or global regulatory authority.¹²¹ As on Dec 2, 2022, 67.1% are fully vaccinated and 72.5% received at least one dose in India.¹²² Altogether, 220,67,31,715 total vaccination doses are given in India as on 15 June, 2023.¹²³ In India, a total of 38 clinical trials were successfully completed and 12 vaccines are approved till date (Table 3). Among 12 COVID-19 vaccines approved in India, 6 non-replicating viral vector (Adenovirus), 2 mRNA, 2 protein subunit, 1 inactivated virus, and 1 DNA plasmid based vaccines. Among those 12 COVID-19 vaccines, 1) Sputnik V (Gam-COVID-Vac), a non-replicating viral vector (Adenovirus, Ad26, Ad5) based vaccine, 2) Covishield, a non-replicating viral vector (adenovirus ChAdOx1) based vaccine, 3) COVAXINTM (BBV152), an inactivated virus fractions based vaccine, and 4) Spikevax, a mRNA based vaccine are the first four approved for restricted use in emergency situation in India.^{122,124} Of these, COVAXIN is the India's first indigenous COVID-19 vaccine developed by the Bharat Biotech in collaboration with the Indian Council of Medical Research (ICMR) - National Institute of Virology (NIV), Pune, India and is authorized for emergency use. Additionally, ZyCoV-D, DNA plasmid-based COVID-19 vaccine is developed by Cadila Healthcare with support from the Department of Biotechnology - Biotechnology Industry Research Assistance Council (DBT-BIRAC). It is the world's first DNA based COVID-19 vaccine approved for emergency use in India on 20 August, 2021. In addition, Bharat Biotech developed iNCOVACC (BBV154, ChAd-SARS-CoV-2-S), an intranasal non-replicating viral vector (adenovirus ChAd) based COVID-19 vaccine and the first of its kind in India and launched officially on January 26, 2023. Notably, two COVID-19 vaccines are approved for manufacture for sale or for distribution in India, namely Serum Institute of India developed Covishield and Bharat Biotech developed COVAXIN for intramuscular administration in two doses with 4 to 6 weeks apart and on Day 0 and 28, respectively in ≥ 18 years subjects on 27 Jan, 2022.¹²⁴

Table 3: List of COVID-19 vaccines approved in India as of date ^{121,122,124}

Name of vaccine	Type of vaccine	Sponsor/Developer of vaccine	No. of countries approved	No. of trials undergoing	No. of countries allowed trials
Sputnik V (Gam-COVID-Vac)	Non-replicating viral vector (Adenovirus, Ad26, Ad5)	Gamaleya Research Institute of Epidemiology and Microbiology, Russia	74	25	8
Jcovden (Ad26.COV2)	Non-replicating viral vector (Adenovirus)	Janssen (Johnson & Johnson), Netherlands, Belgium	113	26	25
Spikevax (Moderna COVID-19 vaccine)	mRNA	Moderna, NIAID, BARDA, USA	88	70	24
Vaxzevria (AZD1222, ChAdOx1 nCoV-19)	Non-replicating viral vector (adenovirus ChAdOx1)	Oxford/AstraZeneca, UK/British-Swedish	149	73	34
Covishield	Non-replicating viral vector (adenovirus ChAdOx1)	Serum Institute of India (Oxford/AstraZeneca formulation)	49	6	1
COVOVAX (Novavax COVID-19 vaccine)	Protein subunit	Serum Institute of India (Novavax/CEPI formulation)	6	7	3
ZyCoV-D	DNA plasmid	Zydus Cadila, India	1	6	1
GEMCOVAC-19	mRNA	Gennova Biopharmaceuticals Limited, India	1	2	1
iNOVACC (BBV154, ChAd-SARS-CoV-2-S)	Non-replicating viral vector (adenovirus ChAd)	Bharat Biotech, India, Precision Virotech, USA, Washington University School of Medicine, USA	1	4	1
Sputnik Light	Non-replicating viral vector (Adenovirus, Ad26)	Gamaleya Research Institute of Epidemiology and Microbiology, Russia	26	7	3
Covaxin (BBV152)	Inactivated virus	Bharat Biotech, India, ICMR, India	14	16	2
Corbevax	Protein subunit	Biological E, India (Texas Children's Hospital and Baylor College of Medicine, USA formulation)	2	7	1

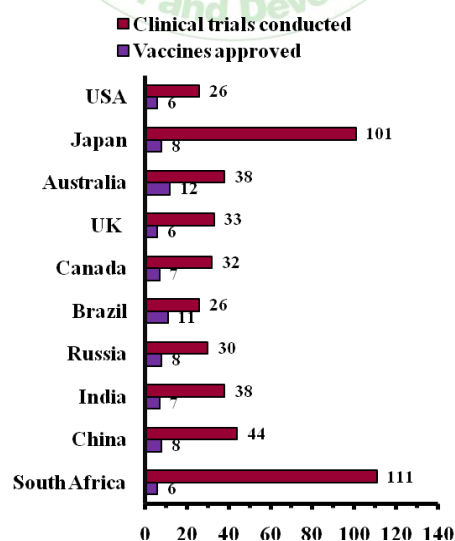
**Figure 1:** Clinical trials conducted and COVID-19 vaccines approved in high-income and middle income growing economies (BRICS) in the world as on 25 May, 2023.

Figure 2: Current status of COVID-19 vaccines in clinical development as on 25 May, 2023.¹²²

There are 201 countries with approved vaccines and the WHO granted emergency use licenses for 11 vaccines. Considering countries in the order of the number of clinical trials conducted and vaccines approved, USA (111, 6), Japan (44, 8), Australia (38, 7), UK (30, 8), and Canada (26, 11) are among the high-income countries whereas China (101, 8), India (38, 12), Russian Federation (33, 6), Brazil (32, 7), and South Africa (26, 6) are among the growing economy and middle-income countries (BRICS) (Fig. 1).¹²² Presently, 242 vaccine candidates are undergoing 821 vaccine trials (various phases) in 80 countries. Among 242 vaccine candidates, 66 in Phase 1, 72 in Phase 2, 92 in Phase 3, and 12 vaccines are no longer progressing (Fig. 2).^{121,122} Hungary granted the maximum (15) number of approvals among all the countries.¹²² Among all the vaccines Pfizer/BioNTech's Comirnaty, a mRNA vaccine has been approved in 149 countries and undergoing 100 trials in 31 countries, though it is not approved in India.¹²² Considering the nature and severity of COVID-19 and its associated complications as well as to achieve strategic goal of IA2030, many more vaccines, monoclonal antibodies based biologics, and drugs are in the pipeline of clinical development and may be approved in near future.

SUMMARY

The world of vaccines have been saving millions of people from death and increasing the life expectancy with unparalleled benefits of strengthening families and public health and helping sustainable growth of nations. In fact, orchestration of microbial genome sequence technologies, genomic databases, indispensable preclinical data, data informatics, and artificial intelligence supported by the experience gained from the recent pandemics have been harnessing advances in vaccine platform technologies for discovery of newer preventive and therapeutic vaccines, including for cancer and Alzheimer's disease. Strategically, the WHO's IA2030 has been emphasizing on vaccines for all and aiming to introduce 500 vaccines by 2030 are further amplifying clinical development processes. Indeed, it is quintessential for biologists, clinicians, and biomedical scientists to understand the world of vaccines and their clinical development, particularly clinical evaluation and regulatory amendments. Further, evaluation of vaccines under controlled hospital settings during Phases 1 – 3 for safety and efficacy and further establishing safety and effectiveness in real-world population in post-authorization studies (Phase 4) can boost public confidence on vaccines and vaccination programs. Moreover, well designed protocols with randomization, blinding, parallel, 'seamless' combined trial designs, and immunobridging trials along with regulatory adaptations in public health emergencies enabled compressed vaccine development timeline and approval times. Inarguably, clinical development and approval of vaccines for COVID-19 within 10 months period is the biggest achievement in medical history to save mankind. The successful approval of vaccines for COVID-19, subsequent massive global vaccination, and the strategies of IA2030 provide opportunities to develop several biologics for vaccine-preventable diseases, motivate for sustainable development, advance vaccine approval rates, and improve global vaccination coverage in the future.

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