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VACCINES VERSUS COVID-19 VACCINES: MANEUVER TIMELINE OF DEVELOPMENT AND TRIAL DESIGNS

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| Article History | Abstract |
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| Received on: 29-04-2023 Revised on: 25-05-2023 Accepted on: 06-06-2023 | Recent pandemic of coronavirus disease 2019 (COVID-19) has made a serious threat to public health and became a global burden with millions of people at risk of death. At that time, there were no approved antiviral drugs and vaccines for COVID-19, but few drugs are repurposed with limited benefit. In less than a year, several COVID-19 vaccines have already been approved and hundreds of vaccines are undergoing clinical evaluation. This review focuses on need for vaccines, benefits of vaccination, the World Health Organization initiated new global strategy 'the Immunization Agenda 2030' (IA2030), stages and timeline of development, and clinical evaluation of traditional vaccines. We have summarized comparison of clinical evaluation between traditional vaccines and conventional drugs in the pre-pandemic era. The review briefly discusses the prioritized approaches, accelerated timeline of clinical evaluation, and seamless and immunobridging clinical trial designs of COVID-19 vaccines in the pandemic period. We have thoroughly searched recent literature and data on this topic and made a summary of current advances, regulatory amendments, and future perspectives of development and approval of vaccines. |
|  | Keywords: COVID-19, Emergency use authorization, IA2030, Immunobridging, Seamless design, Vaccine for COVID-19 |

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Introduction

Vaccine is an immunogenic preparation that is used to stimulate the body's immune response against diseases. Vaccination is the act of introducing a vaccine into the body and a simple, safe, and effective way of activating immune system for protection and prevention of more than 20 life-threatening infectious diseases [1,2]. Vaccinations are common and compulsory in early childhood and the resulting immunization is essential to save billions of lives of all ages, and helping live longer and healthier lives owing to availability of several vaccines. It has been reported that childhood vaccines saved an estimated 3.5-5 million lives from infectious

diseases, such as tetanus, diphtheria, influenza, pertussis, and measles worldwide every year. Vaccinations has contributed substantially to the reduction in global infant mortality rate from 65 per 1,000 live births in 1990 to 29 in 2018, in particular mortality of children less than 5 years of age globally reduced from 93 per 1,000 live births in 1990 to 39 deaths per 1,000 live births in 2018 [3]. It is estimated that more than 50 million deaths can be prevented through immunization between 2021 and 2030, of which vaccination can save approximately 19 million and 14 million lives due to measles and hepatitis B, respectively [4].

Discovery of a vaccine: From small pox to COVID-19

Discovery and development of vaccines are one of the best scientific achievements from the time of the first randomized clinical trial for scurvy conducted by James Lind in 1947 on May 20, which is now celebrated as 'International clinical trial day'. The discovery of the first vaccine against small pox in 1796 by Edward Jenner, the father of vaccination, is an important milestone in the history of medicine [5]. The World War II military purpose remained a powerful motivation lead to the development of vaccines against adenovirus, poliovirus, Japanese B encephalitis virus, and influenza virus between 1930 and 1950. During the last century, large number new and improved human viral vaccines against polio, measles, mumps, rubella, and hepatitis B viruses have been approved,

particularly during 1950-1990, which is considered as golden era of vaccine that revolutionized pediatric vaccination and saved millions of lives. On the contrary, less number of vaccines approved and even there are no vaccines available for certain viruses like human immunodeficiency virus (HIV) and hepatitis C virus (HCV) [1,2,5].

In the recent past, new infectious diseases have emerged lead to outbreaks and epidemics of several viral diseases, including the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002, H1N1 influenza in 2009, the Middle East respiratory syndrome coronavirus in 2012, Ebola virus disease in 2013, and Zika virus in 2015. The first case of infectious disease named coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 was reported to the World Health Organization (WHO) on December 31, 2019, initially declared as viral outbreak on January 30, 2020, later declared as a global pandemic on March 11, 2020, and 6.93 million deaths were reported due to COVID-19 as of May 17, 2023 [6,7]. In the entire world, the first recipient of the first dose of COVID-19 vaccine (Pfizer/BioNTech) was 90 year old UK resident, Margaret Keenan, nicknamed "Patient A" on Dec 8, 2020 dubbed as the COVID-19 "V-Day" and thus starting a marathon vaccination program [8].

Need for vaccines and impact of vaccination

Viruses have been evolving and become more virulent leading to several epidemics, such as Ebola and Swine flu, and increasing mortality. Recent COVID-19 pandemic has made a serious threat to public health and became a global burden with millions of people at risk of death. At that time, there were no approved antiviral drugs and vaccines for COVID-19, but few drugs are repurposed with limited benefit. The US Food and Drug Administration (FDA) has approved several types of vaccines for 29 known variants of pathogens out of thousand of deadly pathogens exist in the world and approved 21 vaccines that include five each for prevention of influenza and meningococcus infections, and four accelerated approvals happened between 2010 and 2020 [9]. Of 419 new approvals, 317 drugs and 102 biologics were approved by the FDA during the same period [10]. Though the number of vaccines undergoing clinical development is less, but their approval has a significant and tremendous effect on global health and world economy.

The estimated mortality impact of vaccinations forecast revealed that projected use of vaccines against ten pathogens, namely *Streptococcus pneumoniae*, *Neisseria meningitidis* serogroup A, *Haemophilus influenzae* type b, Japanese encephalitis, human papillomavirus, hepatitis B, rotavirus, measles, rubella, and yellow fever during 2001-2020 in 73 low- and middle-income countries (LMICs) would avert over 20 million deaths and save USD 350 billion in cost of illness. Considering economics during the same period, deaths and disability prevented by such vaccinations would result in estimated lifelong productivity gain of USD 330 billion and USD 9 billion, respectively, with economic and social value of these vaccinations was estimated at USD 820 billion [11]. Another study estimated that 50 million or 97 million deaths from the same ten pathogens would be averted due to vaccination activities between 2000 and 2019 or 2000 and 2030, respectively across 112 countries. Notably, 52 million more

deaths would occur in children under-5 years born between 2000 and 2030 if vaccination against these diseases not available over their lifetimes [12]. Adding to this, increase in vaccine access, vaccination programs, development and approval of additional vaccines would result in a 72% reduction in lifetime mortality in the 2019 birth cohort [13]. Owing to these statistical estimates and predictions of mortality and economic loss, approximately 143 million and 146 million children were vaccinated against human rotavirus disease (HD) during 2009 to 2019 and pneumococcal disease (PD) during 2011 to 2019, respectively that resulted in avoiding 18.7 million severe rotavirus disease cases and 153,000 deaths due to HD and 5.0 million cases and 587,000 deaths due to PD [14]. During the recent pandemic, despite the prioritized and accelerated clinical evaluation of vaccines for COVID-19 in 2020 and their emergency use authorization (EUA) during 2021, more than 3.5 million deaths as on 8 Dec, 2021 and 5.2 million as on 22 May, 2023 were associated with COVID-19 since 8 Dec, 2020, the first vaccine outside a clinical trial was administered [6]. A mathematical modeling study estimated that rapid and massive vaccinations prevented 14.4 million deaths from COVID-19 in 185 countries during Dec 8, 2020 and Dec 8, 2021 and 19.8 million deaths from COVID-19 averted worldwide during the first year of COVID-19 vaccination. It was estimated that an 41% excess mortality was avoided in high-income countries (HICs) whereas 45% and 111% of deaths could have been prevented if the 20% vaccination coverage target set by the COVID-19 Vaccines Global Access (COVAX) Facility and the 40% target set by the WHO, respectively had been met by low-income countries (LICs) by the end of 2021 [15]. The study revealed that there was low and poorly facilitated COVID-19 vaccination access in LICs. Therefore, the global impact of mortality and poor access to vaccination has been reinforcing the need for vaccines for prospective prevention of infections, equal access, and universal coverage.

Benefits of vaccination: Beyond prevention of infectious diseases

Effective vaccination is the only way to prevent and fully eradicate a infectious disease, but may cause discomfort, pain, redness, or tenderness at the site of injection, (but is replaced with yet compared to the discomfort, pain, and trauma caused by the disease [16]. Immunization protects everyone around including family members in the form herd immunity, which is the indirect protection from an infectious disease. Infections spread when a proportion of a population is susceptible to the disease. 'Herd immunity', also known as 'population immunity', occurs when a relatively large portion of a population is immune to an infectious disease either through vaccination or immunity developed through previous infection. This phenomena reduce the risk of spread of disease from person to person and at the same time give protection indirectly to those who are not immune as ongoing disease spread is very small [2,17]. Moreover, it reduces and/or prevents incidence of secondary infections and cancer that complicate vaccine-preventable diseases and render irrational use of antibiotics [18,19]. Notably, vaccines can help reduce over prescription and consumption of antibiotics thereby reduces antibiotic resistance [18,20]. To help safety of others in a community, it is

highly essential to get vaccinated and subsequently fully immunized. This not only protects one's family, but also helps prevent the spread of these diseases to friends and loved ones. Importantly, vaccine-preventable diseases are not completely eradicated that necessitates receiving a vaccine than to get infection or a disease. Moreover, immunizations can save family time, money, and significantly reduces financial burden to family and society [3,16,20]. It is well known that infections from few vaccine-preventable diseases can result in long-term disabilities and become a toll on economy and public welfare due to poor attendance at schools and colleges, lost time at work places, increased medical bills, and long-term disability care [20,21]. Additionally, such vaccination programs improve social benefits of equity and equality of healthcare and promote empowerment of women [3,22].

Global vaccine action plan and the immunization agenda 2030

These unique invaluable benefits of vaccines have been the driving force behind the research and development programs of vaccines. Essentially, development of vaccines and vaccination is a futuristic cost-effective preparedness for outbreaks, and strengthen community and public health as well as social care infrastructures. Prospectively, immunization protects future generations, improves community health, minimizing the impact on family, improves productivity gains, increase life expectancy, and provide opportunities for nation's development [16,20]. In 2010, World Economic Forum has taken an initiation to develop vaccine and promote vaccination for the next ten years. At the Sixty-fifth World Health Assembly of the World Health Organization (WHO) in 2012, 194 member states endorsed the Global Vaccine Action Plan (GVAP) and supported by several countries to extend the benefits of vaccination and immunization to all by 2020 [23]. Many important milestones and vaccination goals were achieved during this period. Notably, a single measles vaccine averted 23 million deaths, 86% of all infants born vaccinated annually, vaccines available of more than 20 vaccine-preventable life-threatening diseases, and introduced new access to vaccines for cervical cancer, pneumococcal pneumonia, diarrhea, cholera, typhoid, and meningitis in 116 countries between 2010 and 2018 worldwide [20]. Recently, the WHO has initiated a new global strategy 'The Immunization Agenda 2030' (IA2030) with a vision to achieve 90% coverage for essential vaccines in children and adolescents, 50% reduction on rate of vaccine missing out, and introduction of 500 new vaccines in LMICs for the next ten years [20,24]. Though global vaccine coverage was 81% in 2021 against 86% in 2019 and 25 million children missing out on vaccination in 2021 due to the COVID-19 pandemic and associated disruptions, on a positive note, 25 vaccines other than COVID-19 were introduced in 2021 as against 17 vaccines in 2020. Innovative vaccines for dengue, malaria, Ebola virus disease, and respiratory syncytial virus have already been introduced and vaccine candidates for tuberculosis, influenza, and neutralizing antibodies and therapeutic vaccines for cancer and Alzheimer's disease have promising prospects [20,24-26]. Indisputably, the WHO maneuver of IA2030, the ambitious global vision and strategy for vaccines and immunization for the decade 2021-2030, remains intact.

Development of vaccines and drugs: Similarities and differences

In order to meet global demand of vaccines and vaccination, to cope up with spread of infectious diseases, to give protection and save lives, and to promote universal one health, preclinical and clinical evaluation is quintessential for assessment of safe, efficacy, and effectiveness of vaccines [11,20]. However, vaccine development is difficult to execute complex procedures, highly risky due to poor success rate, and costly due to high expenditure involved in the identification and isolation of immunogen, development of process and assay, and clinical evaluation [7,22-25]. The vaccine development process, particularly evaluation of vaccine candidates for a pathogen and its variants, has been advanced, evolved, and transformed for more than two centuries. On the other hand, mRNA, DNA, and recombinant vaccines for several diseases and neurological disorders have also been developed and are at various stages of vaccine development [24-26]. Indeed, vaccine clinical trials aim at establishing the safety/tolerability, reactogenicity, immunogenicity, and efficacy of vaccine candidates in humans prior to being licensed. Though the clinical evaluation of a vaccine typically progresses similar to that of chemical drugs, but there are fundamental disparities in timeline, methodological approaches, sample size, masking, subject selection, randomization, endpoints for primary and secondary outcomes, and passive and active comparison controls [7,9,27]. Treatment plans and dosage and dosing regimens vary between drugs and vaccines as drugs are mostly used to treat a disease therapeutically on daily basis or when required, often one or two doses for symptomatic relief, such as use of paracetamol in headache and antacids in dyspepsia or used multiple times in case of acute diseases, such as use of gepants class of analgesics in migraine and penicillin class of antibiotics in pneumonia [28,29]. On the other hand, drugs are also used for long-term to manage disease progression and complete remission, such as tamoxifen in breast cancer and fluoxetine in major depression or used for whole life in chronic or life-term diseases, such as metformin in type 2 diabetes mellitus and statins in hyperlipidemia [26,30,31]. While a full regimen of vaccines are given prophylactically to toddlers or once in a year before beginning of the season, such as seasonal flu or one prime and one or two booster doses for life-long protection [1,16,25]. Moreover, physiological, biochemical, and immunological changes in the pathogenesis as well as treatment modalities and management paradigms of infectious diseases are different from the organ dysfunction and lifestyle diseases [2,9,27,32]. Infectious diseases are highly contagious, spread rapidly, and may lead to death in few days if not treated well and that necessitates the use of vaccines for complete protection against diseases and saving lives. Simply, conventional drugs treat diseased people whereas vaccines are given to healthy people to prevent the future infection. Vaccines are more sophisticated and sensitive preparations that require qualitative formulation and proper storage at cold or freezing temperatures and any deviation can lead to degradation and loss of efficacy and may result in toxic effects [33]. Indeed, clinical trials of drugs or vaccines provide strongest evidence of safety and efficacy as well as determine the treatment plans and regimens. Considering all these points,

evaluation, endpoints, and outcome of vaccines in humans are viewed unique and clinical trials of vaccines are designed differently from those of chemical drugs. The characteristics of clinical development of traditional vaccines and conventional drugs are summarized in Table 1.

Development stages for traditional vaccines

A typical standard vaccine development timeline takes 5 to 15 years, and at times longer due to clinical evaluation, the regulatory approval processes, and bulk manufacture of vaccine doses for widespread distribution [7,9,34-36]. There are six stages in development of vaccines, namely 1) Discovery/Exploratory stage, 2) Preclinical stage, 3) Clinical development stage (Phases 1-3), 4) Regulatory review and approval stage, 5) Manufacturing stage, and 6) Post-licensure stage (Phase 4). Briefly, the discovery and exploratory stage involves deep research in understanding the virulence factors of pathogens, identification of immunogen(s), and development of appropriate vaccine candidate formulation. On the other hand, preclinical stage involves evaluation of safety/tolerability, purity, reactogenicity, immunogenicity, and efficacy of vaccine candidate in animals before translating and extrapolating beneficial information to humans [7,9,32,36]. It is mandatory to obtain prior approval from regulatory body to initiate a study of vaccine candidate in humans in any phase before getting marketing approval for human use.

The clinical development stage is clinical trial or testing of vaccine candidate in humans that comprises four sequential phases. The first three phases (Phase 1, 2, and 3) are essential for establishing safety/tolerability, purity, reactogenicity, immunogenicity, and efficacy of vaccine candidate in a typical hospital setting whereas Phase 4 involves post-marketing surveillance, pharmacovigilance, and establishing effectiveness of approved vaccine in real-world situation after the stages 4 and 5 [7,32,37]. Based on 21 vaccines approved during 2010 and 2020, an estimate of a median of seven clinical trials were required that includes two for providing evidence of efficacy and one trial was considered fundamental to establish lot-to-lot consistency. In fact, the median number of patients required for safety evaluation during clinical development was 6710 with range of 4576 to 15,997 with a follow-up period of 6 months for assessing **serious adverse events** SAEs [9]. It is reported that the median time taken for clinical development and FDA approval was about 8 years that includes a median of 12 months taken from biological license application (BLA) submission to FDA approval. In general, each clinical trial phase follows successful completion and analysis of data of the previous phase. Adding to this, each trial completion can take a longer time to accumulate infected cases or cases at risk to evaluate vaccine efficacy as the infections and/or cases are sporadic and endemic to one particular territory [7,36,37]. Further, it takes a lot of time to conduct multicentre and multinational trials to generate large data for detailed analysis. If the results of vaccine candidate are promising and successful in achieving optimal efficacy during clinical evaluation then manufacturing capacity is scaled-up after Phase 3 trial and regulatory approval. The stages and timeline of traditional vaccine development and approval are summarized in Table 2.

Development stages for COVID-19 vaccines

In the times of emergency and unprecedented pandemic situations, such as recent COVID-19, there is an increase in demand for a successful effective vaccine as there is no vaccine(s) available for prevention of such disease. The entire world needs well-organized, robust, and reliable evaluation of many vaccine candidates against COVID-19. In fact by considering urgency for developing a COVID-19 vaccine, clinical trials will need larger number of participants and adequate follow-up time for thorough analysis of adverse effects. In the beginning of pandemic, early approval of COVID-19 vaccine was imperative and expected since these trials had recruited tens of thousands of participants that would allow follow-up for safety evaluation in parallel to subsequent trials. Moreover, the criteria of primary outcome and efficacy were marginally altered by the WHO and the FDA such that a COVID-19 vaccine should show only at least 50% efficacy [38-40]. In contrast to a typical standard vaccine development timeline (5 to 15 years), investigators adopt an accelerated timeline in pandemic situations wherein two consequent phases of clinical evaluation are combined, also known as 'seamless clinical trials', and often the next phase is initiated in parallel after getting breakthrough interim results [32,36]. Seamless and concurrent designs and immunobridging studies ensure clinical evaluation to happen in really rapid pace even before the completion of the previous phase due to more number of infected cases accumulate rapidly in short time and multicentre and multinational trials are possible to evaluate vaccine efficacy because of the pandemic [32,36,40-42]. In spite of confident and optimistic views on

Table 1. The characteristics of clinical development of vaccine vs. drug [5,7,35,36,42,50,67]

| Characteristic | Vaccine | Drug |
|-------------------------------------|--|---|
| Preclinical toxicity studies | Acute toxicity studies are compulsory Endpoints: Safety and reactogenicity Duration: short less than a month Subacute and chronic toxicity studies generally not required | Acute, sub acute, chronic toxicity studies are compulsory before human exposure Endpoints: Safety and reactogenicity Duration: short less than a month Subacute and chronic toxicity studies generally not required |
| Phase 0 | Not required Not a regulatory requirement No Pre-IND trial No human exposure before IND approval | Not a regulatory requirement Pre-IND trial (expanded access, compassionate use), Proof-of-concept studies (Safety, efficacy) 2 – 10 patients, First-in-human study for certain cancer drugs, target validation; biological sample preservation, drug analysis, early PD, PK studies |
| Phase 1 | USA: IND; Europe: CTA: CDSCO; IND 10 – 300 healthy volunteers First-in-human study Endpoints: Safety/tolerability, reactogenicity, immunogenicity, hypersensitivity, dose | USA: IND; Europe: CTA: CDSCO; IND 20 – 100 healthy volunteers First-in-human study for most of the investigational drugs Endpoints: Safety/tolerability, MTD, SAD and MAD |

| | | |
|--|--|--|
| | escalation, open/single blinding, dose finding studies for Phase 2 No PK studies | studies, food intervention, preliminary PK study, open/single blinding, dose finding studies for Phase 2 Clinical pharmacology studies |
| Phase 2 | 300 – 3000 healthy volunteers or participants at risk of infection; Proof-of-concept study Endpoints: Safety/tolerability, reactogenicity, immunogenicity on prime and homologous or heterologous booster dose Triple/quadruple blinding Proof of efficacy vs Placebo | 100 – 300 patients Safety/tolerability, full PK study, preliminary PD study, open/single/double blinding, dose finding studies for Phase 3 Proof of efficacy vs Placebo Therapeutic exploratory studies |
| Phase 3 | 3000 – 100,000 healthy volunteers or participants at risk of infection Endpoints: Safety/tolerability, reactogenicity, immunogenicity on prime and homologous or heterologous booster dose, triple/quadruple blinding Proof of efficacy vs. Placebo | 300 – 3,000 patients or patients with co-morbidities; Safety/tolerability, full PD study, dose-dependent therapeutic effects, preliminary PD study, double/triple blinding mostly, dose finding studies for Phase 3 Proof of efficacy vs standard drug/care Therapeutic confirmatory studies |
| Seamless design and immunobridging of studies | Seamless design and immunobridging trials are necessary for expedited progression and approval of vaccine in a pandemic situation | Not a general requirement Employs Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review |
| Safety focus | Solicited short-term AEs; unsolicited AEs; long-term rare events | Unsolicited AEs (short- and long-term) |
| Acceptance of AE | Lower | Higher |
| Specific regulatory competence | WHO prequalification, FDA, EMA, CDSCO, few others | WHO less (or not) involved in national or global registration |
| Manufacturing challenges | Biologics, clinical bridging trials (lot-to-lot comparison) | Well characterized, analytical comparisons |
| Regulatory license issues | Manufacturing and clinical | Primarily clinical |
| Goals | Prevention of disease, complications, improved survival time, Q-o-L, no mortality | Treatment of disease, diagnosis, biomarkers, improved survival, Q-o-L, less hospitalizations and less duration of hospital stay |
| Public health benefit | Herd effect in non-vaccine subjects | Individual effect, reduce spread of infection |
| Proof of efficacy | Immunological surrogates, disease specific markers, efficacy/effectiveness, benefit vs. risk analysis | Specific diagnosis, biomarkers, surrogate endpoints, improvement of symptoms, extended survival, benefit vs. risk analysis |
| Serological tests | Reproducible results prerequisite for license, interlaboratory comparability lower | Not always required, BA and BE is required |
| Outcome studies | Often granted, cost saving | ~USD 50,000; cost per life-year gained as cost effectiveness threshold |
| Pharmacoeconomics | Sponsored by WHO, national public health departments, NGOs, cost of vaccine relatively affordable, subsidized marketing | Benefit over risk, cost of new drugs is often unaffordable, no public health departments or NGOs involved in pricing, pharmaceutical companies have commercial interest |
| Approval | USA: FDA EUA, BLA; Europe: EMA CMA, MAA; India: CDSCO EUA, NDA | USA: FDA NDA; Europe: EMA MAA; India: CDSCO NDA |
| Phase 4 (post-marketing surveillance) | VAERS, PV, VSD, CISAP, BEST, Blue card, Yellow card, registries, observational clinical research | Spontaneous reporting, prescription event monitoring, registries, observation clinical research, ADR reporting, Medwatch, PV |
| Long-term safety | No teratological and organ function disorders reported | Teratologic drugs not approved, boxed warning for serious AEs and organ function disorders |

AE: adverse event; BLA; Biologic License Application; CDSCO: Central Drugs Standard Control Organisation; CTA: Clinical trial application; EMA: European Medicines Agency; FDA: Food and Drug Administration; IND: Investigational New Drug; MAA: Marketing Authorisation Application; NDA: New drug application; PD; pharmacodynamics; PK: Pharmacokinetics; PV: Pharmacovigilance; Q-o-L, quality of life; VAERS: Vaccine Adverse Event Reporting System WHO, World Health Organization

Table 2. Stages and timeline of traditional vaccine development and approval [5,35,36,40,42,67]

| 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-IND approval |

BLA, Biologic License Application; CDSCO: Central Drugs Standard Control Organization; EMA: European Medicines Agency; FDA: Food and Drug Administration; MAA: Marketing Authorization Application; IND: Investigational New Drug over expenditure and additional utilization of manpower in short time, manufacturing capacity is scaled up, but at financial risk, during successful progression of clinical trials.

The FDA has granted accelerated approval for 8 new vaccines that includes 5 seasonal *influenza*, 2 *meningococcus*, and 1 *Haemophilus influenzae* vaccines, based on evidence from a median of 9 clinical studies, including 1 or 2 efficacy trials since 1992. Indeed, most of the FDA required post-approval trials of such vaccines were completed within 3 years after approval which is quicker than required for drug approvals. Moreover, 3 of the 8 vaccines had efficacy benefit confirmed by a post-approval trial using effectiveness as clinical primary outcomes [32,37]. In the pre-pandemic era, the FDA allowed accelerated approval of vaccines based on limited pre-approval evidence, particularly surrogate measures (e.g., antibody levels). At that time, the FDA required completion of post-approval studies to verify clinical benefit in terms of effectiveness in larger population as surrogate measures reasonably expected to predict clinical benefit in terms of efficacy in smaller sample size of participants [36-38]. During the pandemic, the FDA has granted EUA to three vaccines, namely Pfizer-BioNTech COVID-19 Vaccine, Moderna COVID-19 Vaccine, and Janssen COVID-19 Vaccine. The Central Drugs Standard Control Organisation (CDSCO) of India granted EUA to four vaccines, namely Bharat Biotech Covaxin, AstraZeneca-Oxford-Serum Institute Covishield, Gamaleya-Dr Reddy Sputnik V, and Pfizer-BioNTech COVID-19 vaccine [43]. A EUA is a special regulatory process that allows the availability and use of medical products, including repurposing of approved drugs for another indication and vaccines, during public health emergencies. In this accelerated clinical trial, Phase 1 and 2 are combined and interim analysis of accumulated data is done for assessment of safety and efficacy. A seamless Phase 2/3 or Phase 3 study is initiated in tens of thousands of study participants to generate the needed non-clinical, clinical, and manufacturing data. The regulatory agencies expected that more than half of vaccine recipients would be followed for serious adverse events and adverse events of special interest for at least 2 months after completion of the full vaccination (two dose prime-booster) regimen [40,41,44,45]. Moreover, additional clinical trials may be initiated for evaluating such authorized COVID-19 vaccines in large population to generate data and other information needed by the regulatory agencies to determine long-term safety and effectiveness. The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency has also granted conditional marketing authorizations (CMA) for two COVID-19 vaccines, Pfizer-BioNTech COVID-19 vaccine and Moderna COVID-19 vaccine, after a rolling review based on certain criteria of i) providing a scientific clinical evidence of positive benefit-risk balance, ii) addressed potential use of vaccines in an unmet medical condition for a public health emergency, iii) such immediate availability of vaccines would benefit to public health concern that outweighs the inherent risk, and iv) that the applicants provide more comprehensive clinical safety and effectiveness during post-authorization for assessment and understanding long-term benefits and massive vaccination use [43,46]. All these vaccines are authorized for emergency use for the prevention of COVID-19 depending entirely on clinical safety and efficacy in pre-approval trials rather than decision making analysis of vaccine effectiveness in post-approval studies. This adoptive and accelerated timeline for developing and approval of a successful safe

and efficacious vaccine took less than a year (~10 months) that resulted in EUA and CMA of several COVID-19 vaccines across the world [9,35,41,43]. The stages and timeline of accelerated COVID-19 vaccine development and approval are summarized in Table 3. The WHO, which is responsible for international public health, employs the emergency use listing (EUL) procedure to evaluate safety, efficacy, quality, and a risk management plan of unlicensed vaccines during public health emergencies. In this EUL procedure, a rigorous assessment of late Phase 2 and Phase 3 clinical trial data and additional data for synthesis of evidence of anticipated benefits are reviewed by the experts from various national regulatory agencies [47]. Emphasizing the emergency need of COVID-19 vaccines, the WHO issued a total of 11 EULs to accelerate the access and availability of these preventive agents across the globe during pandemic [47,48]. This opportunity of the WHO EUL opens the door for several LICs and LMICs to speed up their own regulatory approval procedure to import and massive vaccination.

Table 3. Stages and timeline of accelerated COVID-19 vaccine development and approval [35,36,40,42,50,67]

| 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 | |
| | | | CDSCO fast-track review; EUA | |
| | | | EMA rolling review; CMA | |
| | | | | FDA BLA |
| | | | | CDSCO IND approval |
| | | | | EMA MAA |

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

Seamless clinical trial design: For development of fast-track vaccines

The traditional clinical trials are conducted sequentially by one phase at one time after reviewing the complete analysis of data generated and considering the objectives of each phase. Importantly, regulatory approval is mandatory to progress from one phase to another phase as there are fundamental differences in study design, number of subjects, characteristics of participants, end points, and purpose of each phase. Contrary to traditional approach of progression of a clinical trial, a 'seamless trial design' combines two separate phases of a trial into one trial, also called 'operationally seamless' [35,41,49,50]. On the other hand, 'adaptive seamless clinical trials' combine two phases into one adaptive design trial.

Importantly, interim analysis of data generated after successful execution of protocol decides on how to adapt the study. In this adaptive design, more treatment groups or cohorts are included in the beginning of the study to compare different doses, regimens, formulations, subjects at risk, or disease states [49-52]. Precisely, additional participant cohorts will be added to the more successful treatment group and less successful treatment groups are discontinued.

Seamless vaccine studies may be open label studies intended to support the translation of safety/tolerability, efficacy, reactogenicity, and immunogenicity data from one formulation, population, and dose and dose regimen in one group of subjects to another. Such study design is called 'early-phase exploratory trials' and is referred to as Phase 1b/2, 1/2,

1/2a, or 1/2b study [41,53-58]. The end points for such clinical studies are usually the clinical safety parameters, relevant immune responses, and immunological persistence and consistence that are evaluated to understand delayed and long-term vaccine safety and how long vaccine-induced immunity lasts [58-61]. Similarly, Phase 2 and 3 trials may be combined as Phase 2/3 trials, referred to as 'seamless Phase 2/3', "combined-phased", or 'discovery into confirmatory' trials. In this design, the first part is a smaller Phase 2 study collects data on safety and immunogenicity in a limited and focused study population whereas Phase 3 is the second part of the trial which may be initiated after considering the interim analysis of 'intermediate' efficacy endpoint of Phase 2 and collects data on safety and vaccine efficacy [35,50,62]. Seamless Phase 2b/3 or 2/3 are conducted as closed, randomized, parallel, placebo controlled, double/triple/quadruple design with a primary purpose of prevention [41,50,60,63].

In public health emergency situations, such as COVID-19 pandemic for which no effective vaccine for prevention available, seamless studies are useful trial designs for decision making and to go ahead next phase for efficacy keeping in view of the future needs, rapid regulatory approval for EUA, bulk manufacturing, and massive vaccination that require longer time period [40-42]. Recently, two Phase 3 vaccine trials have been planned based on interim analysis of safety, reactogenicity, and immunogenicity following dose-escalation and dose-ranging Phase 1/2 studies along with results from preclinical challenge studies [64,65]. In a priority process, priming and booster doses are given 4-6 weeks apart in the same study to generate safety/tolerability, reactogenicity, and immunogenicity of vaccines by evaluating the humoral and cellular immune responses in seamless Phase 2/3 trials [60,66]. By avoiding gap between the phases, seamless trials result in reduction of resources and major saving in time compared with traditional 3 or 4 phase programs. In addition, such design is beneficial in generating long-term efficacy and safety data simultaneously, decide dose selection, incorporation of data from phases in the final analyses due to subject exposure to vaccine candidate from the beginning [49-51].

Immunobridging studies: Evaluation of efficacy of new vaccines

Immunobridging is an important approach in a clinical trial to understand the possibility of a vaccine's protective effect by translating immunogenicity to efficacy. These trials are designed to demonstrate equivalent activity and effectiveness of a vaccine candidate to a similar existing vaccine through an accepted surrogate measure for efficacy (control). The inference is based on the comparison of immunogenicity of a new vaccine with a comparator vaccine with an established protective effect. Various regulatory bodies allowed immunobridging studies, which compare the immunogenicity of new vaccines with that of existing (same or approved) vaccines when the efficacy has previously established [67-70]. A superiority trial design is used when an effective vaccine for the disease is not available while a non-inferiority trial design is used to compare with an existing effective vaccine. In the assessment of efficacy, the risk parameters, such as the reduction in incidence rates and relative risk of disease, with

new vaccine are compared with placebo (superiority) or existing vaccine (non-inferiority) [67,70]. For comparison and decision making, the protection curves representative of vaccine efficacy determined can be used to define the parameters of these non-inferiority or superiority trials [70-72]. It is responsibility of vaccine developers to identify an appropriate same or approved vaccine for comparison as well as to determine the non-inferiority or superiority of novel vaccine to these vaccines in a randomized controlled trial.

Summary

Vaccines, vaccination, and immunization with their unparalleled benefits help sustainable growth of nations. However, the threat of COVID-19 during the pandemic has profound impact on the lives of millions of people around the world. Introduction of a new vaccine against SAR-CoV-2 is the only best strategy over drugs during the pandemic period. Availability of microbial genomics database, indispensable preclinical data, and existing of advanced platform technologies made possible to design a new vaccine for COVID-19. This is further amplified by the robust and real-time united efforts of scientists, regulatory agencies, funding resources, and manufacturers as well as 'seamless' trial designs that reduced the time of clinical evaluation and allowed emergency authorization, and subsequent massive and marathon vaccination. With emphasis on the seamless trial designs and timeline of vaccine development, the availability of a vaccine for COVID-19 in less than 10 months may expedite future preventive and therapeutic vaccine approvals.

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