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Review

Vaccine skepticism and vaccine development stages; inoculation from "cowpox" lesion to the current mRNA vaccine of COVID-19: review

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***Abstract*:** Global pandemics can be tackled by two means: lockdowns and vaccinations. As vaccination has a low impact on economic outcomes and better acceptance by people, it is the preferred method by most governments as a medium- to long-term solution. Vaccines have played a significant role in reducing the global burden of infectious diseases. They are designed to teach the immune system how to fight a particular infection before it causes a disease in subsequent exposures by creating a memory. Although vaccines effectiveness is well known, anti-vaccination movements pose significant challenges, even in high-income settings, leading to outbreaks of life-threatening infectious diseases. Hesitancy to take vaccines is not new and began with the first vaccination of smallpox. At that time, the problem was solved by a regulatory obligation to take vaccines, declared in England and Wales in 1853, which eventually led to its eradication in 1980. Different studies show that there is a decline in awareness of vaccines, hesitancy to take them, and concerns and trust issues regarding healthcare professionals. These problems have been rising over the past few decades for several reasons, notably, because of misinformation spread by social media. Therefore, the objective of this review is to provide a brief overview about vaccine hesitancy and attributable factors, illustrate the different types of vaccines, show the major challenges of vaccine development, and illustrate the pros and cons of each type.

Plain language summary

Hesitancy to take vaccines and stages of vaccine development starting from the first vaccine; inoculation from "cowpox" wound to the current mRNA vaccine of COVID-19: Review

Global pandemics can be tackled by two means: lockdowns and vaccinations. As vaccination has a low impact on economic outcomes, it is the preferred method by most governments as a medium- to long-term solution. Vaccines play a significant role in reducing the global burden of infectious diseases. They are designed to teach our body defense mechanism how to fight a particular infection before it causes a disease in subsequent infections by creating a memory. Although its effectiveness is well known, anti-vaccination movements pose many challenges, even in high-income settings, leading to outbreaks of life-threatening infectious diseases. Vaccine hesitancy is not new and began with the first vaccination of smallpox. At that time, the problem was solved by

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Keywords: mRNA vaccine of COVID-19, vaccine, vaccine hesitancy

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Introduction

Vaccines are biological preparations designed to elicit an immune response against a specific antigen derived from a disease-causing agent.[1] They are the most cost-effective tools for controlling and eradicating infectious diseases, as they can safely induce an immune response against an infectious agent without causing a disease. They teach the immune system how to fight a particular infection by stimulating the body's immune system to recognize the agent as foreign and keeping a record of it so that it can easily recognize and destroy it in subsequent serious infections. Memory cells can respond vigorously to a similar organism before it can cause disease.[2–5]

Global pandemics can be tackled by two means: reducing contact with people, such as lockdowns and vaccination. Because vaccination has a low impact on economic outcomes and is more acceptable to people, it is the preferred method by most governments as a medium- to long-term solution.[6]

Vaccines play a significant role in reducing the global burden of infectious diseases. They have helped control the eradication of many infectious agents worldwide, including the smallpox and rinderpest (aka cattle plague).[7,8] In addition to obliterating these two diseases, the incidence of polio, measles, and many other childhood diseases has also drastically reduced worldwide.[9] Smallpox is a human disease without animal reservoirs that attributed to its successful eradication. However, before its eradication, the global death toll in the 20th century was over 300 million with case fatality rates of approximately 30%.[10] Although there was some *hesitancy* to accept the smallpox vaccine, obligatory regulations to take vaccines declared in England and Wales in 1853 eventually led to its *eradication* in 1980.[11]

Different studies have shown that there is a decline in awareness of vaccines. Besides, hesitancy to take them and concerns and trust issues on healthcare professionals have risen over the past few decades for several reasons.[12,13] Therefore, the objective of this review is to provide a brief overview of the different types of vaccines, show the major challenges of vaccine development, and illustrate the pros and cons of each type.

Lag time in antibody formation

The immune system refers to a collection of cells and chemicals that function in concert to protect against external invaders such as microorganisms, toxins, and cancer cells. It can be broadly viewed as having two lines of defense, namely innate immunity and adaptive immunity. Innate immunity represents the first line of nonspecific defense and acts very quickly when encountering an antigen. Although it provides a rapid response, its molecular pattern recognition of pathogens is limited. This necessitates a more specific defense, which leads to the evolution of the adaptive immune system.[14,15]

The adaptive immune system is known for its specificity to a particular pathogen, lag time of

action, and immunological memory. When B and T cells are exposed to an antigen for the first time, there is a delay in antigen-specific T and B cell responses, referred to as lag time. Shortening the time lag to response is a major goal of vaccinations. The ability to "remember" past exposure to pathogens that could be from infection or vaccination is another essential characteristic of adaptive immunity. During subsequent encounters with the same antigen, memory cells are quickly activated and provide a rapid protective response.[14,16,17] Therefore, the goal of a vaccine is to prime the immune response without causing disease so that the immune system creates a memory that can facilitate a rapid response with minimal lag time. It adequately controls pathogens and prevents disease manifestation.[18]

Challenges to vaccination and the anti-vaccination movement

Fear of vaccines dates back to the vaccines themselves. Notable vaccine objections were observed with the advent of the smallpox vaccine by Richard Jenner as many people doubted the deliberate infection of a person with a disease-causing agent. These skeptics not only refused vaccination but also made an effort to inform others about the dangers of taking it with their propaganda.[19] The primary objections to Jenner's smallpox vaccine came from his fellow medical professionals, mainly because of fear of income loss if smallpox was to be completely cured. Concurrently, some advocates that support this idea started to express their concern that this practice is interference with the natural order and injecting animal material into a person is unnatural and might even introduce animal spirits.[20] Additionally, some critics truly believed that vaccination interfered with the natural order or divine will. They saw disease as something divinely ordained and feared that preventing it might have unforeseen consequences.[21,22]

Vaccine hesitancy influenced by religious beliefs has significant implications for vaccination coverage.[23] A recent survey conducted in the United States among American Muslim women regarding HPV vaccination revealed that 38.36% received only a single dose, while just 33.19% completed the recommended three-dose schedule, both of which were lower than the national estimate.[24] Conspiracy theories often intertwine with religious narratives. For instance, some Christians rejected the COVID-19 vaccine, fearing it might contain microchips and represent "the mark of the beast."[25] Similarly, misconception about the polio vaccine was observed in northern Nigeria, predominantly among the Muslim population. It was because of a false belief propagated by Muslim religious (Sharia) and political leaders in the area that the polio vaccines were deliberately contaminated with anti-fertility agents and the HIV. They strongly believed that the Polio Eradication Initiative in Nigeria was part of broader conspiracy led by Western governments to reduce Muslim populations worldwide.[26,27] Misconceptions about the polio vaccine, such as fears of infertility, sterility, and impotence, discouraged parents from vaccinating their children on time, resulting in a devastating outcomes.[28] The misconception extends to Indian religion where smallpox was historically associated with the wrath of goddess. Shitala, was one of the numerable village goddesses, regarded as the "Mother" who "presides" small-pox, and may prevent, cause or be herself smallpox."[29] Worship of this goddess, and refusal of vaccination for that reason, were still quite strong in parts of northern India during the eradication campaign until recently, the early 1970s that extends to violence to vaccinators.[30,31]

Adverse events following immunization (AEFIs) are any medical events that follow immunization but are not necessarily caused by the vaccine itself. Monitoring AEFIs is crucial, especially for emerging vaccines, to ensure their safety and maintain public trust.[32–34] One notable AEFI linked to recent vaccines is intussusception, which has been associated with rotavirus vaccines (RVVs).[35,36] The risk of intussusception from rotavirus vaccination is very minimal, typically ranging from 1 in 20,000 to 1 in 100,000, and usually occurs within a week after the first or second dose.[37] Despite this negligible risk, safety concerns like the potential for intussusception can contribute to vaccine hesitancy, which is a significant barrier to achieving high vaccination rates.[38] However, a 4-year follow-up study conducted in Vietnam from 2017 to 2021 found no evidence of association between intussusception and the Rotavin-M1 vaccine.[39] Similarly, a study across three Asian countries showed no increased risk of intussusception following rotavirus vaccination.[40]

In the 1960s, inactivated RSV vaccine was tested in children which caused a catastrophic outcome. Eighty percent of children who were primed with the vaccine and then exposed to the wild virus were hospitalized and two of the toddlers died.[41,42] Similarly, the first licensed dengue vaccine, embarked by the Philippines in 2016, became controversial. Sanofi (the manufacturer) announced that Dengvaxia may actually cause "more severe disease" in those who have not had previous dengue infection, though its protection, was more apparent in those who had a prior history of dengue infection. This phenomenon is known as vaccine-enhanced disease.[43,44] Due to the dengue vaccine scare, parents are now refusing to vaccinate their children even against vaccine-preventable diseases, giving rise to vaccine hesitancy. Vaccine confidence levels dropped dramatically from 93% in in 2015, before the incidence, to 32% in 2018.[43,45]

Although accessibility is the main challenge affecting global vaccine coverage, anti-vaccination movements have also posed a great deal of challenge, as evidenced by decreasing vaccine coverage even in high-income settings, leading to outbreaks of life-threatening infectious diseases.[3] Some recent trends of refusal to vaccinate their children have been observed in Western countries because of perceived fear and other reasons. This has caused multiple measles outbreaks in Western countries, where the measles virus was previously considered eliminated.[46] According to a 2018 WHO report, 140,000 measles-related deaths occurred worldwide.[47] In addition, 1300 new cases of measles were reported in 31 states of the United States in 2019, although it was declared to be eradicated in 2000. This measles outbreak was linked to travel-related cases that reached the country *unvaccinated* or vaccinated against measles. Moreover, COVID-19 has also increased the risk of outbreaks, as evidenced by more than 61 million missed or postponed doses of measles vaccine due to COVID-19-related delays, which has increased the risk of larger outbreaks worldwide, including in the United States.[48] In addition to the above reasons, successful vaccination programs by themselves can inadvertently lead to complacency. When a disease becomes rare due to successful vaccination programs, public perception of the risk associated with it may diminish. In the absence of disease, its perceived seriousness can be forgotten, leading to the belief that vaccination against such rare diseases, like those prevented by the MMR vaccine, may seem unnecessary.[49,50] This situation may shift the public attention more toward potential AEFI, even if the actual risk is low, which could contribute to declining vaccination rates over time.[51,52]

Widespread hesitancy was also observed to take the COVID-19 vaccine, which mainly resulted due to the thought-provoking short span of vaccine development. As a result, widespread public confidence in the approved vaccine products is essential to overcome this global concern.[53] Rumors about vaccines disrupting the menstruation cycle and reducing fertility have also contributed to fear of taking it, particularly among women.[54]

Besides all the above reasons, *misinformation* spread by *social media* plays a major role for vaccines hesitancy, with profound negative impact on immunization rates.[55] Social media can be a source of widespread propagation of fake news, as users can post misinformed claims about vaccines, amplifying concerns about vaccines and resulting in increased vaccine hesitancy.[56] A study conducted by Wilson and Wiysonge using a large-n cross-country regression framework revealed that the use of social media to organize offline action is highly predictive of public doubts about vaccine safety.[57] Despite unprecedented level of vaccine access, public health officials struggled to keep pace with misleading or inaccurate online content. Consequently, if social media platforms are the epicenter of misinformation, then social media companies need to be part of the solution.[58] These real or perceived vaccine adverse events reduced awareness of the severity of vaccine-preventable diseases. Moreover, this perceived concerns regarding vaccine safety have been associated with vaccine hesitancy, diminishing trust in healthcare providers and the government has also attributed to vaccine skepticism.[8]

In a study conducted on chronic patients in Ethiopia, for instance, approximately one-third of the participants (28.9%), did not agree that vaccines are safe. In the same study, knowledge of the COVID-19 vaccination was significantly associated with vaccine hesitancy. People with good knowledge had 1.6 times higher acceptance rate. Another reason people were reluctant to take the COVID-19 vaccine was its unprecedented

speed of development.[59] Lack of trust in the pharmaceutical industry and misinformation or false rumors about vaccine side effects from social media were also associated with vaccine hesitancy in Africa.[60] In another study conducted in the United States, vaccine acceptance rates showed a significant variance, ranging from 12% to 91.4%. Being male and having a college degree were associated with a higher acceptance rate.[61]

Brief history of vaccine development

Smallpox and other preventable infectious diseases have devastated humankind for centuries. As a result, inoculation practices were started 500 years ago, although the term vaccine was first described by Edward Jenner in the 18th century.[62] **Dr. Jenner** heard a rumor that milkmaids who had been infected with cowpox (a disease related but milder symptoms than smallpox) were not susceptible to smallpox.[63] He then decided to test this idea and performed the first scientific experiment on an 8-year-old boy by inoculating him with a cowpox lesion from the hands of a dairymaid. He then allowed the boy to recover from the milder cowpox symptoms, inoculated him again with a smallpox lesion, and observed if he developed a disease. Surprisingly, the boy did not develop this disease. Therefore, Dr. Jenner called this inoculum "Vaccine" from the Latin word Vacca, which means cow.[64]

Following Jenner's innovative experiment, it took almost a century (80 years) to develop the next human vaccine based on the principles of attenuation. The first experimental attenuation was performed in the laboratory of Louis Pasteur using the causative agent of chicken cholera in 1878.[65,66] After this achievement, Pasteur learned that he could attenuate a bacterium by exposing it to adverse conditions and was able to develop live attenuated vaccine for anthrax in 1881 and rabies in 1885 using his discovery as a foundation.[7,67,68] Several successful vaccines were then introduced in the 20th century, including those against diphtheria, measles, mumps, rubella, and polio, which considerably reduced the burden of infectious diseases caused by various microorganisms.[63,69]

Types of vaccines

Initially, vaccines were developed empirically, relying primarily on the attenuation or killing of pathogens.[70,71] However, advances in immunology and related sciences have added new perspectives to the field of vaccinology.[72] The different types of vaccines can be broadly classified as *traditional vaccines* and *modern vaccines*. Under the umbrella of the traditional vaccines, live attenuated, killed, and component (subunit) vaccines are included. Modern vaccines on the other hand include nucleic acid-based vaccines: messenger RNA (mRNA) and DNA vaccines, viral vector vaccines, virus-like particles, and recombinant protein (subunit) vaccines.[8,73]

Live attenuated vaccines

These vaccines are derived from live or wild forms of pathogenic microbes that have been weakened by laboratory conditions, resulting in a loss of significant pathogenicity.[74,75] Attenuation represents the process of elimination or significant reduction in the virulence of a pathogen, usually by repeated culturing under abnormal culture conditions or serial passage through an unnatural host in which they do not reproduce well. As they evolve, they begin to adapt to this new cell or environment; thereby, they are less able to live in their natural hosts. They are almost devoid of pathogenicity, but can induce a protective immune response.[76–78] Vaccination that uses a live, attenuated organism can stimulate robust, long-lasting immune responses without the use of extra adjuvants. In fact, the immune system treats live attenuated vaccines as it would an infectious pathogen.[53,79,80]

Since live attenuated vaccines (LAVs) have a higher proximity to natural infections, they are the best "teachers" of the immune system. However, safety is their main concern as they could eventually revert to a virulent phenotype in immune-deficient individuals.[77,81] They are particularly unfavorable for highly pathogenic and largely uncharacterized organisms.[82] Therefore, LAVs are not recommended for individuals with severe immunosuppression, such as patients who receive cancer chemotherapy, children with HIV and CD4-T lymphocyte count below 15%, patients who have received high-dose corticosteroids for a long term, and immunosuppressed patients after organ transplantation (Table 1).[83] Moreover, the manufacturing and handling of these vaccines can be more difficult than other types of vaccines.[84]

Table 1. Live vaccines contraindicated in primary and secondary immune-deficient individuals.

Primary immune deficiency	Disease	Vaccine contraindication	Efficiency, risk, and interpretation
B Lymphocyte	Severe antibody deficiencies (X-linked agammaglobulinemia, variable immune deficiency)	OPV, live influenza, BCG, typhoid fever, varicella, MMR, and rotavirus	If the vaccine is dependent on only humoral immunity, the efficiency of vaccine is unclear
	Mild antibody deficiency (selective IgA deficiency) or other subgroup Ig deficiency	Other than OPV and BCG, all other live vaccine can be administered	All vaccines are efficient, but the immune response may be weak
T Lymphocyte	Complete deficiency (like complete DiGeorge syndrome)	All live vaccines	Inactive vaccine can be administered safely though all types of vaccines are probably inefficient or have low efficiency
	Partial deficiency (partial DiGeorge syndrome, ataxia-telangiectasia, Wiskott–Aldrich syndrome)	All live vaccines	The efficiency of vaccine depends on the degree of immunosuppression
Phagocyte dysfunction	Chronic granulomatous disease, leukocyte adhesion defect, myeloperoxidase deficiency	BCG and typhoid fever	All inactive vaccines are efficient. Other live vaccine other than these two, though they are less efficient
Secondary immune deficiency	Chronic renal disease	LAIV	Pneumococcal and hepatitis B vaccines should be completed
	Cancer, organ transplantation, autoimmune disease, immunosuppressive treatment, radio therapy	All live vaccines depending on the individual's immune status	Vaccine efficiency depends on the immune status
	HIV/AIDS	OPV, BCG, MMRV, LAIV, if severe immune suppression is present varicella vaccines should not also be administered	All inactive vaccines are efficient

Killed/inactivated vaccines

Many of the most-effective vaccines are live attenuated variants of the pathogen, which usually generate long-lasting immunity. However, LAVs have not yet been successfully developed for the treatment of many pathogens. Therefore, to provide vaccination against such organisms, nonliving antigens are used, including whole viruses, inactivated viruses, or single recombinant antigens (Table 2).[85]

Inactivated vaccines are not viable and cannot replicate within cells. As a result, these vaccines cannot cause disease even in immunocompromised individuals. Being noninfectious makes them remarkably innocuous. However, this type of vaccine usually requires repeated injections (booster shots) and adjuvants to provide strong and long-lasting immunity.[76,86] These additional components (adjuvants), provide the help needed to enhance the immunogenicity of a given vaccine antigens.[85] For example, alum-adjuvated inactivated vaccines against COVID-19 have efficiently produced a strong immune response, and have been widely used globally to control the pandemic.[87]

Recombinant vaccines

Conventional vaccine approaches consist of whole pathogens, live attenuated or killed, which usually provide long-lasting immunity against a wide range of dangerous diseases. Despite this success, major obstacles exist in vaccine

Table 2. Comparisons of attenuated and killed vaccines.[7]

Characteristics	Attenuated vaccine	Killed vaccine
Thermo-stability	Usually low	Usually high
Protection provided	Usually long-lasting	Often short duration
Mucosal immunity	Often strong	Variable
Safety	Reversion to virulence may occur. might cause infection in immuno-compromised patients	High safety (no risk of reversion)
Indirect herd protection	May infect and protect non-vaccinated	Can protect non-vaccinated by interrupting transmission

development, particularly for most emerging viruses, which require rapid development and large-scale production. In addition, conventional vaccine approaches may not be applicable to non-infectious diseases, such as cancer. Therefore, the development of more potent and versatile vaccine platforms was the driving force in the development of modern (recombinant) vaccines.[9,88]

There are a number of recombinant vaccines, live viral or bacterial vector vaccines, and non-live vaccines, such as recombinant subunit vaccines, and nucleic acid vaccines (mRNA and DNA vaccines).[89]

Recombinant subunit vaccines

Owing to a number of associated risks and increasingly stringent demands of regulatory authorities that require vaccine compositions to be specified precisely, whole-pathogen vaccines are becoming challenging as they contain undefined molecules. Therefore, the recombinant subunit approach, which uses only a defined subunit of the pathogen, dominates vaccine research in the search for new and effective vaccines. In the last three decades, subunit vaccine development using rDNA, which contains defined antigenic components, has increased.[90,91]

rDNA can be used to manufacture several proteins that are not normally produced in the recipient cells. Thus, different host systems can be used as expression systems, such as in prokaryotic (bacterial) and eukaryotic cells.[92,93]

A segment of DNA called a gene encodes a protein. Gene expression, in simple terms, refers to the process by which the information encoded in a gene is used to direct the synthesis of a functional protein.[94,95] Protein production in eukaryotic cells involves two major steps. First, information in DNA is copied to messenger RNA (mRNA) through a process called transcription. In the second step, the resulting mRNA leaves the nucleus, moves to the cytoplasm, and translates into protein within the ribosome (Figure 1).[96,97] Recombinant subunit vaccines are manufactured in the same manner as described above, by inserting the genetic code into a heterologous host. Epitopes recognized by antibodies are usually found in one or a few proteins present on the pathogen surface. Genes encoding epitope-carrying proteins are isolated, inserted, and expressed in heterologous hosts.[98] These host cells grow and synthesize large amounts of subunit proteins encoded by inserted genes. These proteins are then extracted, purified, and combined with other components such as adjuvants to form a vaccine.[99]

Three critical factors—safety, cost, and efficacy—dictate whether any given vaccine can be successful or not.[89] Unlike DNA vaccines or live organisms, recombinant subunit antigens do not invade the host genome or replicate within the body, thereby eliminating the risk of genetic recombination, providing better safety. Moreover, they can be scaled up in a more cost-effective manner than other vaccine types, and once expressed, can be rapidly purified and administered at high concentrations.[89,100]

Viral vector vaccines

Recombinant subunit vaccines are not without problems. Their primary problem arises due to

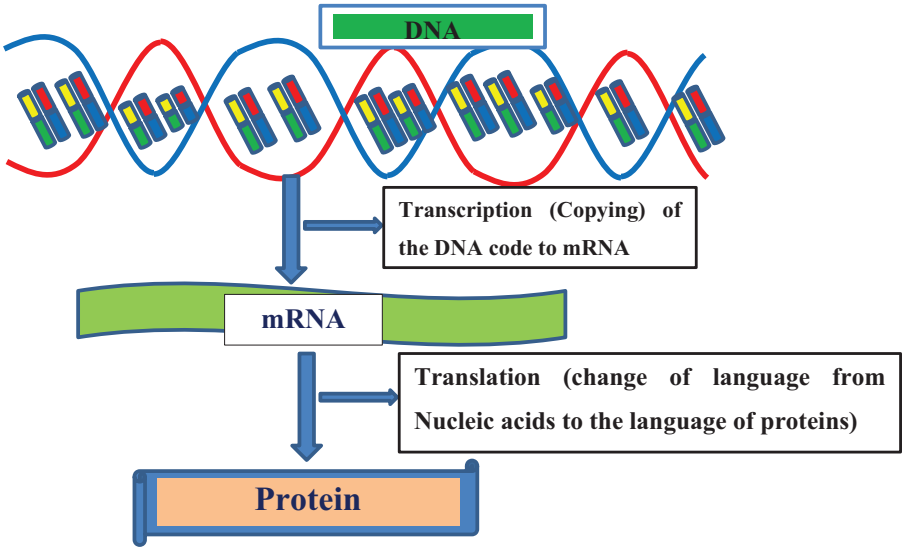

Figure 1. Conversion the DNA code into proteins.

elicitation of lower immunogenicity, which usually requires additional components called adjuvants for a better immunogenic response.[101,102] In addition, they do not multiply intracellularly which only evoke humoral immunity. Recombinant viral vectors have the potential to solve all the above problems as they provide a better immunogenic response without the need for adjuvants and can induce a robust cell-mediated response in addition to humoral immunity to eliminate virus-infected cells as they multiply intracellularly (Figure 2).[85,103] Viral vectors are genetically engineered viruses made by removing their virulent genes responsible for causing disease in the host. As they are genetically modified, they do not contain disease-causing genes, and therefore no safety concerns regarding these vectors. They serve as delivery vehicles for exogenous genes encoding key antigens of disease-causing pathogens. Various viruses have been developed as vectors, including adenovirus, influenza virus, measles virus, and cowpox virus.[104] Because of their ability to express heterologous antigens and induce antigen-specific cellular and antibody mediated immune responses, they have become promising vaccine platforms that provide long-lasting and, in some cases, *life-long* immunity.[105,106]

mRNA vaccines

The mRNA vaccine was not a new science that came after the coronavirus pandemic; scientists have been working on it for decades. However, COVID-19 pandemic has catalyzed the most rapid vaccine development in history, with mRNA vaccines at the forefront. The milestone experiment for mRNA therapy was conducted in the late 1987 by Malone who mixed strands of messenger RNA with droplets of fat and bathed it with human cells. The cell then absorbed the mRNA and began producing proteins from it.[107,108]

RNA vaccines consist of mRNA that encodes antigenic proteins of the desired pathogen for which a vaccine must be developed, encapsulated, and stabilized by lipid nanoparticles. After administration into cells, there is transient expression and translation of mRNA to antigenic proteins coded by the pathogenic organism that are recognized by the immune system as foreign. The immune system, upon discovering this foreign protein, that is, antigen, normally responds by producing antibodies.[109,110] Compared to other vaccine platforms, RNA vaccines have a number of advantages, such as versatility, use of host protein machinery, ease of design, short developmental time, and induction of both humoral and cellular responses. Therefore, despite being a relatively new technology that has not been previously approved for any use, RNA vaccines were developed rapidly and became the first to be authorized for COVID-19.[109,111]

No treatment for COVID-19 can directly kill the virus, which is why vaccines were the last hope to

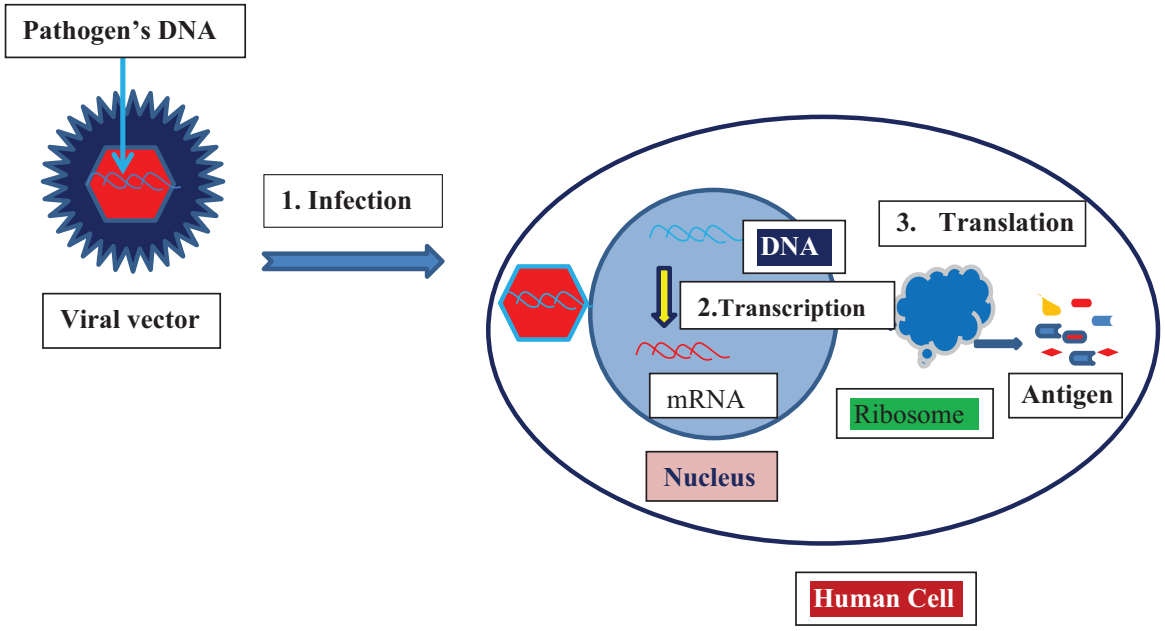

Figure 2. The use of genetically modified virus to carry a foreign DNA to be translated within the host cell.

stop the pandemic. However, vaccine development is generally a time-consuming process that requires years to complete. However, modern biotechnology delivered a vaccine named mRNA-1273 42 days after the spike protein-coding sequence of severe acute respiratory syndrome coronavirus (SARS-CoV-2) was published in 2020. Overall, it takes less than a year to complete the design, manufacture, test for safety and efficacy, and evaluation and approval for use.[111] The implementation of vaccines against SARS-CoV-2 was of a paramount importance for slowing the coronavirus pandemic.[112]

DNA vaccines

DNA vaccines imply the direct inoculation of DNA- based expression vectors that carry the sequence of the pathogen's protein antigen.[113] They are purified plasmid preparations containing one or more gene of the disease-causing agent that will be translated to protein within the human cell that is capable of inducing an immune response against a pathogen.[114] The idea behind the DNA vaccine system is that the antigen can be expressed directly by the cells of the host in a way similar to that occurring during viral infection.[72] DNA vaccines have a number of advantages, such as elicitation of humoral as well as cell-mediated immune response as the synthesis of the encoded antigens takes place within the host cell.[102,115,116] The ability to mimic the effects of LAV without its associated risk is another unique advantage of these vaccines. Moreover, plasmid DNA is very stable even beyond a cold chain that makes the storage, transportation, and distribution of DNA vaccines more practical and also cheaper.[117,118] Though DNA vaccines have a number of advantages, there are some concerns related to them. One major fear to such type of vaccines is the risk of genomic integration into the host's chromosomes and the resulting threat of mutagenesis and oncogenesis. As a result, WHO recommends integration studies as part of preclinical safety test for DNA vaccines though minimal risk. Besides, these types of vaccines have a low transfection efficiency into cells (Table 3).[72,82]

Conclusion

Vaccination has played a significant role in protecting the world's population from countless diseases that previously took the lives of millions each year. It is evident that while measures like lockdowns can control pandemics, vaccination offers a more sustainable means with minimal economic burden, making it the preferred strategy by many governments as a medium- to

Table 3. Summary of some features of recombinant vaccines platforms.

Essential features	Recombinant subunit vaccine	Viral vector vaccine	DNA vaccine	mRNA vaccine
Versatility	+	+	+	+
Induction of cellular immunity	–	+	+	+
Possibility to repeat vaccine application	+	±	+	+
Safety of vaccine	+++	±	+	++
Immunogenic response	–	+	±	±
Fear of integration into the host DNA	–	–	+	–

long-term solution. Despite the critical role of vaccines in public health, global vaccine coverage still faces significant challenges. Accessibility issues is still there, though a more pressing concern is the growing influence of anti-vaccination movements, which have led to decreased vaccine uptake even in high-income settings. This has resulted in the outbreaks of life-threatening infectious diseases in Western countries that were previously thought eliminated. The number one driver of vaccine skepticism is the spread of *misinformation* on *social media* that undermines public awareness on the seriousness of vaccine-preventable diseases. Addressing such challenges is crucial to improving global health.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contributions
Chernet Tafere: Conceptualization; Formal analysis; Investigation; Visualization; Writing – original draft; Writing – review & editing.

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