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REVIEW

# Vaccine and vaccination as a part of human life: In view of COVID-19

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## Abstract

**Background:** Vaccination created a great breakthrough toward the improvement to the global health. The development of vaccines and their use made a substantial decrease and control in infectious diseases. The abundance and emergence of new vaccines has facilitated targeting populations to alleviate and eliminate contagious pathogens from their innate reservoir. However, along with the infections like malaria and HIV, effective immunization remains obscure and imparts a great challenge to science.

**Purpose and scope:** The novel Corona virus SARS-CoV-2 is the reason for the 2019 COVID-19 pandemic in the human global population, in the first half of 2019. The need for establishing a protected and compelling COVID-19 immunization is a global prerequisite to end this pandemic.

**Summary and conclusion:** The different vaccine technologies like inactivation, attenuation, nucleic acid, viral vector, subunit, and viral particle based techniques are employed to develop a safe and highly efficient vaccine. The progress in vaccine development for SARS-CoV2 is much faster in the history of science. Even though there exist of lot of limitations, continuous efforts has put forward so as to develop highly competent and effective vaccine for many human and animal linked diseases due to its unlimited prospective. This review article focuses on the historical outlook and the development of the vaccine as it is a crucial area of research where the life of the human is saved from various potential diseases.

KEYWORDS
COVID-19, herd immunity, immunization, transmission, vaccine

## 1 | INTRODUCTION

The term "vaccine" originated from Latin "*Variolae vaccinae*" successively after Edward Jenner demonstrated the prevention of cowpox in 1798. Vaccines are considered as a biological preparation that has the ability to enhance immunity, for disease prevention (prophylactic vaccine) or for treatment (therapeutic vaccine). Immunization is considered as the ultimate achievement to public health care system during 20$^{th}$ century, according to the Centers for Disease Control and Prevention (CDC).[1] The vaccines are normally administered in their liquid form by injection, rather than oral or intra-nasal routes. The capability of the human body to distinguish and tolerate the indigenous material as self to the body and to recognize and eliminate the foreign material as non-self referred as "immunity." The ability to discriminate microbes as foreign substance by the immune system provides protection toward infectious diseases. Generally immunity is indicated by the occurrence of antibody to a specific organism or closely related

**Abbreviations:** BLA, biologic license application; CDC, centers for disease control and prevention; COVID-2019, Corona virus disease 2019; Hib, hemophilus influenzae type b; HIV, human immunodeficiency virus; HSV, herpes simplex virus; mAb, monoclonal antibodies; Nab, neutralizing antibodies; NDA, new drug application; RBD, receptor binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization

  

organism. Active and passive are the two basic mechanisms to acquire immunity. The active immunity provides protection that are produced by the person's own immune system. Usually this type of immunity lasts for many years or for a lifetime. Passive immunity enables effective protection by products produced from humans and transferred to another human usually by injection but wanes within weeks, months, or by years.

Vaccines are usually effective but rarely provide permanent or complete protection from infectious diseases.[2] They generally comprise both the whole/entire disease causing organism and their active constituents that can induce immunogenic response. They are produced by attenuation by growing the disease causing organism under sub-optimal conditions which lessen their disease causing ability. The pathogenic organisms were inactivated using thermal or chemical methods. Some vaccines are developed from components of pathogens such as nucleic acid or from specific proteins or polysaccharides. Another type of vaccine is inactivated toxins from toxin producing microbes. The effectiveness of the polysaccharide vaccine in young children was increased using conjugation of polysaccharides with proteins.

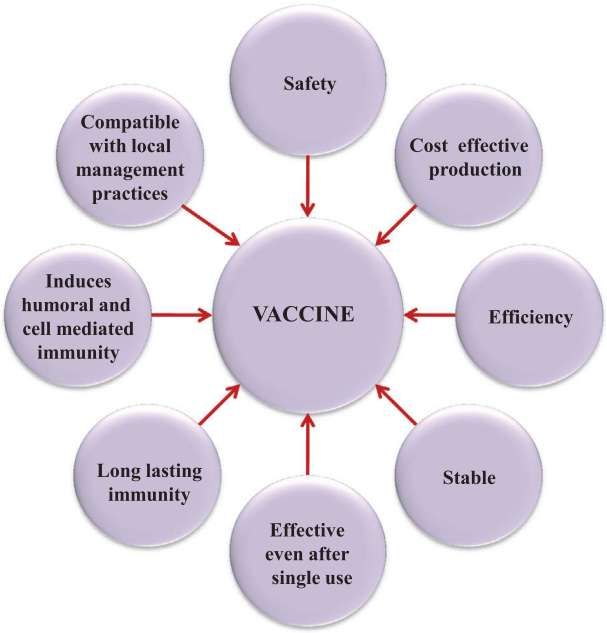


**FIGURE 1** Characteristics of a vaccine

## 2 | CORONA VIRUS DISEASE 2019 (COVID-2019) PANDEMIC

The novel beta-corona virus family member SARS-CoV-2 (severe acute respiratory syndrome coronavirus) is the causative agent for the pandemic COVID-19. The disease mainly spreads through the respiratory droplets from the infected person. As of July 9, 2021- 185,291,530 cumulative cases have been reported globally with 4,010,834 deaths as reported by the World Health Organization (WHO).[3] Until now, no particular treatment strategy has been demonstrated to be effective against the COVID-19. The mutation that occurs to the viral genome leads to the antigenic shift and drift, and it keeps spreading from one population to the other. These susceptible mutations ultimately generate unusual variants that let the virus to get away from the immune system even after the vaccine administration.[4] Scientists across the world are joining hands to introduce an innovative approach to remodel drugs, expand vaccines or devices to hinder/obstruct the progression of this devastating pandemic. It is therefore much anticipated that the vaccine should be appropriate for all age groups including pregnant ladies, and lactating mothers out to have quick protection by a single dose, and the protection should last for at least one year ought to give a quick onset of defense with a single dose and should persist the protection for at least one year of administration.

Vaccines, generally inherent in a complex multi-scale system which includes clinical, biological, behavioral, social, environmental, and economical relationships.[5] The action of vaccines is by making our immune system more organized and co-ordinate to identify and remember the foreign pathogenic microbes. Thereby vaccination aids in the generation and storage of antigenic specific memory cells. In future, the frequent susceptibility to the actual disease can make our immune system quickly respond to opsonize the bacteria or viruses more effectively. The benefits of vaccination, one of the most economic public health interventions, have not wholly reached target beneficiaries in many low and middle income countries.[6] According to WHO, vaccination imparts an important and successful means to prevent infectious diseases. Due to infectious disease the mortality rate among children can be reduced by the massive immunization plan that mainly hang on with the accessibility of the highly economic and immunologically protective vaccines against most dreadful infectious conditions.[7] There are so many strategies and assured properties associated with the making of a vaccine (Figure 1).

Vaccines are generally unique and are administered to large groups of typically healthy individuals including infants and children too. It is really unsatisfactory that when vaccine itself can induce side effects which creates burden even though the illness itself can exhibit severe fatal side effects. The vaccination should provide a much economical approach thereby reducing childhood disease burden, rather compared with clean water and improved sanitation facility that definitely can reduce transmission of disease but require time consuming and expensive infrastructure investments.[8]

## 3 | VACCINE AGAINST COVID-19: PRESENT STATUS OF DEVELOPMENT

Covid-19 is an ailment brought about by the serious intense respiratory syndrome caused by corona virus 2 (SARS-CoV-2) which belongs to Coronaviridae. SARS-CoV-2 was first recognized in the city of Wuhan, China, in December 2019, after a group of patients with pneumonia of obscure reason were accounted for to the WHO. The episode was pronounced a general wellbeing crisis of global concern on January 30, 2020, and the malady brought about by SARS-CoV-2

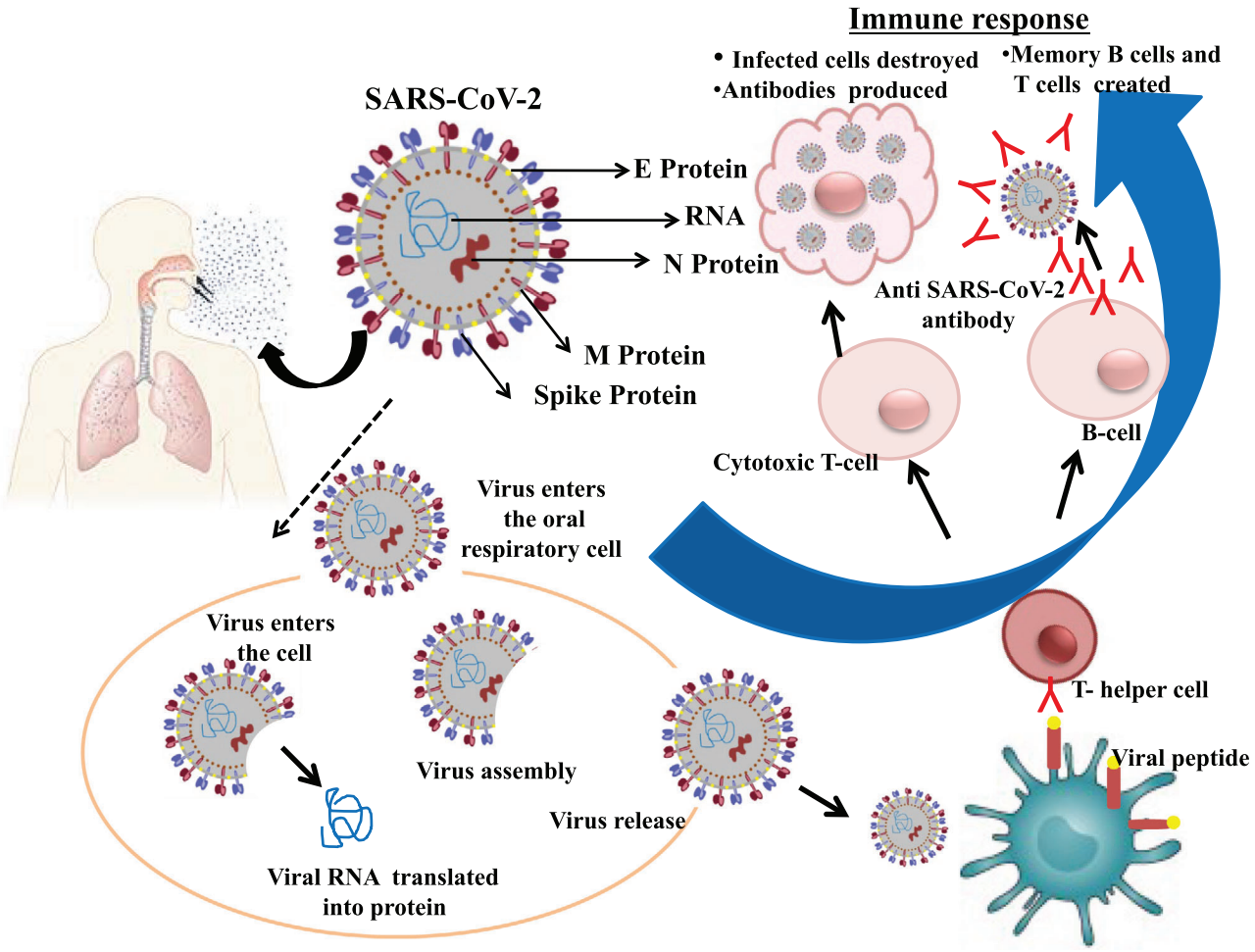


**FIGURE 2** Transmission of SARS-CoV-2 causing COVID-19

was authoritatively named COVID-19 on eleventh February 2020. Subsequent to surveying the flare-up and following transmission of the infection in numerous different nations around the world, on eleventh March 2020 the WHO declared COVID-19 a pandemic. This implies the infection has spread around the world, and it is the first time that a corona virus has led to a pandemic. The virus mainly spread through respiratory droplets from the infected persons. Corona viruses are structurally pleomorphic, enveloped virus attributed with projections comprising of S protein on their outer surface. Their genome is operationally functional with positive sense of ssRNA complexed with nucleocapsid (N) protein which forms helical nucleocapsids. The four structural proteins present in SARS-COV2 virus are spike (S), nucleocapsid (N), envelope (E), and membrane (M) proteins encoded at 3′end of the viral genome (Figure 2).[9]

The urgent need for vaccine development against SARS-CoV2 virus was due to the pandemic announcement of COVID-19 disease by WHO. The succeeding widespread mortalities and morbidities in most countries alarmed researchers and scientists to stood together to eradicate this deadly pandemic. Even tough for normal development of vaccine, it would take more than 10 years but the vaccine against SARS- COV2 goes at really quick pace making a breakthrough in development of vaccine through several reputed research centers and vaccine manufacturing companies to put an end to the fast spreading pandemic.[10] Due to this epidemic situation, the whole process of vaccine development and the clinical trial phase were shortened, so that the vaccine has to get fast tracked within 16–18 month duration without reducing its efficiency and efficacy. There are more than 150 candidate vaccines under development process and further 100 vaccines are in highly advanced stages of development.[12]

For developing effective and safe drugs and vaccines against COVID-19 considerable restless efforts have been contributed by the researchers worldwide to end this pandemic. As a result of this continuous hard work within this limited time span, vaccines of different category has entered the clinical trials. The fast genetic sequencing of SARS- CoV-2 remarkably triggered and hastens up the exploration for effective vaccine. But the most challenging research task obtained in the laboratory for this potential vaccine is evidence of clinical safety and efficacy within this short period. At present, vaccines of different origin such as inactivated, nucleic acid, and vector based vaccines have already entered for human trials. But research is going on to identify the most precise treatment measure to stop

this deadly disease. According to the latest report from Ministry of Health and family welfare, Govt. of India on August 2021 that the Central Drugs Standard Control Organization (CDSCO) has approved for restricted use of US FDA, UK MHRA, etc., which is listed in WHO under emergency situation.[11] The SARS-CoV2 vaccine production landscape in the world reveals that there are 112 candidates under clinical trial vaccines and among 185 vaccines in different early stages of development.[12] There are many institutions that are committed in developing the COVID-19 vaccine, including many academic/research and vaccine manufacturing companies in India. In association with Oxford University and Astra Zeneca, the Serum Institute of India developed ChAdOx1 nCoV-19 (CoviShield). The first vaccine is developed in collaboration with National Institute of Virology, Pune (Indian Council of Medical Research) and previously in process of developing an inactivated vaccine called "Covaxin." This vaccine has successfully completed the trials in animal models such as mice, guinea pigs, and rabbits and remarkably exhibited strong immunological response of the inactivated vaccine. In the development of every new vaccine, including SARS-CoV2 has to face several challenges. The simultaneous promotion of many vaccines started at the early beginning of 2021. As of July 7, 2021- 3,078,787,056 doses of vaccine has been administrated according to WHO records.[3]

The rapid drift and several genomic alterations undergone in the new SARS-CoV2 virus have been identified. The safety and effectiveness of the vaccine can only be reviewed when a huge number of factors are considered in various cultural and ecological locations. Regardless of the availability of the safe and effective vaccine, the impartial distribution to the most vulnerable will be the foremost challenge. The next principal challenge to be fulfilled is by procurement of logistics, their safe dispensing, efficient storage depot, unbroken cold chain (chamber) facility, and their administration at community level. For the perfect accomplishment of COVID-19 vaccine, it should be able to apply for humans in routine, so that it should disrupt the spreading of pandemic from person to person and also defend against both clinical diseases as well as viral transmission.

## 4 | IMPORTANCE OF IMMUNIZATION AND VACCINATION

Vaccines can protect our existence and avoid diseases and disabilities, moreover signify good worth between health mediations. Due to the progression in medical sciences, vaccination protected children from many infectious and contagious diseases. One of the greatest attainments is the eradication of polio. Immunization assists getting protected from dreadful ailments and furthermore prevents spreading of the sickness. In order to introduce immunological memory and thereby defend against the effects of infection, immunization is an approach of stimulating the host's defense in case of a particular pathogen.

### 4.1 | Children

Immunization is the principle health intervention used to reduce child mortality. Low paces of immunization not just leave many young children at danger for different serious vaccine-preventable diseases yet additionally serve as an indicator of inadequacies in getting other preventive medical care administrations.[13] Due to the significance of immunization, it is vital that the executions of the program against vaccine preventable illnesses are checked intently. Also, one confronts of this program is defaulting immunization – neglecting to receive the recommended vaccination at the suggested time. The implementation of childhood vaccination by World Health Organization's (WHO) reduced childhood mortality. They included the early day's vaccine series including MMR, DTP, Hib, hepatitis B, varicella, and polio vaccines.

In vaccinated children the long term sequelae related with certain childhood illness such as neurological impairments, hearing loss, and various other physical disabilities can be avoided. In children, constant or recurrent infections in early childhood can lead to poor stunted growth, which in turn adversely affects the adult health, cognitive capacity and finally facing the economic productivity.[14–16] For example, in children due to measles infection will wipe out the already existing antibodies to different pathogens in months following infection period and made their health state more vulnerable, prone to multiple infections, and possibly leads to death.

### 4.2 | Adults

In adults, immunization protects themselves from numerous acute contagious diseases and their associated complication which varies from inherited rubella syndrome to Hepatitis B and malignancy connected with Human papilloma virus (HPV). The elder adults were advised to receive yearly influenza and pneumococcal polysaccharide vaccines, with decennial tetanus diphtheria boosters which are recommended for all adults. For some individuals additional vaccines are also suggested for their precise occupational, behavioral, or travel exposures as well as for several chronic disease situations. There exist several challenging concerns associated with safety of vaccine and their acceptance, vaccine cost and investment, constancy and safety measures of vaccine supply, approaches for accomplishing more adolescents and adults, and enhanced awareness for pandemics of influenza. The safety of the vaccine is considered to be a major public concern and with this regard the requirement for vaccine-induced protection have been related to recent outbreaks of vaccine-preventable diseases such as measles[17] and higher rates of exemptions from school-entry vaccine requirements.[18,19] In the H1N1 influenza pandemic reported in 2009–2010, vaccine safety monitoring was the foremost preference.[20,21]

## 5 | HISTORY OF VACCINE

Until now, vaccination is regarded as the most expected efficient as well as cost effective interventions for prophylactic precaution against numerous infectious or contagious diseases.[22] During 15th century, the first evidence of purposeful attempt made to stimulate immunity was accomplished by the Chinese and Turks. Various reports supported and suggested that dried crusts obtained from the small pox pustules were either insert into small scratches in the skin or inhaled into nostrils to attain immunity against smallpox by a technique called variolation. The positive effect of variolation was examined in 1718 by Lady Mary Wortley Montagu on their native resident population and also imparted the technique in their children. Edward Jenner, the English physician is considered as the founder of vaccinology as he notably improved the technique of variolation and tested by him and observed the fact that milkmaids were immune to the fatal disease small pox after exposure to cowpox infection. Later Jenner performed the clinical trials and broadcast the result outcome to the world.[23,24] By the end of 1980, the worldwide eradication of smallpox was attained by the introduction of variolation in 17th century and followed by the concerted vaccination programs made it a complete success.[25]

However, despite of the remarkable achievements of Jenner and due to lack of sufficient knowledge about microbiology, it took eight decades to pass for the next step toward the history of vaccine which happened in the Louis Pasteur's experimental laboratory. The term "vaccine" was coined by Louis Pasteur toward the respect of Jenner's significant insight. The concept of attenuation was most specifically formulated by Pasteur and his colleagues confirmed its effectiveness first with the diarrheal disease in chickens caused by *Pasteurella multocida*,[26] the anthrax an infectious bacterial disease in sheep and most horrible rabies virus in animals and humans.[27] During the last decade of 19th century, there was a tremendous development in vaccine technology. The key development methods to inactivate whole bacteria for the making of vaccine, the antitoxin production, and the understanding of serum components (antibodies) capable of neutralizing toxins or inhibiting bacterial growth led a great breakthrough in the history of vaccine production. Later, during the last years of 19th and the initial years of the 20th century, inactivated whole vaccine for plague,[28] typhoid,[29] and cholera[30] were developed and examined.

The eminent workers responsible for unraveling, and developing the "perception of serum antibodies" were Emil von Behring, Shibasaburo Kitasato, Alexandre Yersin, Almworth Wright, Emile Roux, and Paul Ehrlich. During 1923, Alexander Glenny and Barbara Hopkins demonstrated that, due to the action of formalin the diphtheria toxin can be converted into a toxoid.[31] During the initial years of the 20th century, Calmette and Guerin introduced the more effective technique of serial cultivation of a pathogen by in vitro or in unnatural hosts and they passaged 230 times bovine tuberculosis bacteria in artificial media containing bile to achieve an attenuated strain to defend against human tuberculosis-BCG vaccine.[32]

In 1926, a "killed vaccine" was developed for whooping cough using whole *Bordetella pertussis* and followed in 1927 led to the development of tetanus toxoid and in late 1940's tetanus toxoid was combined with diphtheria and pertussis (DTP) as children vaccine. In the era of 1950's put forward the expansion of poliovirus vaccine, in which both an inactivated vaccine and live vaccine were developed. The former by Jonas stalk[33] in 1954 and latter by Alfred Sabin[34] (1961), an oral polio vaccine were easy to deliver and eliminated the spread of polio. In 1960's, three attenuated vaccine were developed- for measles (1963) by Samuel Katz and John Enders,[35] for mumps (1967) by Maurice Hilleman,[36] and for rubella virus (1970) by various workers.[37–39] While in 1971 MMR single vaccine were developed after combining measles, mumps, and rubella vaccines. In 1964 the killed rabies vaccine was developed by administering in the abdomen with 30 painful shots and finally in 1980 a newer version was introduced with five shots to be given in arm to protect from fatal rabies. The 1980s witnessed the birth of two important approaches for vaccine development by application of conjugation in bacterial capsular polysaccharides to proteins and by means of genetic engineering. The conjugate vaccines was developed using a part of the bacterial cell wall to develop a safe antigen for meningococcal, pneumococcal, and *Hemophilus influenzae* type b (Hib). These vaccines protected from infections in blood, life threatening meningitis, and a variety of pneumonia. Toward the last decades of the 20th century, Sellards and Laigret[40] serially passaged yellow fever virus in mice and later by Theiler and Smith[41] more successfully attenuated yellow fever virus in chicken embryo tissues.

The early vaccine emerged through genetic engineering was against hepatitis B virus which was licensed in 1986 by an antigen cloned rather grown and hepatitis A was developed in 1990 as a killed vaccine. Three primary vaccines were developed by reassortment: live and inactivated influenza[42,43] as well as one of the two rotavirus vaccines.[44] The chickenpox vaccine for children was licensed in 1995 and the first DTaP (1996) vaccine got approved by combining merely parts or fractions of *B. pertussis* organism with diphtheria and tetanus which considerably diminished pertussis induced death following DTP vaccination. By the development of influenza vaccine in 2000 made a remarkable reduction in premature death. The foremost therapeutic vaccine derived from blood cell infusions were approved in 2010 for prostate cancer. The discovery of hepatitis C virus by the Nobel Laureates of 2020 directed towards a landmark achievement in the current battle against viral diseases. This will allow the rapid development of antiviral drugs and vaccines directed against hepatitis C which greatly improves global health and hoping for the complete eradication of the virus from the world population.[45] By employing the novel reverse vaccinology, a multi-component recombinant vaccine was developed and commercialized against meningococcus in 2013. The much advancement in structural biology and reverse vaccinology could be able to describe more effective antigens, while systems biology probably resolve to understand of how modification in the expression level of specific genes connected with protecting immune responses.[46–49] Therefore, the approach enhances our knowledge of how to induce specific immune responses and, thus, the development of highly specific and potent novel vaccines.

## 6 | CLASSIFICATION OF VACCINES

The progress and improvement of vaccines against many diseases causing organism denotes a key innovation in the history of modern medicine. The conventional vaccine strategy has relied on basically two types of microbial compositions of which one to generate vaccine for immunization or rather to produce a protective immune response. During the initial phase, living infectious microbes which are prepared in their weaker stage that are incapable to induce disease was used as vaccine. In later stage of vaccine preparations, inert, inactivated, or subunit groups of antigens were used. However, with the recent and considerable progress in the field of molecular biology contributed much advanced alternative strategies that enhance the development of vaccines. There exist numerous approaches to designing and developing vaccines against various microbes. They mainly depend on the fundamental information available about the microbes including the mechanism of infection in the host and the immune response exhibited by them. Following are some of the types of the vaccines based on their course of development.

- Live-attenuated vaccines
- Inactivated vaccines
- Recombinant subunit vaccines
- DNA vaccines
- Conjugate vaccines
- Toxoid vaccines

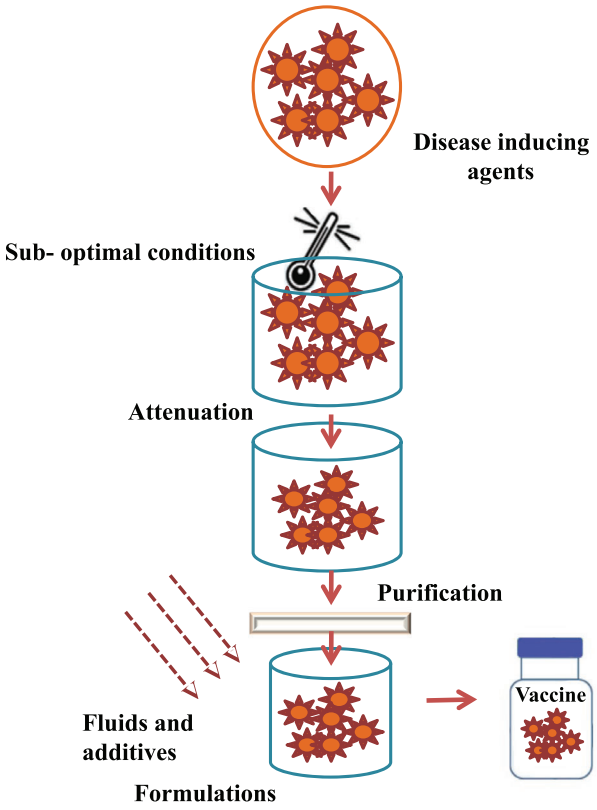


**FIGURE 3** Live attenuated vaccine

### 6.1 | Live attenuated vaccine

The attenuated vaccine contains a new adapted version of pathogenic microorganisms that has been attenuated or made weak by culturing it in vitro so it has lost its pathogenicity (Figure 3). Mainly they are accomplished by serially growing the pathogenic microbes in a deviant host such as by in vitro tissue culture technique, fertilized eggs, and in vivo animals models used for multiple passages or generations. Majority of the traditional vaccines that are currently administered in humans and animals are raised in an unnatural host. The vaccine developed against 17D strain of yellow fever was developed by passaging the virus in mice and subsequently in chick embryos. In case of polio vaccine, viruses were continuously passaged in monkey kidney cells and afterward in chick embryo and measles in chick embryo fibroblast.[50]

The live-attenuated vaccines were prepared after attenuating the viral strain thereby making them completely devoid to induce pathogenicity or without virulence but are highly competent to trigger a protective immunological response. The examples of presently available live attenuated vaccines against viral infections comprises cowpox, MMR, influenza, oral polio vaccine, and yellow fever. The vaccines for BCG, tuberculosis, and oral typhoid are live-attenuated bacterial vaccines. One of the major advantages of the live-attenuated vaccine for virus is relatively easy to develop but more complicated to generate for bacteria due to the presence of several genes. However, utilizing the benefits of recombinant DNA technology might help in the removal of several key genes. The mechanism of live-attenuated vaccine is similar to that of natural infection without causing any infection but elicit a better immunological response conferring immunity for lifelong with one or two doses. One of the major disadvantages of the attenuated vaccine is that the reversion of virulence after secondary mutation which might lead to disease progression. People who are immune-compromised, with weak or damaged immune system and in pregnancy cannot receive the live vaccine. Another drawback of the live-attenuated vaccine is that, it requires strong cooling system to stay effective and highly skilled health care workers which limits their widespread use. It would create extra cost while conducting a massive immunization program.

### 6.2 | Inactivated vaccines

The inactivation of the antigen is typically done by using heat or chemicals like formaldehyde or by radiation (Figure 4). After the chemical exposure, the multiplication capability of the pathogen was hindered but has to retain the structural immunogenic intactness as that of its original natural or basic appearance. It is extremely essential to maintain the structural integrity of antigenic epitopes of surface antigens. Therefore, inactivated whole organism vaccine ensures

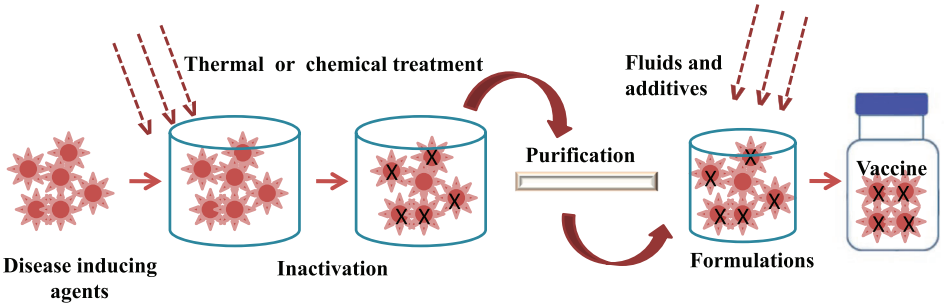


**FIGURE 4** Inactivated vaccine

**TABLE 1** Comparison between live attenuated and inactivated whole virus vaccine

| Features | Live | Dead |
|---|---|---|
| Dose | Low | High |
| No. of doses | Single | Multiple |
| Need for adjuvant | No | yes |
| Duration of immunity | Many years | short |
| Antibody response | IgG | IgA IgG |
| Cell mediated immunity | Good | Poor |
| Reversion to virulence | Possible | Not possible |

the protection by directly evoking the humoral and cell mediated immunological response against the pathogen.

Examples of presently accessible inactivated vaccines for viruses are polio, influenza, hepatitis A, and rabies. The vaccines for pertussis, typhoid, plague, and for cholera comes under the category of whole inactivated bacterial vaccine. The greater advantages of inactivated vaccine than live vaccine are that, they are further steady and safer as it contains deceased microbes that cannot mutate back or revert to their pathogenic/virulent state. These vaccines generally do not need cold storage facility as well as shifting in freeze-dried form thus making them much more economical and can be made easily accessible to the people. Most inactivated vaccine induces weaker immunological responses than live vaccine. Therefore they require boosters of multiple doses to maintain their potential immunological response. Moreover, too much treatment for inactivation of pathogen might devastate immunogenicity, while inadequate treatment exposure can build infectious virus capable of inducing diseases. Also there exists a risk toward allergic reactions due to the occurrence of unrelated structural particles of microbes in the body. An assessment of live-attenuated and inactivated whole virus vaccine is illustrated in Table 1.

## 6.3 | Recombinant subunit vaccine

The immense progress achieved in biotechnology has made to recognize the peptide site encircling the most important and potential antigenic sites of viral antigens. Therefore, as an alternative of using the whole pathogenic microbe for immunization only the major subunits

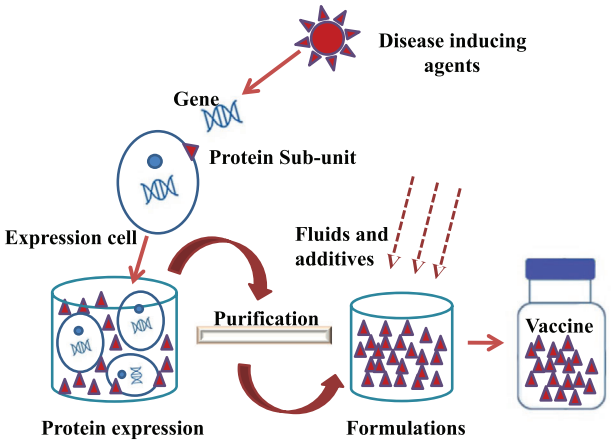


**FIGURE 5** Recombinant subunit vaccine

components of antigens which are more prevalent to induce immunologic response are sorted and used as vaccine (Figure 5). Only the specific antigenic determinants of antigens were used for the development of this type of vaccines so that it significantly lowers the adverse risks associated and the chances of virulence reversal could be completely abolished. The vaccine against influenza virus *Hemophilus influenzae* A and B and hepatitis B surface antigen are examples of subunit vaccine.

## 6.4 | DNA vaccines

One of the greatest achievements in the vaccine technology is the development of the DNA vaccines. The DNA vaccine development requires the direct positioning of a plasmid into the appropriate tissue site holding entire gene expression cassette that encodes alone with unique antigens to which the necessary immune response is essential.[51] Another method is the implementation of viral vectors to deliver genetic material coding the preferred antigen into the host cell. The viral vector is not in their virulent form and does not cause any infection. They enable the antigen expression within the cell and induce cytotoxic T cell response. Immunization using DNA helps in stimulating effectively both the humoral and cellular immune response to antigenic proteins. Genes encoding specific antigens are expressed, and their gene products would undergo glycosylation and

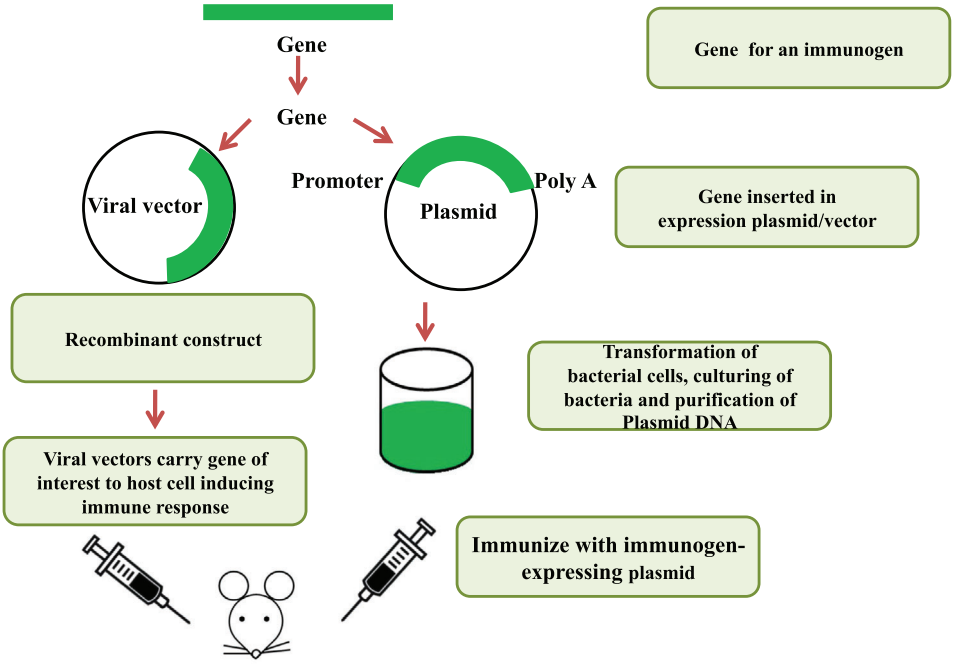


**FIGURE 6** Development of DNA vaccine

alterations in post-translational modifications comparable to natural infections. It has been practiced for many years by utilizing the genetic material to transport the genes for several therapeutic purposes (Figure 6).[52]

DNA vaccines are considered as the third generation vaccine that underwent the immunization process to a new stage of technology. The usage of DNA vaccine encodes almost the entire gene for all the significant antigens. DNA vaccine for pathogenic microorganism would induce a powerful antibody response toward antigen released by the cells. The main advantage of the DNA vaccine is that it cannot induce as they consist of only copies of few genes of pathogens and not the whole microbe. Moreover, DNA vaccines are comparatively simple and less expensive to plan and develop. This vaccine can be administered directly into the body using a needle or needleless device by applying high-pressure to get the DNA coated microscopic gold particles directly into the cells. The DNA naked vaccine against herpes and influenza virus were tested in humans.

### 6.5 | Conjugate vaccine

Some pathogenic bacteria possess a polysaccharide outer envelope and generally mimics human polysaccharides. So infant's immature immune system and also in younger children could not recognize or respond to the encountered infection.[53] The conjugate vaccines were developed by chemically attaching the polysaccharide to a strong T-cell stimulating antigen such as tetanus and diphtheria toxoids (Figure 7). This leads to the enhanced stimulation of the immature immune system against the linked protein and polysaccharide providing sufficient protection against disease causing organism. Examples of the conjugate vaccines include influenza vaccine (HiB), for pneumococcal and meningococcal.

### 6.6 | Toxoid vaccines

Bacterial toxins are generally termed as toxoids secreted as exotoxins by pathogenic microbes which are able to produce disease symptoms after getting into our body. Toxoid vaccines are prepared from purified bacterial exotoxin. By the application of heat or chemical treatment the toxicity of the purified exotoxins are made suppressed or inactivated without harming the capability to trigger immunogenicity. Such detoxified exotoxins can be used as vaccines. The immunization with toxoids produces anti-toxoid antibodies that comprise the capability to bind with toxin and to neutralize the harmful effects of normal exotoxin. The procedure for the preparation of toxoid vaccines was strictly regulated in order to attain the detoxification or inactivation devoid of extreme structural alteration to the antigenic epitopes (Figure 8). The best examples for toxoid vaccine were against diphtheria and tetanus.

## 7 | ROLE OF ADJUVANT IN VACCINE

The chemical agents supplemented along with vaccine formulation to maintain and induce suitable protective immunological response against infections are the adjuvants. Adjuvant enhances the immunogenicity of the antigen, without acting themselves as antigen. The practice of using right adjuvant helps in vaccine formulation to trigger selectively an adaptive or innate immunity to achieve antigen specific immune responses. Thus adjuvant assists the proteins to turn into more

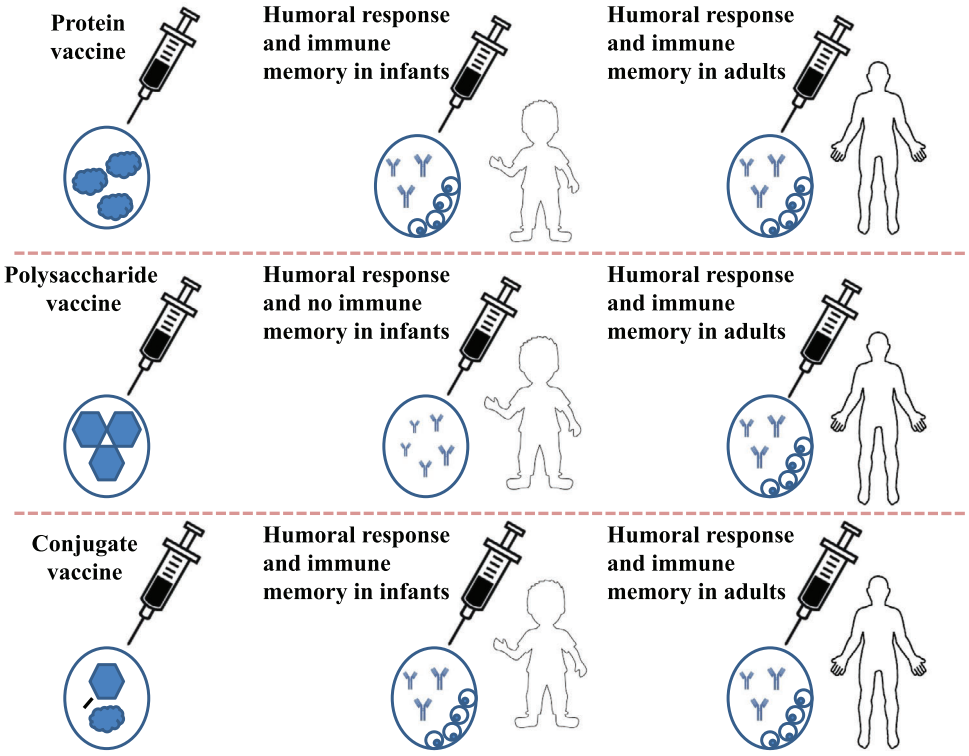


**FIGURE 7** Development of conjugate vaccine

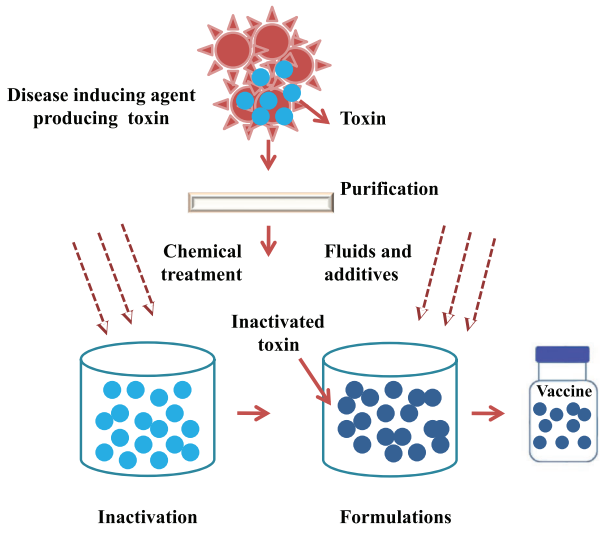


**FIGURE 8** Toxoid vaccine

effective vaccine by inducing protective, strong, and durable immune response. The approved and licensed vaccine adjuvants are listed in Table 2.[54]

The importance of the adjuvant is growing significantly with aging of the population. According to many experts, adjuvants would be an important component for widespread usage of vaccine in entire population since they can promote the immune response in vaccinated old people. Most commonly used adjuvants for human vaccines are aluminum salts, eliciting a complex mechanism to favor antibody induction. Currently, new forms of adjuvants have been proposed for different vaccines which mainly includes the bacterial products [heat labile enterotoxin B (LTB) subunit, cholera toxin B (CTB) subunit], viral products (viral-like particles), plant derived products (saponin derivative), oil-based emulsions, biodegradable particles (liposomes), synthetic and molecular adjuvants.[55] But safety is the primary consideration of the proposed adjuvants. Hence, while preserving the efficacy of an adjuvant it is essential to introduce a method to eliminate the reactive actions of an adjuvant. For the efficient use of adjuvants, they can be combined with particular route of delivery such as transcutaneous or intranasal, oral immunization for stimulating mucosal immunity.

Although diverse in composition and the capacity in stimulating immune system; virosomes, liposomes, and ISCOMS can be assembled around the idea of a lipid vesicle to which both antigenic targets and immunomodulatory molecules can be substituted.[56] The ionic charge can be modified to requirements based on their lipid composition and production system, physical properties, size of the vesicle. The above mentioned criteria affect the capability of the delivery system to develop depot, which gets attached to antigen-presenting cells (APCs) and the antigen that loads to the delivery system.[56] In several means, these adjuvants enclosed with lipid and associated proteins resemble naturally enveloped bacteria or viruses. The virus-like particles (VLP) take this process a step advanced; where the lipids and antigenic target derives the pathogen directly thus arbitrating a delivery vehicle that is similar to a pathogen lacking the genes required initiating the infections.[57] The accurate and acceptable combination of

**TABLE 2** Approved and licensed vaccine adjuvants for human use

| Adjuvant | Year | Class | Description |
|---|---|---|---|
| Alum | 1926 | Mineral salt | Improves HI and Th2 response, used in more than 80% human vaccine |
| MF59 | 1997 | Oil in water emulsion | Improves HI and CMI response, used in influenza vaccines |
| Virosomes | 2000 | Liposome | Improves HI and CMI responses, used in influenza and hepatitis A vaccine |
| AS03 | 2009 | Oil in water emulsion | Improves HI and CMI responses, used in H1N1 pandemic |
| AS04 | | Alum-adsorbed TLR4 agonist | Improves HI and CMI response, used for HPV and HBV vaccines |

antigens and adjuvant concentration to optimize is a critical task for the subsequent downstream adaptive immune response in the development of any novel vaccine.

## 8 | STRATEGIES FOR DEVELOPING VACCINE AGAINST SARS-CoV2

In spite of substantial advancement made by vaccination for many dreadful diseases, the unexpected and highly contagious entry of novel SARS CoV-2 created a serious threat to the community and affected the health services due to unpredictable nature of spreading and disease symptoms. The rapid ongoing Corona Virus Disease-2019 (COVID-19) has significantly increased the demand of introducing most suitable vaccine for this pandemic. Another fact is that due to increased mortality and morbidity, created panic situation among healthcare workers and people throughout the world.[58,59] This significantly made an urge for the need of vaccine as no proper treatment strategies were effective. The vaccination successfully can create herd immunity thus inhibit or limit the further spreading of virus.

For the successful development of vaccine, the potential antigen selection is one of the important criteria. The corona virus replicate in cytoplasm has positive single strand RNA, constituting mainly with four structural proteins (S protein, E-envelope protein, M-membrane protein, and N-nucleocapsid protein).[60] The S protein mainly triggers the immunological response during disease progression.[61] The types of vaccines developed against SARS- CoV2 are inactivated and live attenuated, nucleic acid based, adenovirus mediated vector, and recombinant subunit vaccines. The inactivated vaccine was prepared by making the non-infectious virus by physical or chemical treatment methods presenting most of the multiple type viral proteins for immune recognition and activation. They can express the stable conformation dependant antigenic epitopes and can be produced in large scale. The inactivated vaccine candidates BBIBP-CorV[62] demonstrated safety and potency in animal studies and PiCoVacc expressed the induction of neutralizing antibodies against SARS CoV2 in rat, mice and Rhesus macaques. The inactivated vaccine developed by Sinovac containing aluminum hydroxide as adjuvant were highly tolerated and developed good immunological response (6 $\mu$g/0.5 ml or 3 $\mu$g/0.5 ml doses) in healthy individuals during trials.[63] Currently there is attenuated SARS- CoV2 vaccine which utilizes a weakened virus as antigen by genetical modification. One advantage of attenuated vaccine is that it can be administered intranasal and can trigger mucosal immune response that can protect the upper respiratory tract. However, the reversion of the virus to its virulent form creates a major concern in this type of vaccine.

The mRNA and DNA vaccine are popular among the nucleic acid vaccine. These vaccines are transcribed to viral proteins after delivery into human cells. Among the four structural proteins, S protein is the most important one that can induce the immunological response. The mRNA vaccine is the most promising substitute method of vaccine development compared with any other conventional method due to their high potency, high immunological response and economical and rapid production technique.[64,65] mRNA-1273 was first developed mRNA vaccine developed within 10 weeks after the genetic sequencing of SARS- CoV2. Another four mRNA based vaccine BNT162a1, b1, b2, and c2 constituting separate mRNA coding genes for diverse antigens.[66] CVnCoV, mRNA vaccine developed using non-chemically adapted nucleotides of mRNA.[67] However, the physicochemical properties of mRNA and their distribution toward cellular and organ level, safety, and efficacy in humans remain unidentified. RNA vaccine are usually delivered through lipid nanoparticles (LNPs).On the other hand DNA vaccine enhances the T-cell induction and antibody production, they have low cost production technique and stable long shelf life[68] but their major disadvantage is to cross the nuclear membrane to get transcribed and exhibited very low immunogenicity. The study conducted in rhesus macaques developed both humoral and cellular immune responses towards different DNA vaccine candidate encoding S protein and showed protective level of neutralizing antibodies titers.

The adeno or pox virus are mainly used for the production of vector vaccine in which they act as carrier virus engineered to bear the appropriate gene mainly the S gene for the SARS CoV2. One of the advantages of this technique is that the expression of immunogen upon heterologous viral infection which triggers the innate immunity requisite for adaptive immune response.[69] In contrast, this approach has the possibility to induce earlier immunity towards adenovirus and thereby insufficient to present only negligible amount of SARS CoV2 antigen to the host immune system. The clinical trials of adenovirus type 5 (AdV5) vector carrying recombinant SARS CoV2 works best with the dosage $5 \times 10^{10}$ viral particle per ml and produced comparable immune response to $1 \times 10^{11}$.[70] The chimpanzee adeno (ChAd) – vectored vaccine incorporated with full length codon for SARS-CoV2 protein (ChAdOx1 nCoV-19). Their clinical trials showed a very safe and tolerated immunologic response. Besides exhibited systemic and local

reactions including pain, muscle ache and mild febrile response are reported and reaction subsided upon paracetamol administration.[71] The pre-clinical study of Ad26COVS1 containing Ad26 vector encoded with pre-fusion stabilized S protein induced effective neutralizing antibodies.[72] Another approach is the use of inactivated virus vectors in which the viral vectors that present spike proteins on their surface but are inactivated before use.[73] This method can offer the safety of the viral vector not being able to replicate even in immunocompromised hosts after the inactivation process.

The subunit and virus like particle vaccine (VLP) are another category of vaccine. In subunit vaccine, viral proteins are injected to the host to trigger the immune response and exhibited efficacy in protecting animals and humans from viral infections. These vaccines do not exhibit entire antigenic complexity. The major limitation in this type of vaccine is that it may create an unbalanced or uncontrolled immune response.[74] The study conducted by the Yang and co-workers developed subunit vaccine using baculovirus expression system containg 319–545 of CoV2 receptor binding domain (RBD). Virus like particle vaccine comprises the protein based vaccine containing the protein from the capsid.[75] For controlling the spread of viral infection, neutralizing antibodies (NAb) can plays a pivotal role.[76] The generally used antibody forms are functional antigen binding fragments, single chain variable fragments, single domain and monoclonal antibodies (mAb). The NAbs can be isolated from the patients who are recovered from the CoV2 infection. NAbs specifically targets RBD's of SARS CoV2 which can serve as an important treatment approach towards viral infection.[77,78]

While considering the immunogenicity in terms of neutralizing antibodies; inactivated and AdV5 vector vaccines are at the lower end, mRNA, and ChAdO×1 nCoV-19 are on the medium range and the recombinant protein elicit higher titer values of neutralizing antibodies. The tolerability of the inactivated and recombinant protein is comparatively good followed by mRNA which exhibited increased reactogenicity after second dose and then the AdV vectored vaccine.[79] Old individuals often require higher titers than younger individuals. So vaccine with higher titer such as the mRNA and AdV vectored vaccine might improve the titers in this age group. But the vaccination for the children should be handled with great concern as they show much reactogenicity than adults and low dose might be preferable for this group especially for mRNA and AdV vaccine. In terms of immunogenicity, inactivated and AdV5 based vaccine shows lower rank followed by ChAdO×1-based and mRNA vaccine and finally the best performance was exhibited by adjuvated, protein based vaccines.[79] Many of the vaccine candidates are administrated intramuscularly and provide increased production of IgG level and provide better protection towards the lower respiratory tract than the upper respiratory tract. The vaccine that can be functional through intranasal route especially live attenuated or viral vector vaccine can aid strong mucosal immunity as well as IgG response which create a great advancement towards the vaccine against SARS-CoV2.

## 9 | DEVELOPMENT OF VACCINE

For the identification of antigens that are appropriate for disease avoidance, detailed and thorough information of their biology, etiology, and structural arrangement of the pathogen, communication with cellular receptors in host system and its disease inducing mechanism are essential. It is also important to know the route of entry and subsequent replication sites and cycles of the desired pathogen. Because knowing these details are crucial that different vaccination strategies might be implemented to protect against pathogens entering via different routes such as the respiratory (influenza, pneumococcus), gastrointestinal (*Salmonella*) or genital tracts (Herpes simplex virus [HSV] or HIV), or entering the bloodstream by injury/injection (hepatitis B/C) or mosquito bite (malaria, filariasis, dengue).[80–82]

Generally, less than one tenth of the vaccine candidates achieve licensure due to the high failure rate of the unpredictable nature of the biological organisms required for the vaccine production and the variability of how the human immune system will detect process and react to the vaccine antigen. Appropriate levels of immune response may be produced by some vaccine candidates but they may induce significant adverse reactions. But some may be safe but ineffective at preventing diseases. Although incorporating multiple antigens into one single vaccine, the challenges related with developing safe and effective vaccines are even greater. The continuous research towards the discovery of a new vaccine antigen and novel approaches to immunization usually take years for the fulfillment and cost millions of dollars. After successful discovery, to reach the final licensing point many improvements must be conducted.

### 9.1 | Pre-clinical stage of vaccine process

In the pre-clinical stage of the development, initial study is based on understanding the pathogen and disease condition mainly focused to resolve most appropriate vaccine characteristics concerning both potential antigens and the type of immunological response that the vaccine must exert to defend against infection by humoral and/or cell-mediated immunity.[83] During vaccine development, consistent manufacturing procedure that would ensure a product conformity from lot-to-lot all the way through clinical studies are followed and as well as on the market.[84] A number of in vitro and in vivo tests are executed to demonstrate potential immunogenicity of the purified antigen, by using suitable established animal models for this study. Initial toxicity evaluation and dose-response studies were also carried out.

### 9.2 | Phase I: Clinical trials

The prime objective of phase I trials determines the safety of the candidate vaccine in dose-setting studies with a small group (i.e., tens to hundreds) of human volunteers.[85]These study are either performed in

open-label/blinded trials. The phase I trials are executed in healthy individuals; on the other hand, if the vaccine's target population varies such as infants, older adults, pregnant women are involved, phase I trials may be united with phase II trials as a time and cost-saving measure.[86] In this particular instance, a small group of participants are brought together to complete the phase I section of the trial, pursued by large number of participants in phase II trial.

### 9.3 | Phase II: Clinical trials

The major aim of phase II trials is to assess the safety and tolerability of the vaccine in wider study population (hundreds to thousands) that display more immunogenicity by surrogate markers of the candidate vaccine.[85] To predict the vaccine's protective effect, the immunologic markers selected should be suitable to the preferred response. For example, cell mediated immunity represents an imperative role to prevent *Varicella zoster* reactivation. As a result, activated CD4+ T-cell incidents were assessed to evaluate immunogenicity of the newly developed vaccine candidate.[87,88]

### 9.4 | Phase III: Clinical trials

Phase III vaccine trials, conducted particularly in large study group containing more than 10,000 volunteers, multicenter, randomized and controlled trials participating at risk for the targeted disease condition.[85]The vaccine efficacy (VE) is the primary outcome obtained from this controlled study is about the, which signifies the risk reduction (RR) in developing a predetermined result in the vaccinated population compared to the unvaccinated population:

$$\text{Vaccine efficacy} = [(1 - \text{RR}) \times 100\%]$$

The infection incidence (e.g., polymerase chain reaction to confirm varicella zoster virus) or some other neurological complication (e.g., postherpetic neuralgia) may be interpreted by the pre-specified result.

### 9.5 | Licensure and phase IV

In India, Central Drugs Standard Control Organization (CDSCO) under the Directorate General of Health Services, Ministry of Health and Family Welfare is the major functional national regulatory authority that takes the actions for the central and state regulators for the drugs and cosmetic regulation. They grant the approval of drugs, to conduct clinical trials and also control over the quality of imported drugs in the country. Along with the state regulators the CDSCO grant the license for I.V fluids, blood and blood products, sera and vaccines. Apart from this each country has its own regulatory mechanism for licensure and phase IV approval.

In United States, FDA approves new vaccine candidates by the same method as similar to that of biological products. Initially, before commencing clinical trials an Investigational New Drug application (NDA) has to be proposed. After successful completion of phase III trials, a Biologic License Application (BLA) is send to FDA for review before commencement of vaccine to the market.[89] The FDA intends to make a decision on at least 90% of new BLAs within 10 months of approval as mandated by the goal set by the Prescription Drug User Fee Act (PDUFA).[88] However, according to estimates, only 50% to 60% of new NDA's were accepted during the financial years 2010 to 2014. BLA will obtain approval upon initial application followed by the submission of the additional details provided as per requisition by the FDA. The time between application and approval may be as long as 2 years.[89,90] After the vaccine is brought to market and administered, phase IV trials continue to wider population than in clinical trials to collect safety and efficacy results.[89] These studies are essential requisite for the FDA on a case-by-case basis, to describe additional safety and effectiveness in various sub-populations.

## 10 | DELIVERY OF VACCINE

The first administration of vaccination were performed through scarification (i.e., disruption of the epidermal layer of skin), but today's vaccination administered by means of hypodermic needle and syringe into muscle (i.m.), subcutaneous tissue (s.c.), or skin (i.d.).[91] It can also be delivered through mucosal route, that is, orally or nasally, but particular formulations are required for the delivery route to avoid antigen degradation or inactivation. Due to the adverse and highly acidic location in which the vaccine must endure inside the gastrointestinal tract, oral administration is highly recommended to ensure adequate absorption and prevent low bioavailability.[92,93] Based on the different availability of vaccine, different administration route is required based on the formulation of the vaccine, cellular uptake or tissue vascularity. Therefore, each administration route has its own benefits and drawbacks.

### 10.1 | Intramuscular immunization

While considering the quickness and simplicity for vaccine delivery the most common route is by intra muscular or subcutaneous administration. By this method relatively large doses can be delivered in thigh muscle angled at 90° "deltoid or anterolateral" where sufficient blood supply is seen. Majority of vaccines to date have been administered intramuscularly. Examples include DT, hepatitis A and B, influenza, HiB, HPV, pneumococcal, and meningococcal.[94]Generally, i.m. or s.c. administrations have been recorded to be painful and less effective in arising broad immunogenicity consequently necessitating higher levels of vaccine immunogen levels compared to the skin-based immunizations.[94–98]So that multiple applications are generally needed to evoke a strong immunological response.

### 10.2 | Subcutaneous immunization

In comparison to intramuscular administration, subcutaneous injections are administered into adipose tissue (buttocks) at 45° angle. Subcutaneous injections can result in extended antigen retention because of the limited drainage and vasculature. Although the prolonged existence of antigen may lead to increased immunogenicity due to prolonged absorption, that may leads to an amplified number of incidence of local adverse reactions like granulomas and abcesses predominantly when co administered with adjuvants. Overall few vaccine are administered s.c. than i.m. they are varicella, Q-fever, IPV, and some MMR/MMRV vaccines.[94] Some vaccines such as pneumococcal, MMR, yellow fever and rabies can be administered either by s.c. or i.m. depending upon the manufacturer's instruction.[94]

### 10.3 | Cutaneous immunization

The first method of immunization was performed by scarification on the skin surface, accompanied by the topical administration of cow pox or vaccinia virus to cross react to provide protection against small pox. Mantoux on early 20$^{th}$ century was first to described the cutaneous immunization, which involves the introduction of substance with a needle parallel (<30°) into the skin resulting in a bleb formation.[99] One of the most possible alternatives to conventional immunization is the intradermal injections as they take advantage of the skin's unique immune system to elicit a strong immunological response. While compared to i.m. immunization, i.d. demonstrated improved immunogenicity 5–10 folds much better against influenza,[95,100–104] rabies[105] or HBV vaccines[106,107] but difficulty to administer due to the thin layer of dermis. Only BCG immunizations are currently performed by i.d. Skin barrier disruption is considered as physical injury that induce local tissue damage or trauma to which immune system responds by releasing danger signals such as heat shock proteins, dsDNA, monosodium uric acid, and other substances that set off triggers cascade of immunological reactions.[108,109] Biolistic injections,[110] electroporation,[111–113] iontophoresis,[114] ultrasound,[115,116] and tattooing devices[117–120] are instances in which cutaneous immunization technique were employed.

### 10.4 | Mucosal immunization

Mucosal tissue immunization has benefit of accumulating the vaccine in or near vicinity to the primary site of infection, thus enhancing secretion of IgA by eliciting natural or humoral immune response.[106] The most important benefit of mucosal or specifically oral routes is that they are much easier to administer than any other parenteral administration method and are very less likely to transmit blood borne diseases. Though, several challenges connected to mucosal immunization however have yet to be resolved. For the successful antigenicity, it must withstand the low pH and enzymatic digestion in the gastrointestinal tract as well as need to enter the epithelial barrier.[121] This can be accomplished only by adapting, enhancing, and improving the vaccine formulation.

## 11 | EFFECTIVENESS AND ROLE OF VACCINES

Vaccines have made significant impact on public health-care system. Their impact on reducing mortality rate stood second only while considering the importance and provision of safe drinking water.[121] Individuals are given vaccine to protect them from several infections, but vaccination imparts a major role in shielding whole population from infectious disease exposure. The effectiveness and the level of vaccine coverage achieved in the given population are the two main important factors that contribute to the capability of a vaccine to eliminate or control disease progression. The response may differ to some extend from country to country. But FDA licensed vaccine are considered highly effective for preventing disease progression everywhere.

Vaccination programs protect people from infectious diseases both directly and indirectly. According to Haber when a population is infected direct protection occurs by lowering the possibility of vaccine recipients being infected or lessen the infectiousness of vaccinated individuals when a widespread of infection happens in a population [122] (Figure 9). Indirect protection is attained by declining disease spreading within the population, thus reducing the disease transmission rate for both vaccinated and unvaccinated individuals. Vaccine effectiveness measures the defensive effects of vaccination by reducing the vaccinated individual's risk of infection compared to that of susceptible and non-vaccinated individual.[123] Greenwood and Yule in 1915 designed and calculated VE for the typhoid and cholera vaccines. VE studies measures and ensures the several possible outcomes such as disease attack rates, medical visits, hospitalizations, and costs.

Vaccine effectiveness is the potentiality of the vaccine to prevent the outcome of interest in the real world. Vaccine effectiveness can be divided into- direct, indirect, total, and overall effects. The direct effectiveness compares the risk associated in the randomly selected individuals with vaccinated individual.[122] The indirect effect estimates of the dissimilarity in the degree of safety received by unvaccinated individual in the incidence or lack of a vaccination program. The total effectiveness covers the relative infection risk rate in vaccinated individual compared to non-vaccinated individual before the commencement of a vaccination program.[124] As a consequence, the overall effectiveness of vaccination demonstrates the outcome of the vaccination program as well as the influence of individuals who is vaccinated.[125] The disease transmission reduction rate for an average individual in a population with a specified degree of coverage of a vaccination program compared with average individual in an equivalent population without vaccination program is generally referred as vaccination program effectiveness.[124,125] Therefore the overall effectiveness is taken into account to estimate the influence of immunization programs at the population level and also it depicts the benefits attained by both immunized and non immunized individuals.[126,127]

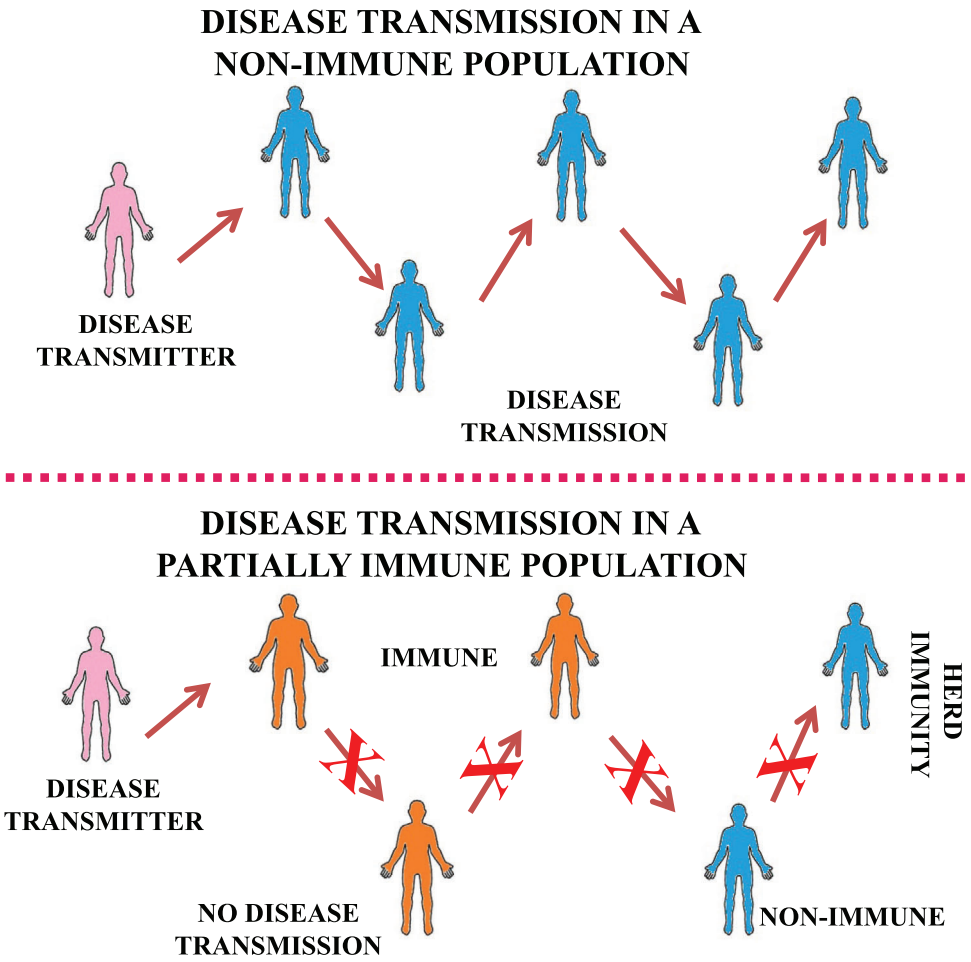


**FIGURE 9** Herd immunity

## 12 | SAFETY AND RISKS ASSOCIATED WITH VACCINE THERAPY

The term "safety" is related the nature of the damage or harm occurred to an individual. Second, while connected to vaccines, there is the risk occurring at the time of vaccination, weeks later or even years or decades later. There is a chance that the appearance of a disease state is mere accidental through vaccination rather than caused by vaccination which is an issue that is very hard to resolve to the satisfaction and justification of both injured personal and the vaccinators. With regard to the above concern, each individual's immune mechanism system varies and there is an unexpected chance or unusual situation in which vaccination causes the disease that is intended to avoid, or it can trigger allergic or adverse reactions as a result of defective immune system. When dealing with population or cohorts of millions of individuals it is difficult to assume that all the vaccine recipients will be unharmed as a result of vaccination instead we expect a lesser chance that a certain proportion could be discomforted due to the variation in immune response toward the vaccine. It must be considered in the combination with the "benefits" that accrue after the use of vaccine not just the "risks." One of the greatest problem remains is that, people are more likely to project the disadvantages of the current injury as more believable and powerful than the observed benefits of the absence of disease to be expected in future. This would definitely distort the approval of the safety of a vaccine.

The vaccine safety is a key concern for the public, manufacturers, immunization providers, and vaccine recipient. The benefits of vaccination are indisputable. To maintain a public confidence in immunization program is critical for preventing a decline in the vaccination rates that leads to the outbreaks of diseases. The vast majority of vaccine related adverse effects are mild and are temporary. Naturally pain at the injection site and mild fever may occur. The mild or adverse reactions towards the vaccine are mainly due to the individual differences in the immune responses. There are government authorities that regulate the clinical developments of vaccine. Prior to the grant of a government license, a rigorous review of vaccine safety must be carried out. During an immunization program, the nature and incidence of the adverse events following immunization is monitored continuously.

Vaccines have been shown in human clinical trials to cause common side effects such as discomfort and inflammation at the site of injection, fatigue, malaise, and mild fever. Measurement of inflammatory cells at the site of injection, reduce food intake, loss of body weight, and changes in body temperature could be the mostly exhibited side effects in animals.[128] The adverse reactions after immunization are

unexpected and undesirable. The each components present in vaccine may aid complications; it must be ensured that vaccine components do not pose a risk to vaccine safety either separately or in combination. Any adverse medical hazard that happens after immunization but not necessarily happen based on the vaccine side effects usually referred as Adverse Event Following Immunization (AEFI). These unexpected actions can be categorized into five based on the cause of the event. These events are associated with the vaccine products and quality defects, due to immunization mistake, because of over anxiety about immunization and some coincidental events. The adverse events due to vaccines occur only with a certain frequency. The frequent and minor reactions after vaccination usually exhibited are fever and malaise. The allergic reactions toward vaccine antigen or its component may cause unusual and serious reactions. Vaccine development has a lot of challenges to face, including the identification of safe and effective adjuvants, antigens and the most acceptable suitable delivery mechanism and it should be significant in balance with cost, risks, and benefits.[129]

## 13 | CONCLUSION

Human vaccines have several kinds of benefits, but their potential for further impact is also significant. Scientific advancements can be implemented to accelerate production and thereby simplify the delivery of vaccines, but the commitment toward the society for the immunization programs that must be maintained to gain the full benefits of this incredible medical breakthrough. Vaccine development against more complicated infections like tuberculosis, malaria, and HIV has been demanding and are facing difficulty with few successes to date. The final success against these infections occurs only when combinations of vaccines are administered or each component has the ability to activate and stimulate different arms of the immune system. Vaccines are more likely to be used to prevent or modulate the pathogenesis of some non-infectious diseases in the long run. A great advancement has already been attained with therapeutic cancer vaccines and has other possible probable targets including alcoholic/drug addiction, diabetes, hypertension, and also for Alzheimer's disease. The scientific and medical groups are making continuous efforts to mitigate Covid-19 pandemic and related waves of viral transmission by introducing preventative vaccines and re-purposing accessible drugs as possible therapies. This novel corona virus has consequently alarmed the scientific community to use alternative approaches to hasten the vaccine development process. The utmost goal is to provide economic vaccine that can create spontaneous, strong, and extended immunity with least potential side effects, executed without the need for expensive cold chain system.

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### CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

### DATA AVAILABILITY STATEMENT

The authors declared that the research data referred to correctly cited in the manuscript's reference section.

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