CURRENT UPDATES ON COVID-19 VACCINES

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ABSTRACT

COVID-19 caused the world to shut down and made us critically look out at our advanced healthcare systems that are well-prepared for heart diseases, cancers, organ transplantation but not for attack of a tiny virus. WHO and other authorized bodies are continuously issuing advisory on preventive measurements, tracking the outbreak and distributing vital medical kits. Besides, scientific community and vaccine experts have developed and started to distribute safe and effective immunization worldwide. Effective deployments of vaccines are reliant on sophisticated technology, scalable production rate and provided funds. The paper outlines several developed and developing immunization vehicles that will hit global market in year 2021. Different platforms including mRNA, DNA, Viral vectors, Synthetic peptides etc. are also covered here that are globally involved for elimination of SARS-CoV-2, a causative virus of COVID-19.

Keywords: COVID-19, Vaccine, Viral vector, SARS-CoV-2, Synthetic peptide.

INTRODUCTION

The first human coronavirus was reported in the year 1960. Until now seven different genera of coronaviruses are known. All are infectious and causes mild respiratory symptoms to mortal outcomes. In December 2019, SARS-CoV-2 emerged that causes COVID-19, a severe respiratory illness worldwide. The scientific and medical communities are developing effective weapons to defeat this threat. Development of vaccine requires approximately 10–15 years for research and clinical testing (phase study), but year 2020 let the scientists to embark on a fight against COVID-19 by formulating safe and effective vaccines within months. Worldwide eminent researchers are aggressively engaged round the clock for the development of effective inoculation. Preclinical and clinical trials including phase study are restraining steps for the formulation of vaccine to avoid severe adverse effects [1]. Urgent need of effective COVID-19 vaccine insisted combination of phase 1 and 2 in clinical trials. Authorized bodies allow emergency use of developed vaccine to lessen worldwide morbidity and mortality rates. In this pandemic situation, when corona has been continuously engulfing millions of lives, worldwide countries are co-operating each other to fight against COVID-19 through sharing research and scientific information [2]. Several active international organizations such as World Health Organization (WHO), Bill and Melinda Gates foundation (BMGF), Gavi Alliance, Coalition for Epidemic Preparation Innovations (CEPI), and Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) are conjoining for effectively elimination of virus, ensuring for sufficient funding and fair vaccine distribution [3]. According to reports gathered on Jan 2021, researchers are involved in analyzing 64 vaccines as clinical trials on human beings [4]. Approximately 85 vaccines are under preclinical testing for their active ingredients in animals whereas 20 vaccines are in final stage of phase study. Development of vaccine involves various steps such as exploratory phase, preclinical phase, phase 1, phase 2, phase 3, approval, and post-marketing surveillance [5]. Fig. 1 illustrates step by step preclinical and clinical trials conducted both on animals and humans for evaluation of safety and efficacy.

The global endeavor to develop a potent and safe COVID-19 vaccine is now commencement with fertile results. Till date, few vaccines are been approved around worldwide for deployment (Table 1).

DIVERSE PLATFORMS FOR THE DEVELOPMENT OF COVID-19 VACCINES

Coronavirus, causative agent of epidemic COVID-19, is positive-sensed, single stranded RNA virus containing helical nucleocapsid. It belongs to family Coronaviridae with four genera, that is, alpha, beta, delta, and gamma. Genera beta-coronavirus is accountable for causing severe acute respiratory syndrome, that is, SARS-CoV-2 [6]. Positive stranded SARS-CoV-2 has four structural proteins, that is, nucleocapsid (N) protein, spike (S) protein, envelope (E) protein, and matrix (M) protein [7]. The S protein is heavily glycosylated and decorated on viral surface that directly bind to the host Angiotensin Converting Enzyme 2 (ACE2) receptor which facilitates virus entry into target cells [8].

Globally, first infected case was reported in December 2019 in China through transmission from bats to human [9]. Afterward almost all countries of world suffer with this fatal virus with typical clinical manifestations such as dyspnea, cough, fever, myalgia, loss in taste, fatigue, and sore throat [10]. Population that represent more severe symptoms such as shortness of breath, pneumonia, continuous pain in chest, and bluish lips need immediate medical attention and should be hospitalized [11]. Elevated level of creatinine protein, lactate dehydrogenase, prothrombin time, and reduced albumin is noted down in pathological reports of the sufferer. Mostly geriatric, immune-compromised, hypertensive, and diabetics are victims of virulent corona virus [12]. Literatures stated that patients with high levels of troponin I (beyond 13.75 ng/L) and aspartate aminotransferase (up to 280 IU/L) are more likely to develop undesirable outcomes [13]. Current updates on spreading of COVID-19 augmented transmission chain through human-to-human. Direct/indirect contact and dissemination of respiratory droplets from infected person in crowded premises mediate SARS-CoV-2 transmission [14]. In this context, the WHO has been provided basic preventive guidelines related to maintenance of personal hygiene (frequent hand wash with soap, and minimum touch of face), use of medical mask, proper disposal of used tissue and mask and maintain 2 m social distancing to avoid contact with other person [15]. Moreover, a COVID-19 diagnostic kit is also arranged in clinical testing laboratories. RTPCR (Reverse Transcriptase Polymerase Chain Reaction) along with chest X-ray, lung ultrasound CT scan, etc., is employed for identification of corona infection. Increased mortality was reported with cardiac and diabetic patients [16].
Researchers immensely analyzed core structure of highly contagious corona virus (SARS-CoV-2) for designing infallible treatment/vaccine through targeting its surface protein. As surface of corona virus is composed of trimeric glycoprotein (S protein) that has two subunits, that is, S1 (controls receptor binding site) and S2 (facilitates membrane fusion). This "S" protein is diverse in nature that endures momentous conformational change during pre-fusion and post- fusion with host [17]. Recent researches emphasize that viral vaccine expressing over N protein causes induction of T cells dependent immunity hence open new arena for fabrication of anti-SARS-Co-V-2 candidates [18].

A safe and effective COVID-19 vaccine would protect the population in either of two ways. First as direct protection where high risk people are to be immunized to avert the disease and second is indirect prevention through vaccinate in touch people to lessen COVID-19 transmission rate.

Researchers and vaccine experts have designed several vaccines (Fig. 2) through targeting S protein present on surface that gets bind to the host cells. Various vaccines development platforms reliant on mRNA, DNA, inactivated corona virus, synthetic multiple, and multitope peptides and non-replicating viral vectors are acknowledged by researchers.

Inactivated vaccines

Inactivated vaccines are widely administered for the treatment of Flu, Polio, and Rabies since 1880s. Purified inactivated virus candidate is

| Vaccine nature | Name | Country of origin | Developer | Approved by | Dose and storage |
|----------------|------|-------------------|-----------|-------------|-----------------|
| mRNA-based (95% efficacy, muscle injection) | BNT162b2/Comirnaty/Tozinameron | Multinational (New York and German) | Pfizer, BioNTech, Fosun | UK, US, EU, Saudi, Singapore, Oman | 2 dose/3 weeks apart Freezer storage (−94°F) |
| mRNA-based (94.5% efficacy, muscle injection) | mRNA-1273 | Boston, US | Moderna, BARDA, NIAD | US and Canada | 2 dose/4 weeks apart 30 days in refrigerator and 6 months at −4°F |
| Replication deficient viral vector vaccine (90% efficacy, muscle injection) | AZD1222 (Covishield in India) | The University of Oxford, The Jenner Institute | The University of oxford, AstraZeneca, Serum Institute of India | Britain | 2 dose 4 weeks apart Stable in refrigerator for 6 months |
| Inactivated Vaccine unknown efficacy | Yet to be named | China | Wuhan institute of biological products, Sinopharm | Limited to emergency used in China and United Arab Emirates | Unclear |
| Inactivated vaccine (0% efficacy) | CoronaVac (formerly PiCoVac) | China | Sinovac | Limited use China | 2 dose 2 weeks apart Stable in refrigerator |
| Inactivated vaccine (79.34% efficacy, muscle injection) | BBIBP-CorV | China | Beijing Institute of Biological Products and Sinopharm | China, Bahrain, United Arab Emirates | 2 dose 3 weeks apart |
| Non replicating viral vector (91.4% efficacy, Muscle injection) | Sputnik-V (formerly Gam-COVID-Vac) | Russia | Gamañeya research institute | Russia | 2 dose/3 weeks apart Freezer storage |
| Peptide vaccines (Unknown efficacy, muscle vaccine) | EpiVacCorona | Russia | Gamaleya research institute | Russia | 2 dose 3 weeks apart Stable for 2 years in refrigerator |
| Inactivated corona vaccine (Unknown efficacy) | Covaxin (BBV152 A, B, and C) | India | Bharat Biotech, ICMR and National Institute of Virology | India | 2 dose 3 weeks apart Stable in room temperature for a week |

Table 1: List of vaccines developed by eminent developers

Fig. 1: Schematic illustration of development process of a vaccine
been explored for the vaccine development and mitigation of influenza. These preparations are quite stable and easy to produce in limited resources [19]. Here, the virus is rendered inactive by chemical or physical treatment. After administering the vaccine, the immune system encounters the all sum virus. The system defenses the host cells through detecting viral spike protein (S protein) and nucleoprotein. Collaborated efforts for development of two inactivated vaccines (Table 2) are intimated by Wuhan Institute of Biological Products, Beijing Institute of Biological Products and Sinopharm against SARS-CoV-2 [20]. In this context, Zhang et al., 2020, have investigated tolerability, safety, and immunogenicity of developed inactivated vaccine, that is, CoronaVac, Sinovac Life Science, China. Two doses of the CoronaVac vaccines (0 and 28 days) were well tolerated in mice, rates and non-human primates. However, administered doses (3 μg and 6 μg) were moderately immunogenic in adult human of age group between 18 and 59 years. The adverse effects by both doses were almost similar and suggested dose-independent safety concerns. Thus, CoronaVac vaccine, 3 μg was channelized for production and global distribution. Inactivated vaccine Coronavirus produced mild fever and pain at site compare to other RNA vaccine, DNA vaccine, and viral vector vaccine [21]. Valneva’s inactivated vaccine VLA2001 against SARS-CoV-2 is currently in phase 1/2. This vaccine contains inactivated whole corona virus particle with high density of S protein in amalgamation with alum, two adjuvants and CpG 1018, a component of HEPLISAV-B vaccine. Valneva plans to get initial regulatory approval for distribution of VLA2021 vaccine across worldwide in the fourth quarter of 2021 as it believes to complete phase 3 study at that time. An agreement between Valneva and UK authority has been announced in September 2020 for distribution of 60 million doses of VLA2001 in the year 2021 and additional 130 million doses to the UK government in the duration of 2022–2025. Moreover, the company has a positive discussion with European commission for the supply VLA2001 vaccines (approximately 60 million doses) if the development goes successful.

Indian vaccine “COVAXIN (BBV152)” is developed by Bharat Biotech with joint collaboration of Indian Council of Medical Research and National Institute of Virology. The vaccine is composed of inactivated whole virion (SARS-CoV-2) with Algel and Algel-IMDG as adjuvants. The report claims no serious adverse effects after immunization to 375 participants. The inoculum is planned to administer in two doses, 4–6 weeks apart and can be stored at cold temperature (2°C–8°C), hence ideal for national immunization programs [22].

Another inactivated whole virus vaccine is been introduced by Wuhan Institute of Virology, China. Xia et al. investigated safety and immunogenicity of intramuscular administered developed vaccine. Submitted interim report of phase 1 and phase 2 trails demonstrated immunogenicity with low rate of adverse reactions such as site pain and fever. Further, phase 3 study is ongoing by Chinese clinical trial agency (ChiCTR2000031809) to evaluate efficacy and long-term adverse effect if any [23].

DNA vaccines

These vaccines are third generation vaccines, generally composed of circular piece of bacterial DNA or genetically engineered plasmids that produce unambiguous antigen (template) from a pathogen. Immune response is activated when pathogen’s protein are identified through DNA template [24]. Among several technologies of vaccine development, DNA vaccines are promising candidates as it has ability to produce both humoral and cellular immunity. Further, their production, scalability, stability, and storage are feasible [25]. On January 4, 2021, INOVIO and Advaccine Biopharmaceuticals Suzhou Co. declared exclusive right to develop and commercialize INO-4800, a DNA based vaccine in China, Hong Kong, Taiwan and Macao. Recombinant DNA technology is used to develop
Table 2: Status of vaccine candidates under development

| Vaccine nature                      | Name of vaccine                     | Sponsor/developer                     | Institution                                                      | Trial phase |
|------------------------------------|-------------------------------------|---------------------------------------|------------------------------------------------------------------|------------|
| Recombinant epivaccine             | Convidicea or Ad5-nCoV              | CanSino Biologics                     | Tongji Hospital, Wuhan, China                                    | Phase 3    |
| Non-replicating viral vector       | JNJ-78436735                        | Johnson and Johnson                   | John Hopkins Hospital, Baltimore, MD, US                        | Phase 3    |
| Nanoparticle vaccine               | NVX-CoV2373                         | Novavax                               | Novavax                                                         | Phase 3    |
| DNA vaccine                        | INO-4800                            | INO10 pharmaceuticals                 | Center for Pharmaceutical Research, Kansas City, Philadelphia   | Phase 2/3  |
| mRNA-based vaccine                 | CVnCoV                              | CureVac                               | CureVac                                                         | Phase 2/3  |
| Plant-based adjuvant               | VIR-7831                            | Medicago, GSK, Dynavax                | Medicago                                                        | Phase 2/3  |
| DNA vaccine                        | ZyCoV-D                             | ZydusCadila                           | ZydusCadila                                                    | Phase 2    |
| mRNA-based vaccine                 | BNT162                              | Pfizer, BioNTech                      | EMA, North America, Canada, Shanghai, China                   | Phase 1/2/3|
| rVSV (Recombinant vesicular stromatitis virus vaccine) | IHR-100                             | Israel Institute for Biological Research | Medical center                                               | Phase 1/2/3|
| Conjugate vaccine                  | Sobernna 1 & 2                      | Finlay institute of vaccine           | Finlay institute of vaccine, Korea                             | Phase 1/2/3|
| Inactivated vaccine                | VLA2001                             | Valneva, National Institute for Health Research (NIHR) | Multiple National Institute for Health Research sites | Phase 1/2/3|
| SP9 cell vaccine                   | Yet to be named                     | West China hospital Sichuan           | West China hospital Sichuan                                      | Phase 1/2/3|
| DNA vaccine                        | GX-19                               | Genexine, Inc.                        | University                                                      | Phase 1/2/3|
| DNA vaccine                        | AG303-01COVID19                     | AnGes, IncJapan                       | Japan agency for medical research and development               | Phase 1/2/3|
| Self-amplifying RNA vaccine        | LNP-nCoVaRNA                         | Imperial college London               | Imperial college London                                         | Phase 1/2/3|
| Protein subunit vaccine            | Yet to be named                     | Sanofi, GSK                           | Various sites                                                   | Phase 1/2/3|
| Self-Repetiting RNA vaccine        | ARCT-021 or Lunar covid             | Arcturus Therapeutics and Duke-science | Duke-NUS Medical school, Singapore                              | Phase 1/2/3|
| Inactivated vaccine                | Yet to be named                     | Chinese Academy of Medical science    | West China Second University                                    | Phase 1/2/3|
| Adenovirus-based vaccine           | AdCLD-CoV19                         | CellId, LG Chem                       | Korea University Guro Hospital                                  | Phase 1/2/3|
| RNA vaccine                        | HDT-301 (HGCoV19)                   | HDT Bio Corp, University of Washington| HDT Bio Corp, University of Washington                         | Phase 1/2/3|
| Live attenuated (Intransal) DNA plasmid vaccine | COV1-VAC                           | G杆菌                                     | Serum Institute of India                                        | Phase 1/2/3|
| Modified virus virus Ankara vector | MVA-SARS-2-S                        | German center for infection research, Philadelphia University | Providence Portland medical center                             | Phase 1/2/3|
| Multiple peptide vaccine           | pVAC                                | Marburg medical center                | University Hospital Tuenberg                                    | Phase 1/2/3|
| Multivalent recombinant protein vaccine | COVAX-19                         | Vaxine Pvt. Ltd                       | University Hospital Tuenberg                                    | Phase 1/2/3|
| Bifidobacteria monovalent oral vaccine | BactRL-Spike                        | Symvivo                               | Symvivocorporation                                              | Phase 1/2/3|
| Replicating viral vector           | DeN1S-2019-nCoV-RBD-OP1             | BeizngWanbiological pharmacy, Xiamen University | Jiangsu provincial centre for disease control                  | Phase 1/2/3|
| Adenovirus-based vaccine           | GRAd-COV2                           | ReifThera, Leukocare                  | Lazarrapallananz, national institute for infectious disease     | Phase 1/2/3|
| Protein subunit vaccine            | UQ-CSLV451                          | CSL                                    | The University of Queensland                                    | Phase 1/2/3|
| Protein subunit vaccine            | SCB-2019                            | Sanofi, GSK, Dynavax, CEPI            | United Biomedical Inc.                                          | Phase 1/2/3|
| Multiprotein peptide vaccine       | IHR-61                            | COVAXX                                | Merck & Co., IAVI                                              | Phase 1/2/3|
| Vesicular stomatitis virus vaccine (recombinant) | V590                             | Merck & Co., IAVI                     | Merck & Co., IAVI                                              | Phase 1/2/3|
| Adenovirus type 5 vector (Recombinant) | VXA-CoV2-V1                      | Vaxart                                 | Vaxart                                                          | Phase 1/2/3|
| Measles vector vaccine             | V591                               | University of Pittsburgh's Center for Vaccine Research | University of Pittsburgh, Themis Biosciences                      | Phase 1/2/3|

(Data gathered from reference literature "COVID-19 treatment and vaccine tracker" (https://covid-19tracker.milkeninstitute.org, and https://www.who.int/ publications/m/item/draft-landscape-of-covid-19-candidate-vaccines)
RNA vaccines

RNA vaccines are composed of mRNA strand that contains genetic codes for a disease specific antigen. mRNA vaccines are favorable inoculum compare to conventional technologies due to its high potency, rapid development, scalability, and cost-effective parameters[28]. Once the system is injected, the coded mRNA serves as template for the host cells that trigger immune system[29]. Moderna, an American based company has developed mRNA-1273 vaccine. As the vaccine is injected, the immune cells start to target spike "S" protein adorned in coronavirus. On September 2020, Moderna Inc. announced second interim analysis of phase 1 study that its vaccine candidate was well tolerated in two doses (25 μg and 100 μg) given in 28 days apart to 40 healthy adult volunteers in two age cohorts (age 56–70 and 71+). Clinical trial study pursued by National institute of Allergy and Infectious Diseases suggested better use of this vaccine to the elderly rather than younger ones [30,31]. Another mRNA vaccine (BNT162B2) introduced by Pfzerer (US) and BioNTech (Germany) has enabled to target full length spike S protein. The system is encapsulated in lipid nanoparticles that has potent into enter into host cells, enhances cellular uptake through endocytosis. On November 2020, Phase 3 first interim efficacy analysis of BNT162B2 vaccine was conducted against SARS-CoV-2 participants that suggested potential for prevention of COVID-19. Both Pfzer and BioNTech are jointly working to collecting safety and efficacy data related to second dose of vaccine for the submission to FDA to get further potential emergency use authorization. HDT 301 (repRNA-CoV2S), an Alpha-virus derived self-replicating mRNA vaccine is formulated with lipid inorganic nanoparticles for the enhancement of vaccine release, stability and immunogenicity. Research outcomes from UW medicines and HDT Bio displayed production of anti-SARS-CoV-2 S proteins on single immunization into mice and primates. The vaccine potentially neutralizes coronavirus and induces production of IgG antibody isotypes related to helper T cells in the lungs and spleen within 2 weeks of administration. Applied novel nanoparticle approach in this vaccine enables easy in vivo delivery of inoculum after bare mixing that induces desired immune response and provides stability at room temperature for one week. The development of self-replicating mRNA vaccine is easy to formulate, stable, and need not 2 times immunization as in conventional nucleic acid vaccines [32].

ARCT-021 (LUNAR-COV-19), a self-replicating mRNA vaccine designed by Arcturus Therapeutics Holdings Inc. San Deigo, California. The company has received FDA approval for Phase 2 clinical trial. Phase 1/2 study provides sufficient data on well tolerability (in younger of age and older) and both cellular/humoral immunogenicity after administration of single dose (7.5 μg). Dose-dependent immune response is observed through 43 days.

Viral vector vaccines

Here, immunogens are used to induce pathogen-specific antibodies and immune response. It includes killed, attenuated pathogens, or recombinant pathogens [33]. As these vaccines are prepared through carrier virus (an adenovo virus or pox virus) and contain usually S gene/protein for competing SARS-CoV-2. After administration in the host, the system induces innate immunity [34].

Sputnik V vaccine is first registered inoculating candidate against COVID-19. The vaccine is different from conventional as they do not contain antigen rather induce body’s cells to produce the same. There is a modified virus vector that gets activated after interacting with spike proteins of SARS-CoV-2 and delivers genetic codes for antigen. Virus vector lacks genes responsible for replication and making its copies in body cells. It is used to deliver genetic material from another virus that is targeted for vaccination. A genetic code of S protein from SARS-CoV-2 virus is inserted into two different viral vectors that develop immunity against delivered S proteins after prime and boost immunization. Gamaleya center of Russia used unique and novel technology using two adenovirus vectors (Ad 26 and Ad 5) that boosts immunity after 21 days.

Oxford University and AstraZeneca, a pharmaceutical company both are engage in developing Covishield vaccine. Its Indian partner “Serum institute” Pune, is enduring for production of viral vector vaccine as brand name AZD1222. This contains weakened, genetically modified, non-replicating strains of SARS-CoV-2 and adenovirus (causative of common cold). The vaccination course consists of two doses (each 0.5 ml) and should be administered within 4–6 weeks apart. The interim study notified production of plentiful dose-dependent anti-Spike S Protein immunoglobulin G (Oxford University press release). From the interim analysis, AZD1222 is found 70.4% efficacious against prevention of COVID-19 with no prominent adverse effects. UK medicine and health-care products regulatory agency has authorized distribution of AZD1222 to the above 18 years individuals. The company has started vaccine weekly trial on United Kingdom participant regardless symptoms [35]. Moreover, AstraZeneca is involved for sufficient production and distribution of approximately 1 million doses of vaccine in the UK with the support of National Health Service, England. The company continuously seeks emergency use approval of AZD1222 from the WHO and tries to make ease of availability in low and middle income provinces at no profit base.

Live attenuated vaccines

This kind of vaccine is composed of live coronavirus whose virulence has been lessened under laboratory conditions. The system allows less virulent virus to replicate in host cells and produce mild pathogenicity if any. This kind of approach has been successfully demonstrated for the combat of viral infections including smallpox and polomyelitis [36]. However, geriatrics and diseased patients are not suitable for this kind of vaccination [37]. The Serum Institute of India has allied with US pharmaceutical company “Codagenix” for the development of live attenuated COVID vaccine “Covi-Vac.” Intranasal Covi-Vac has completed its preclinical studies and currently in phase 1. The administration of vaccine does not necessitate skilled person hence appropriate for mass immunization operation. The production of Codagenix vaccine can be scalable due to ease of cell culture and sufficient doses can be formulated to meet worldwide needs. The vaccine was found to be safe and protective on single dose administered in gold standard animal model. However, due to its nature (live attenuated), this vaccine cannot be suitable approach for elderly individuals. Interestingly, the vaccine is designed to develop immunity against all kinds of proteins present on SARS-CoV-2 virus which would elicit vigorous response with long term cellular and humoral immunization [38].

Peptide vaccines

The approach displays unique features, that is, selectivity and specificity toward the SARS-CoV-2. The peptide based vaccine candidate implies identification of both epitopes, that is, host cells and capsid of virus, be suitable approach for elderly individuals. Interestingly, the vaccine is designed to develop immunity against all kinds of proteins present on SARS-CoV-2 virus which would elicit vigorous response with long term cellular and humoral immunization [38].

EpiVacCorona, a peptide vaccine is developed by Russian Institute “CanSino Biologics, Vektor State Research Center of Virology and Biotechnology.” The system contains fragments extracted from virus and synthetic peptides that form active antigens in body [39]. EpiVacCorona vaccine stimulates body to produce immunogenic responses by releasing antibodies into host's blood and lymph. The vaccine does not persuade reactogenic responses and is considered for high safety. EpiVacCorona vaccine provokes an immunogenic response against SARS-CoV-2 and maintains future immunity. Russian authorities’ claim its effectiveness and prepare for mass immunization in 2021. At present, the vaccine appears in phase 3 including clinical trials (NCT04527575) on adults and pregnant ones as it does not exhibited embryotoxic activity.
Another, pVAC, a DNA plasmid vaccine of the University hospital Tübingen, is categorized in dendrimers and cyclopeptides. It is designed to stimulate humoral immunity through intramuscular injection hence neutralizes antibodies. The antigenic multiplets, present in vaccine, are supposed to be position on the surface of muscle cells that are taken up by antigen presenting cells and mediate the process major histocompatibility complex Class II pathway. Similarly, the UB-612 (COVAXX) of United Biomedical, New York is designed for activation of multiple epitopes and stimulation of both cellular and humoral immunity against SARS-CoV-2 virus. The vaccine is totally synthetic with no biohazardous factor and targeted for the Receptor Binding Domain (RBD) of S protein. The preliminary studies based on clinical aspects, demonstrated that COVAXX will produce high immunogenicity against live virus. In addition, the data suggested generation of more than 1,000,000 anti-S1-RBD titers when measured through ELISA. Reputed worldwide organizations such as the World Health Organization, Gavi, Coalition for Epidemic Preparedness Innovations, and the Vaccine Alliance are seeking measures for sufficient production and delivery of more than 100 million doses in first quarter of 2021. In the arena, COVAXX (Table 2) is trying to establish scalable, low cost vaccine production platform among other developed vaccines candidates.

**Recombinant protein vaccine**

This immunization approach includes recombinant proteins encrypted by DNA that supports expression of genes and mutant protein thus eliminates post-vaccination adverse responses [41].

The development of recombinant protein vaccine includes various versions of spike "S" proteins as antigen component [42].

"Convidicae" or " Ads-nCoV" of CanSino Biologics (China) is the first recombinant protein containing anti-SARS-CoV-2 vaccine candidate. Adenovirus based this strategy is currently in phase 3 (Table 2). Novel recombinant strains including replication-defective adenovirus and pneumococcal protein antigens are genetically engineered to target spike protein and made on SARS-CoV-2 coronavirus. Russian Health Ministry has permitted massive international phase 3 clinical trial (NCT04526990) organized conjointly by CanSino biologics and Petrovax company.

Apart from above quoted conventional approaches, researchers are designing some unconventional strategies for the effective abolition of SARS-CoV-2. In this context, Alivita Biomedical Inc. has formulated autologous dendritic cells "AW-COVID-19" encoded with corona virus antigens. This novel formulation is derived of patients monocytes amalgamated with SARS-CoV-2 antigens incubated dendritic cells [43]. At present, the formulation undergoes phase I/II clinical trial for the evaluation of efficacy and safety in volunteers (NCT04586252). Another, Symvivo Corporation designed bacTrU-Spike vaccine containing live *Bifidobacterium* and synthetic plasmid DNA to combat COVID-19. In this series, researchers of Nanjing University are engaged to find out binding potential of plant micro RNA (MIR2911) with SARS-CoV-2 mRNA. The outcomes revealed inhibition of coronavirus replication through blocking of protein translation. The formulation is also facing phase I clinical study (ChiCTR2000031432) in China for its tolerance and safety in patients [44].

There are few issues on developed vaccines that create question marks for complete and successful abolition of corona. The probability of rapid disappearance of developed antibody, chances of reinfection, antibody dependent enhancement (ADE), clearance of antigen-antibody complex through another mode, and safety for all age group population are to be resolved out [45]. A study on experimental SARS-CoV-2 stated that re-infection to a vaccinated individual may be more complicated and fatal compare to non-vaccinated person. The developed effective COVID-19 vaccine need to address such issues to control current pandemic, its re-occurrence, and future epidemics [46]. Moreover, most of the developed vaccines does not faced clinical trial on elderly, immunocompromised and comorbidities persons so their effectiveness without serious side effects are also unanswered [47].

**CONCLUSION**

Numerous academic institutions and companies of worldwide have developed and evaluated several vaccines after extremely compressed clinical trial agendas. Several developers such as Pfizer and BioNTech, Moderna, AstraZeneca, and Bharat Biotech are ready with their esteemed products for the management of pandemic COVID-19. India itself is now supplying Covishield and Covaxin inoculums under grant assistance to its neighboring countries, that is, Bangladesh, Bhutan, Myanmar, Nepal, Maldives and Seycelles from January 20, 2021. Sundry pharmaceutical technologies reliant on genetics, nanoengineering, and biotechnology are integrated for successful development of these anti-SARS-CoV-2 inoculums. Taking account on conditions of more vulnerable community including immunocompromised, geriatrics, and comorbidities patients the safety and efficacy of vaccine are yet to be monitored. Moreover, unforeseen outcomes of immunization in the varied demographic regions, different races, variant age groups and diseased conditions are to be under surveillance. Thus, post-marketing surveillance (phase IV study) becomes more important as it will provide real observance of efficacy and associated adverse effects once population get immunized.

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**AUTHOR'S CONTRIBUTION**

Dr. R.K. Yadav proposed the current title and conceptualized the article. Dr. Devender Pathak critically reviewed the whole content. Dr. Kamla Pathak supervised the collected details and data. Dr. Shashi Kiran Misra envisaged literatures and drafted the manuscript.

**CONFLICT OF INTEREST**

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**REFERENCES**

1. Sempowski GD, Saunders KO, Acharya P, Wiehe KJ, Haynes BF. Pandemic preparedness: Developing vaccines and therapeutic antibodies for COVID-19. Cell 2020;181:1458-63.
2. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy 2020;75:1730-41.
3. Corey L, Mascola JR, Fauci AS, Collins FS. A strategic approach to COVID-19 vaccine development and R&D. Science 2020;368:948-50.
4. Le TT, Cramer JP, Chen R, Mayhew S. Evolution of the COVID-19 vaccine development landscape. Nat Rev Drug Discov 2020;19:667-8.
5. Dai L, Zheng T, Xu K, Han Y, Xu L, Huang E, et al. A universal design of betacoronavirus vaccines against COVID-19, MERS, and SARS. Cell 2020;182:722-33.
6. Zhang J, Zeng H, Gu J, Li H, Zheng L, Zou Q. Progress and prospects on vaccine development against SARS-CoV-2. Vaccines (Basel) 2020;8:153.
7. Walls A, Park Y, Tortorici M, Wall A, McGuire AT, Veesler D. Structure, function and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell 2020;181(2):281-92.
8. To KK, Tsang OT, Leung WS, Tam AR, Wu TC, Lung DC, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: An observational cohort study. Lancet Infect Dis 2020;20:565-74.
9. Letko M, Marzi A, Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. Nat Microbiol 2020;5:562-9.
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Asian J Pharm Clin Res, Vol 14, Issue 5, 2021, 17-23

Unclear issues regarding COVID-19. Eurasian J Med 2020;52:191-6.
11. Centers for Disease Control and Prevention. Coronavirus Disease 2019 (COVID-19): Symptoms. Available from: https://www.cdc.gov/coronavirus/2019-ncov/symptoms.html. [Last accessed on 2020 Mar 14].
12. Bogoch II, Watts A, Thomas-Bachil A, Huber C, Kraemer MU, Khan K. Potential for global spread of a novel coronavirus from China. J Travel Med 2020;27:taaa011.
13. Toraih EA, Elshazli RM, Hussein MH, Elgamal A, Amin M, El-Mosawy M, et al. Association of cardiac biomarkers and comorbidities with increased mortality, severity, and cardiac injury in COVID-19 patients: A meta-regression and decision tree analysis. J Med Virol 2020;92:2473-88.
14. WHO Coronavirus Disease (COVID-19): How is it Transmitted? Available from: https://www.who.int/news-room/q-a-detail/coronavirus-disease-covid-19-how-is-it-transmitted. [Last accessed on 2020 Dec 11].
15. World Health Organization. Rational Use of Personal Protective Equipment for Coronavirus Disease 2019 (COVID-19). Available from: https://www.who.int/news-room/q-a-detail/2019-ncov-IPCPE_use-2020.1-eng.pdf. [Last accessed on 2020 Mar 14].
16. Vashist SK. In vitro diagnostic assays for COVID-19: Recent advances and emerging trends. Diagnostics (Basel) 2020;10:202.
17. Sharpe HR, Gilbride C, Allen E, Belij-Rammerstorfer S, Bissett C, Ewer K, et al. The early landscape of coronavirus disease 2019 vaccine development in the UK and rest of the world. Immunology 2020;160:223-32.
18. Wang N, Zhao J, Jiang S, Du L. Subunit vaccines against emerging pathogenic human coronaviruses. Front Microbiol 2020;11:298.
19. Roper RL, Rehm KE. SARS vaccines: Where are we? Expert Rev Vaccines 2009;8:887-98.
20. Sinopharm Says Second COVID Vaccine Found to Be Safe; 2020. Available from: http://www.sinopharm-says-2nd-covid-vaccine-found-to-be-safe-in-testing. [Last accessed on 2020 Jul 10].
21. Bar-Zeev N, Kochhar S. Expecting the unexpected with COVID-19 vaccines. Lancet Infect Dis 2021;21:150-1.
22. Wang H, Zhang Y, Huang B. Development of an inactivated vaccine candidate, BBIBP-CorV, with potent protection against SARS-CoV-2. Cell 2020;182:713-21.
23. Xia S, Duan K, Zhang Y, Zhao D, Zhang H, Xie Z, et al. Effect of an inactivated vaccine against SARS-CoV-2 on safety and immunogenicity outcomes: Interim analysis of 2 randomized clinical trials. JAMA 2020;324:951-60.
24. Zhang F, Chow KY, Hon CC, Law KM, Yip CW, Chan KH, et al. Characterization of humoral responses in mice immunized with plasmid DNAs encoding SARS-CoV spike gene fragments, Biochem Biophys Res Commun 2004;315:1134-9.
25. Silveira MM, Moreira GM, Mendonca M. DNA vaccines against COVID-19: Perspectives and challenges. Life Sci 2021;267:118919.
26. Nascimento IP, Leite LC. Recombinant vaccines and the development of new vaccine strategies. Braz J Med Biol Res 2012;45:1102-11.
27. Seo YB, Suh YS, Ryu JI, Jiang H, Oh H, Koo BS, et al. Soluble Spike DNA Vaccine Provides Long-term Protective Immunity against SARS-CoV-2 in Mice and Nonhuman Primates. New York: BioRxiv; 2020.
28. Dong Y, Dai T, Wei Y, Zhang L, Zheng M, Zhou F. A systematic review of SARS-CoV-2 vaccine candidates. Signal Transduct Target Ther 2020;5:237.
29. Armbruster N, Jasny E, Petch B. Advances in RNA vaccines for preventive indications: A case study of a vaccine against rabies. Vaccines (Basel) 2019;7:132.
30. Jackson LA, Anderson EJ, Rouphael NG, Roberts PC, Makhene M, Coler RN, et al. An mRNA vaccine against SARS-CoV-2 - preliminary report. N Engl J Med 2020;383:1920-31.
31. Pfizer Press Release. Pfizer and BioNTech Choose Lead mRNA Vaccine Candidate against COVID-19 and Commence Pivotal Phase 2/3 Global Study. Available from: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-choose-lead-mrna-vaccine-candidate-0. [Last accessed on 2020 Jul 27].
32. Erasmus JH, Khandhar AP, Megan A, Walls AC, Hennam EA, Murapa P, et al. An Alphavirus-derived replicon RNA vaccine induces SARS-CoV-2 neutralizing antibody and T cell responses in mice and nonhuman primates. Sci Transl Med 2020;12:eabc9396.
33. Lu B, Huang Y, Huang L, Li B, Zheng Z, Chen Z, et al. Effect of mucosal and systemic immunization with virus-like particles of severe acute respiratory syndrome coronavirus in mice. Immunology 2010;130:254-61.
34. Afrough B, Dowsall S, Hewson R. Emerging viruses and current strategies for vaccine intervention. Clin Exp Immunol 2019;196:157-66.
35. Lipstick M, Dean NE. Understanding COVID-19 vaccine efficacy. Science 2020;370:763-5.
36. Minor PD. Live attenuated vaccines: Historical successes and current challenges. Virology 2015;479-480:379-92.
37. Amanat F, Krammer F. SARS-CoV-2 vaccines: Status report. Immunity 2020;52:583-9.
38. Sharma O, Sultan AA, Ding H, Triggel CR. A review of the progress and challenges of developing a vaccine for COVID-19. Front Immunol 2020;11:58534.
39. Li W, Joshi MD, Singhania S, Ramsey KH, Murthy AK. Peptide Vaccine: Progress and challenges. Vaccines (Basel) 2014;2:515-36.
40. Skwarczynski M, Toth I. Peptide-based synthetic vaccines. Chem Sci 2016;7:842-54.
41. Tripathi NK, Shrivastava A. Recent developments in recombinant protein-based dengue vaccines. Front Immunol 2018;9:1919.
42. Pollet J, Chen WH, Strych U. Recombinant protein vaccines, a proven approach against coronavirus pandemics. Adv Drug Deliv Rev 2021;170:71-82.
43. Li YD, Chi WY, Su JH, Ferrall L, Hung CF, Wu TC. Coronavirus vaccine development: From SARS and MERS to COVID-19. J Biomed Biotechnol 2020;12:eabc9396.
44. Zhou LK, Zhou Z, Jiang XM, Fu Z, Xiao G, Zhang CY, et al. An Alphavirus-derived replicon RNA vaccine induces SARS-CoV-2 neutralizing antibody and T cell responses in mice and nonhuman primates. Sci Transl Med 2020;12:eabc9396.
45. Wang J, Zand MS. The potential for antibody-dependent enhancement of SARS-CoV-2 infection: Translational implications for vaccine development. J Clin Transl Sci 2020;5:1-4.
46. Jiang S. Don't rush to deploy COVID-19 vaccines and drugs without sufficient safety guarantees. Nature 2020;579:321.
47. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutierrez-Ocampo E, Villamizar-Pena R, Holguin-Rivera Y, Escalera-Anteza JP, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel Med Infect Dis 2020;34:101623.