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Chronicles, Classes, Constituents, and Creation of Traditional Vaccines and COVID-19 Vaccines

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Abstract

Vaccination prevents 3.5 to 5 million deaths annually from infectious diseases. But the sudden emergence of the coronavirus disease, the fast rollout of vaccines, compulsory government vaccination regulations, and huge profit margins of vaccine manufacturers contributed to vaccine hesitancy and conspiracy theories about the COVID-19 vaccines. This hesitancy was fueled by a lack of information about vaccine contents and production processes. We show that vaccines are neither a recent idea, nor an offshoot of the COVID-19 pandemic, and we show the constituents of traditional vaccines and COVID-19 vaccines. Vaccine classes include live attenuated vaccines, whole inactivated vaccines, toxoid vaccines, subunit vaccines, recombinant vector vaccines (RVVs), and nucleic acid vaccines (NAVs). COVID-19 vaccines approved for emergency use by WHO are mostly RVVs and NAVs. They have similar ingredients and mechanisms of action to traditional vaccines. Approval of vaccines goes through rigorous phases of research and development, clinical trials, tests by regulatory authorities, and continuous improvement. Production workflow follows generating, releasing, isolating, and purifying the antigen, adding other ingredients before packaging and storage. Some challenges of vaccination are injection pain, negative beliefs, vaccine side effects, and microbial complexities. Compared to other chemotherapeutics, vaccines hold the highest potential in preventing and eradicating infectious diseases.

Keywords: Vaccine, Adjuvant, COVID-19, Stabilizer, Edward Jenner, Variolation, Nucleic Acid Vaccines

Introduction

A vaccine is a biological or synthetic antigenic preparation made to confer immunity to a disease or amplify immune response to a disease. The use of vaccines for this purpose is called vaccination, and the protection derived from vaccines is called immunity. Their mechanism of action is to imitate an infection in the body and trigger an immune response, but with weak pathogens or their components (CDC, 2022a). Importantly, they create memory in the body against the antigens that the pathogen presents, which will prevent against future infection with the pathogen (CDC, 2022a). Ever since vaccines were established as safe and effective against infectious disease, vaccination has formed an integral part of human and animal disease prevention and medical research globally. But while the topic of vaccines may not have been popular among the general public before the year 2020, the emergence of the COVID-19 pandemic brought it to the forefront. As millions of people contracted the virus worldwide and many died from infection (WHO, 2022a), vaccine production companies scurried to produce suitable vaccines to protect mankind from the disease. This led to the production of different brands of

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vaccines and many countries passed laws of compulsory COVID-19 vaccination as a prerequisite for public activities.

The sudden emergence of the COVID-19, suspicion towards the government and pharmaceuticals, the speedy release of vaccines, and general hesitancy towards vaccines were among reasons that caused public distrust towards the COVID-19 vaccines (Moore et al, 2021; Chayinska et al, 2021). Some sections of the public across several countries also believed that the COVID-19 was intentionally created to make huge economic profit for parties involved in vaccine manufacture (Chayinska et al, 2021). Indeed, manufacturers made billions of dollars from sales of COVID-19 vaccines and governments earned huge taxes. Pfizer's sale of the COVID-19 vaccine in the year 2021 was estimated at $15-30 billion; Moderna's at $18-20 billion; Johnson & Johnson/ Janssen's reached up to $10 billion, and $2-3 billion for AstraZeneca (Kollewe, 2021). But COVID-19 vaccine skeptics also admitted that a lack of information about vaccine contents and their effects on the body was behind their distrust and hesitancy (Moore et al, 2021). One would be inclined to reject any suspicious drug being shot into their body that they know little about, by assumed government representatives. Therefore, first, in writing this review, we show from a historical standpoint that vaccination has been in existence and has proven useful for thousands of years and is not a recent offshoot of the COVID-19 pandemic. It is not a recent medical afterthought or government gimmick. We also explore the different classes of vaccines, the origin, and peculiarities of each class. Likewise, this paper gives a general overview of the contents of traditional vaccines and recombinant vector vaccines (RVVs), including nucleic acid vaccines (NAVs) such as the mRNA vaccines that were approved for use against the coronavirus disease. Furthermore, we discuss the steps involved in vaccine production. These processes are thorough, highly regulated, and similar to the production of other types of chemotherapeutics. Therefore, through this paper, we hope to unveil the unknowns about vaccines that generate doubt and controversies. Armed with this knowledge, one can make an informed decision on vaccine use, rather than depending on rumors, imagination, and conspiracy theories. We end the review by stating the benefits, concerns, and limitations of vaccines.

Of all chemotherapeutic advances known to man, vaccines hold the greatest potential to protect large populations from infectious disease in the shortest possible time and to eradicate infectious disease. They are second only to clean drinking water in reducing infectious disease worldwide (Plotkin, 2009).

Chronicles of Vaccination

Vaccination, though uncommon for a long time in history, had been practiced for many centuries before it was popularized by Europeans. Evidence exists that it may have existed in ancient China, Africa, and Turkey, as early as 1000 B.C. (Lewiecki, 2015). But it was introduced to the West in 1717 through the writings and influence of Mary Wortley Montagu, wife of the British ambassador to Turkey in the early 18th century, in the heydays of smallpox (Case & Chung, 1997; Breman, 2021). Because smallpox was a deadly scourge, ancient physicians tried various methods to get rid of it, including variolation—the inoculation of scabs or fluid from lesions of infected patients into uninfected patients (Case & Chung, 1997; Little, 2021; Breman, 2021). In the height of the smallpox pandemicity, a farmer named Benjamin Jesty was the first to discover, by variolating his wife and two sons in 1774, that the cowpox virus confers immunity against smallpox (Thurston & Williams, 2015; Breman, 2021). Physician John Fewster in 1776 (Little, 2021), and Peter Plett around 1790 (Plett 2006) were also pioneers who published ahead of the much-publicized experiment by British surgeon, Edward Jenner, that cowpox infection confers immunity against smallpox.

Still, the history of vaccination took a new turn with Edward Jenner's contributions. Jenner observed that milkmaids were usually immune to smallpox, and he wanted to know why. He soon hypothesized that the milkmaids and farm workers transmitted an equine disease, which he called "the grease", to cattle, that the disease gave cattle cowpox, and that this cowpox was subsequently transmitted to the farm workers (Tizard, 1999). Subsequently, the patients never got infected with smallpox when they got healed of cowpox (Tizard, 1999). To test his hypothesis, Jenner extracted cowpox pus from a milkmaid named Sarah Nelmes, who got infected while handling an infected Gloucestershire cow called Blossom (Behbehani, 1983). He inoculated this pus into an eight-year-old boy named James Phipps (Behbehani, 1983; Riedel, 2005). The boy developed a mild case of cowpox and soon recovered without any severe reaction. In the process, Jenner discovered that cowpox can be transmitted human-to-human, and not just from cattle (Riedel, 2005). Phipps was reinoculated with the cowpox pus, but this time, he showed no symptoms (Riedel, 2005). Subsequently, he was exposed to the smallpox virus, and again, he showed no symptoms (Riedel, 2005). Jenner reported his findings with Phipps and a history of thirteen other individuals who were immune to smallpox after getting exposed to cowpox (Behbehani, 1983).

Jenner's method brought the subject of variolation to the public glare. There were mixed feelings over his approach. While some hailed it as a miracle against the plague of smallpox, there was a bitter outcry from much of the public (Riedel, 2005). Perhaps James Phipps' age (8 years old) further enraged many in society. At any rate, the success of his findings led to an initially reluctant but eventual widespread acceptance of his method, as people were desperate to protect

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themselves from smallpox. Jenner's friend, surgeon Richard Dunning, named the method "vaccination", from "vacca", the Latin word for "cow" ("vaccinia" is the Latin word for cowpox), but the word was popularized by Louis Pasteur (Behbehani, 1983; Cavaillon & Legout, 2022). What the general public initially frowned at has become a law and an important requirement for persons of all ages all over the world today. Fortunately, in 1979, WHO declared the world smallpox-free. But some vials of the pus are preserved with the CDC, in Atlanta, Georgia, USA, and in the State Research Centre of Virology and Biotechnology, VECTOR, Koltsovo, Novosibirsk Oblast, Russia (Breman, 2021). Success against smallpox was a collective effort with a long history, but it is largely credited to Edward Jenner's unconventional method which gained public fame.

Many years passed before another major milestone was recorded in vaccine development. Louis Pasteur, with his remarkable contributions to microbiology, was the next major contributor, although chance played a huge role in his discovery. In December 1878, Pasteur received from Henri Toussaint, a sample of a guinea pig's heart inoculated with a highly virulent fowl cholera bacterium, *Pasteurella multicoda*, which was killing hens (Cavaillion & Legout, 2022). Pasteur reportedly left the sample on the bench and went on vacation for some weeks (Duclaux, 1896). When he returned, he inoculated some hens with the same bacterium he left on the bench before his vacation. However, the bacteria failed to kill the hens (Duclaux, 1896). Pasteur then prepared a fresh culture of the same deadly *Pasteurella multicoda* and injected the chickens with it. Again, they survived this lethal injection (Duclaux, 1896). This chance event taught him that vaccinating with live attenuated virulent organisms was a way of developing immunity to deadly pathogens. Pasteur later published his findings (Pasteur, 1880). Applying this principle led Pasteur to develop anthrax, rabies, and pig erysipelas vaccines, in addition to fowl cholera vaccine (Cavaillon and Legout, 2022). Pasteur's findings kicked off massive scientific interest in vaccinology (Entrican & Francis, 2021; Cavaillon & Legout, 2022). At first, scientists made vaccines by bacterial culture or tissue homogenates for unculturable bacteria, followed by the use of cellular subunits and toxoids (Entrican & Francis, 2021). The scientist with the greatest success in vaccine production was Maurice Hilleman, who successfully developed more than 40 different vaccines, including those against infectious diseases like measles, meningitis, hepatitis B, chicken pox, mumps, rubella, pneumonia, and *Haemophilus influenzae* type b (Hib) (Newman, 2005). The use of vaccines has since been recognized as a cheap, fast, and efficient way to protect human and animal health from infectious disease. Immunization prevents 3.5 to 5 million deaths annually from infectious diseases like tetanus, diphtheria, whooping cough, measles, and influenza (WHO, 2022b).

Classification of Vaccines

Vaccines can be classified in several ways. First, they can be classified based on their valency as either monovalent or polyvalent. A monovalent vaccine is one that contains only one strain or serotype of a single antigen. Initial rollouts of the COVID-19 vaccine targeting only one strain of the SARS-CoV-2 without giving protection against mutants are monovalent. Conversely, a polyvalent vaccine is one that contains more than one strain or serotype of the same antigen or pathogen. Examples are the bivalent oral polio vaccine (bOPV) (Schlingmann et al, 2018) (manufactured by the Beijing Bio-Institute Biological Products); and Moderna's Spikevax bivalent vaccine, made against the original (Alpha) strain and the Omicron BA.1 variant (European Medicines Agency (EuMA), 2022a). This vaccine was also recommended for use against the BA.4 and BA.5 variants (EuMA, 2022a). Pfizer-BioNTech's Comirnaty bivalent vaccine is another one used against the Alpha strain and the Omicron variant BA.4/BA.5 (Pfizer-BioNTech, 2022). Vaccines can also be classified as either adjuvanted or nonadjuvanted, depending on whether or not they contain adjuvants (adjuvants are explained in section 4). Fluad Quadrivalent influenza vaccine, manufactured by Sequirus, is an example of a vaccine adjuvanted with MF59 (CDC, 2022b). Again, Comirnaty mRNA vaccine and the Johnson & Johnson adenovirus vaccine are nonadjuvanted vaccines (CDC, 2022c).

Furthermore, vaccines can be classified based on their spectrum as either narrow-spectrum or broad-spectrum. This method considers the number of diseases that the vaccine protects against. However, grey areas arise concerning the definition of "narrow" and "broad". We have no conclusive or universal answer as of now as to how many infections a vaccine should prevent against to be termed "narrow" or "broad". A combination of vaccines administered against different diseases to make a single "super" vaccine is called a "combination vaccine" (CDC, 2022d). Examples of these are MMR vaccines, used against measles, mumps, and rubella (CDC, 2022d). The DTaP vaccine against diphtheria, tetanus, and pertussis, is another common example (CDC, 2022d). DTaP-IPV-HepB is another combination vaccine. It protects from polio and hepatitis B, in addition to diphtheria, tetanus, and pertussis (CDC, 2022d). Likewise, DTaP-IPV/Hib, which adds protection against *Haemophilus influenzae* type B bacterial infection to the DTaP-IPV (CDC, 2022d). Different manufacturers can make the same combination vaccines in their own way and give it their trade name. Combination vaccines afford fewer injections, lower production and procurement costs, and less productive time compared to taking multiple vaccines (CDC, 2022d). But the most popular method of classifying vaccines is based on the type of active component/antigen in the vaccine. Based on this mode of

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classification, vaccines are divided into (a) live attenuated vaccines (LAVs), (b) whole inactivated vaccines (WIVs), (c) toxoid vaccines (TVs), (d) subunit vaccines (SVs), (e) recombinant vector vaccines (RVVs), and (f) nucleic acid vaccines (NAVs). These are discussed as follows:

(a) Live, Attenuated Vaccines (LAVs): These are vaccines produced with a live but weakened form of a complete bacterium or virus. This ensures that all components and properties of the pathogen are in place, but the pathogen is incapable of carrying out processes that lead to an infection. The result is a very good immunogenic response to the antigen, as though there were a real infection. Immunity is usually long-lived, and one shot is often sufficient (Vos et al, 2014; Kallerup & Foged, 2015). These vaccines often do not need adjuvants (Vos et al, 2014). To reduce the risk of infection, one approach employed in producing LAV active components is the use of a very similar or closely related pathogen to the etiological agent of the disease they aim to prevent. Edward Jenner's use of live cowpox virus to produce immunity against smallpox in 1798 provides a template that is followed. Applying harsh treatments like extreme temperatures on a pathogen is another way to attenuate the LAV active component (Kallerup & Foged, 2015). Moreover, *passaging* a strain is a third way to produce the LAV active component. This involves continuously replicating a virus in tissue culture until it loses its virulence (Mak & Saunders, 2006; Vos et al, 2014). This method is patterned after Louis Pasteur's model. Pasteur collected pieces of the spinal cord of a rabid street dog and inoculated by trepanation under the *dura mater* into the cranium of healthy rabbits (Pasteur, 1885). This virus was allowed to grow in the rabbit and was transferred from rabbit to rabbit until it was consistently virulent. He then took pieces of spinal cord from a rabbit down the line and exposed to dry air (made dry by placing fragments of potassium beneath the container) for as long as 15 days (Pasteur, 1885). This dry air-exposed virus conferred protection on other dogs and later humans (Pasteur, 1885). An example of an LAV made by passaging is the influenza vaccine which is made by passaging the influenza virus in embryonated eggs for an extended period (Mak & Saunders, 2006). Attenuation can also be achieved by isolating mutant strains of the pathogen that have different growth requirements such as significant temperature difference than the original pathogenic strain (Mak & Saunders, 2006). And with recombinant DNA technology, virulence genes can easily be manipulated to generate a mutant strain. LAVs carry the risk of the attenuated pathogen reversing to virulence and causing a disease. This is more common in bacteria (Mak & Saunders, 2006). For example, one of the viral strains of the Sabin OPV is reported to revert to a virulent form while transiting through the small intestine, leading to a vaccine-associated paralytic polio (Mak & Saunders, 2006). Another risk of LAVs is that some viruses used may induce transient immunosuppression that can predispose the vaccinee to other infections (Mak & Saunders, 2006). In addition, contaminations in the production of the mutant strain can incorporate other pathogens into the vaccine (Mak & Saunders, 2006). Finally, LAVs must be stored at cold temperatures all the time throughout the supply chain from the manufacturer to the vaccinee to preserve their effectiveness (Mak & Saunders, 2006). This is a major challenge in areas where this cannot be guaranteed. These challenges have limited the use of LAVs to only when they are absolutely necessary.

(b) Whole Inactivated Vaccines (WIVs): Salmon & Smith in 1886, and Roux & Chamberland in 1886 are credited as pioneers of WIVs (Plotkin, 2014). The first to apply inactivated vaccines on human subjects are Pfeiffer & Kolle (1896) in Germany, and Wright & Semple (1897) in England, both teams producing typhoid vaccines. Like LAVs, WIVs are made from whole bacteria or viruses with all their components intact. The difference is that unlike LAVs, WIV active components have been killed with heat, chemicals, or irradiation. WIVs mostly induce a humoral response (Vishweshwaraiah & Dokholyan, 2022) but may not produce an immune response in B cell immunodeficiency or combined immunodeficiency (Pollard & Bijker, 2021). Unlike LAVs, WIVs do not require refrigeration for their continued effectiveness. This gives them an advantage in areas with poor handling and unstable electricity. Also, WIVs are safer for immunocompromised individuals due to a lower risk of virulence (Vishweshwaraiah & Dokholyan, 2022). Despite these advantages, the lack of active proteins may diminish their immunogenicity. Immunity provided by WIVs is also shorter-lived, which calls for multiple shots (Vishweshwaraiah & Dokholyan, 2022), and they are normally prepared with adjuvants (Pollard & Bijkard, 2021). Another challenge with WIVs is that inadequate inactivation can leave traces of life in the pathogen and poses the risk of virulence, while excess treatment can inhibit immunogenicity (Vishweshwaraiah & Dokholyan, 2022). Polio, hepatitis A, and Japanese encephalitis vaccines are other examples of licensed vaccines in this category (Pollard & Bijker, 2021). LAVs and WIVs come at a higher production cost compared to subunits and recombinant vaccines. And they require a high biosafety level and specialized laboratories to culture the disease pathogen that will be used as the active component of the vaccine (Qin et al, 2021).

(c) Toxoid Vaccines (TVs): TVs are created when the disease pathogen itself does not cause a disease, but

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the toxins they produce cause the disease, such as in botulism, tetanus, and diphtheria (Vaccine Knowledge Project (VKP), 2022). These processed toxins are called toxoids because they are not harmful like original toxins. Notwithstanding, they trigger a strong response from the body's immune system (VKP, 2022). Toxoids are made from purifying a toxin from a pathogen, denaturing the toxin or making it harmless, for example, by heat or formaldehyde. The treated toxin still maintains its antigenic property after the treatment procedure. Glenny & Hopkins (1923) first demonstrated that the diphtheria toxin can lose its toxicity by the action of formalin. Its toxicity was reduced but could only be administered with an antitoxin (Plotkin, 2011). However, a stable, nontoxic diphtheria toxoid was finally produced by Ramon (1923).

(d) Subunit (Purified Antigen) Vaccines (SVs): A subunit vaccine is one whose active component is made up of one or more parts of the disease pathogen but not the entire pathogen. Earlier researchers discovered polysaccharide capsules sheathing bacterial cells and unveiled that antibodies against these capsules promote phagocytosis of the bacterial cells (Plotkin, 2014). With this information, Gotschlich et al (1969) developed the first vaccine against *Neisseria meningitidis* polysaccharide. The success opened the door to more research and development of other subunit vaccines. Subunits can be made by lysing the pathogen, followed by a process of purification and use of the desired component or secretion as a vaccine active component. In making these kinds of vaccines, the focus is on the antigen(s) that the antibodies bind to, while eliminating redundant parts of the pathogen. Virus-like particles are more recent vaccine subunits. Nanoparticle, viral capsid proteins, and recombinant viruses are utilized for subunit vaccines (Kim et al, 2022), as are plant viruses and chimeric viruses (Balke & Zeltins, 2019). Conjugate vaccines are subunit vaccines that target bacteria that evade the immune system in children by being coated with a capsular polysaccharide layer (Rappuoli et al, 2019). The capsular polysaccharide hides the bacterial antigens, making them invisible to antibodies. To circumvent this protective adaptation, antigenic carrier proteins are attached to these polysaccharides, making them recognizable by antibodies (Rappuoli et al, 2019). This method was introduced in the 1980s (Rappuoli et al, 2019) after expanding on an earlier discovery by Oswald T. Avery & Walther Goebel (1929) that bacterial capsular polysaccharides become highly immunogenic when covalently linked to a carrier protein. Outer membrane vesicles (OMVs) are another group of subunits. Gram-negative bacteria include many medically important species to humans and animals. This group possess a bilayered outer membrane. From this membrane, all known Gram-negative bacteria secrete OMVs (Li et al, 2020). OMV formation starts with the breakage of the links between the bacterial OM and the Gram-negative peptidoglycan layer (Zhu et al, 2021). OM regions that detach from the peptidoglycan layer protrude to form vesicular buds on the exterior until they detach from the membrane and form OMVs (Zhu et al, 2021). Each OMV is about 30-250 nm in size (Cheng et al, 2021). Their composition is similar to the rest of the outer membrane, comprising lipopolysaccharides, membrane proteins, and peptidoglycan (Zhu et al, 2021). In addition, they contain components of the periplasmic space (Zhu et al, 2021). With these components, OMVs contain outer membrane antigens and complexity in their natural form, a property that ordinary proteins lack (Zhu et al, 2021). OMVs can contain bacterial toxins (Kulp & Kuehn, 2010). They can fuse with a host cell like a normal bacterial membrane and deliver these toxins into the host cell. Leveraging on the antigenicity and other properties of OMVs, vaccines can be made from treated OMVs against real bacterial OMVs (Kulp & Kuehn, 2010; Zhu et al, 2021). This technology is also very useful in tumor immunotherapy (Cheng et al, 2021). Antimicrobial resistance caused primarily by antibiotic abuse and bacterial adaptation mechanisms is widespread and on the increase. Outer membrane vaccines represent an alternative way to protect against these bacterial pathogens without putting additional pressure on antibiotics (Zhu et al, 2021). With the emergence of recombinant DNA technology, proteins from one species can be produced by inserting the gene segment for the protein of interest into the genome of another species such as yeast. When the gene of interest is expressed in the non-native species, the protein has the same conformation and properties as it does in the native species. The proteins are purified and then used to make subunit antigens. These types of vaccines are called recombinant vector vaccines (RVVs). Examples of vaccines made this way include GlaxoSmithKline's Infanrix-hexa (diphtheria, tetanus, pertussis, polio, hep B, and Hib) (Electronic Medicines Compendium (EMC), 2021a), Merck Sharp & Dohme's HBvaxPRO (hep B) (EMC, 2021b), and Merck Sharp & Dohme's Gardasil 9 (HPV) respectively (EMC, 2022), all of which employ recombinant yeast to generate the proteins of interest. Generally, subunits offer a safety advantage over LAVs and WIVs since there is absolutely no chance of replication. Additionally, subunits are cheaper to produce and maintain than whole pathogen vaccines (Kallerup & Foged, 2015; Abinaya & Viswanathan, 2021). Vaccines produced against *Neisseria meningitidis*, *Streptococcus pneumoniae*, and Hib are usually made with subunits (Kallerup & Foged, 2015). A lack of the other components of the bacterium or virus may reduce the effect of the subunit vaccine. To

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compensate for this, adjuvants are needed to enhance the immunological response (Kallerup & Foged, 2015).

(e) Recombinant Vector Vaccines (RVVs): These use an attenuated virus or bacterium to introduce inserted nucleic acid into the vaccinee. "Vector" refers to the virus or bacterium used as the carrier. In nature, viruses latch on to cells and transduce their genetic material into them. Scientists utilize this process to insert strips of the genetic material from other microbes into them and allow the vector virus to ferry the foreign DNA to cells. The first viral vector expressing a foreign gene was engineered in 1972 with the SV40 virus (Jackson et al, 1972). RVVs are made by deleting genes that are necessary for the development of a productive and deleterious function and replacing them with the gene coding for the antigen of interest (Daian e Silva & da Fonseca, 2021). Attenuated bacteria also can be used as vectors. Such bacteria are called live attenuated bacterial vectors (LABVs) (Kumar, 2019). In this case, the inserted genetic material causes the bacteria to display the antigens of other microbes on their surface, causing an immune reaction. *Vibrio cholerae*, *Listeria monocytogenes*, *Mycobacterium bovis* strain *Bacillus* Calmette-Guérin, *Escherichia coli*, and *Shigella spp.* have been used as LABVs of heterologous proteins of vaccines and other chemotherapeutics (Kumar, 2019). Expression of the transgene is an important consideration when creating a viral vector. Likewise, the type and size of genome, route of entry into the cell, possibility of genome integration, its inflammatory potential, and viral tropism (Daian e Silva & da Fonseca, 2021). The right dosage that will deliver sufficient amounts of the vector or vaccine without causing toxicity or strong side effects must also be considered (Daian e Silva & da Fonseca, 2021). Viral vectors are beneficial in some ways. They induce high levels of immunogenicity without adjuvants (Henao-Restrepo et al, 2016; Mahony, 2021). But adjuvants are being tested to further improve their efficacy (Milicic et al, 2017). Their effects are long-lasting, and they may offer protection after only one dose (Reyes-Sandoval et al, 2012; Henao-Restrepo et al, 2016). Viral vectors can be engineered to target specific kinds of cells rather than having a systemic function (Travieso, 2022). Another advantage of viral vectors is that they elicit cellular responses that clear infected host cells (Travieso, 2022). This is useful to prevent perpetuation of the viral genome in the body. Also, viral vectors are replication-incompetent. They need an exogenous promoter from the host to express the gene of interest. This gives them another safety advantage. Viral vectors can be engineered to deliver multiple genes of interest for different antigens and pathogens (Travieso et al, 2022). The disadvantages of viral vectors mainly depend on the virus being used. For example, retroviruses and lentiviruses have tumorigenic potential when used as vectors (Ura et al, 2014). Retroviruses have the capability to become replication-competent, and they only infect dividing cells (Ura et al, 2014). Vaccinia virus, Sendai virus, cytomegalovirus, and adenovirus need pre-existing immunity to be effective; adeno-associated virus tends to produce low titers of antibodies; and cytomegalovirus has the risk of pathogenesis in some individuals (Ura et al, 2014). Jcovden COVID-19 vaccine by Johnson & Johnson/Janssen is an example of an RVV. The adenovirus type 26 (Ad26.COV-S) used as the active component causes mild cold symptoms. But it was engineered to carry the SARS-CoV-2 spike protein (EuMA, 2022b). When the cell is infected with this non-replicative virus, the cell expresses the spike protein gene, and the protein develops on the cell surface (EMA, 2022). This triggers the body's immune response against the foreign spike proteins to destroy it. Subsequent infection with the actual SARS-CoV-2 will cause a similar reaction of antibodies against the spike protein. Oxford-AstraZeneca's Vaxveria COVID-19 vaccine is another RVV. Human clinical trials had been conducted for other RVVs against malaria, HIV, respiratory syncytial virus, Zika virus, influenza virus (CDC, 2021), rabies, and measles, (Travieso et al, 2022) before the approval of RVV COVID-19 vaccines.

(f) Nucleic Acid Vaccines (NAVs): These make use of pieces nucleic acid as their active component. Nucleic acid vaccines are essentially of two types: DNA vaccines and mRNA vaccines. DNA vaccines are made from engineered bacterial plasmids that express genes for proteins of interest when administered in-vivo (Liu, 2011). These plasmids then successfully transfect infected cells. The use of DNA plasmids to induce immunity was first published by Yankauckas et al (1993). They injected plasmid DNA containing the nucleoprotein gene of the influenza virus into mice, resulting in the production of nucleoprotein-specific cytolytic T cells and antibodies. The mice were subsequently protected from a lethal infection of the live influenza virus for one year. Research has been ongoing for decades on the use of DNA vaccines in chemotherapeutic interventions against allergies, autoimmune disorders, cancer, (Rodríguez-Gascón et al, 2014) Zika virus disease (Shan et al, 2018), and other diseases. DNA plasmids are replicated in bacteria, which are then screened based on antibiotic resistance mediated by antibiotic-resistance genes carrying resistance markers using the prokaryotic origin of replication (Qin et al, 2021). After the vaccine is received, the DNA is imbibed by somatic cells and transported into the nucleus where it is transcribed into mRNAs which are translated in the cytoplasm (Qin et al, 2021). Since RNAs are

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simply transcripts of DNA sequences, it makes sense that they may hold some vaccination potential. The in-vivo vaccination benefit of mRNAs can be traced to Wolff et al (1990) who observed successful expression of different proteins in mice after direct injection with mRNA. When mRNA vaccines are injected, they are transported directly to antigen-presenting cells (APCs) (Qin et al, 2021). When they successfully access APCs via efficient methods, such as nanocarrier transport, the mRNAs can be released in the cytoplasm and translated into antigenic proteins (Qin et al, 2021). They are further processed into peptide epitopes, which are combined with the major histocompatibility complex (MHC) class I via a cross-presentation pathway (Qin et al, 2021). MHCs are then transferred to the APC cell surface, which activates $CD8^+$ T cells and results in an immune response. NAVs can completely eradicate any infectious agent and they have higher purity levels than other types of vaccines. Their use can prevent the inclusion of foreign matter into the vaccine, like egg proteins from egg cultures. They can eliminate several allergens associated with the production process. They offer better protection than proteins and subunits alone (Qin et al, 2021). This technique is also useful in targeting antigens of other diseases like cancer (Qin et al, 2021). Nevertheless, DNA vaccines so far have low immunogenicity levels which restrict clinical application (Qin et al, 2021). Additionally, the potential of the vaccine nucleic acid permanently integrating into the host genome, leading to insertional mutations, is another risk associated with NAVs (Qin et al, 2021). NAVs delivered through gene gun or electroporation produce the best results in-vivo. However, because they can only be delivered via needles in humans, rather than directly into the cell, it reduces their effect. But the efficiency can be improved by coupling the NA acid with efficient delivery vehicles like nanocarriers (Qin et al, 2021). NAVs, and, in particular, mRNA vaccines, were made popular by the COVID-19 pandemic. Some licensed COVID-19 vaccines employed mRNAs as the active components. Pfizer-BioNTech's Comirnaty (EuMA, 2022c) and Moderna's Spikevax COVID-19 vaccine (EuMA, 2022d) are examples. A latecomer COVID-19 vaccine, and the world's first DNA vaccine, ZyCov-D, manufactured by Indian Pharmaceutical, Cadila Healthcare, has joined the mix (Sheridan, 2021; Blakney & Bekker, 2022). ZyCoV-D has received India's Emergency Use Authorization to tackle COVID-19 (Sheridan, 2021). Several other DNA vaccines are undergoing development and trials (Sheridan, 2021; Blakney & Bekker, 2022).

Constituents of Vaccines

The ingredients in a vaccine should be stated on the vaccine package. The licensed official administering the vaccine must be aware of all allergies before administering it. Moreover, anyone with an allergy should discuss with their doctor before taking a vaccine. Constituents of a vaccine are discussed in this section:

Constituents of Traditional Vaccines

Antibody-Specific Antigen: The antigen is the active component of the vaccine and can be derived as explained in the previous section. Small amounts of the antigen are purified and stored for use. The active ingredient is grown in the right medium and purified when sufficient quantities are produced (Gomez & Robinson, 2018). Bacteria for vaccine production are grown in bioreactors with media and conditions that balance antigen growth optimization with maintenance of integrity (Gomez & Robinson 2018). Recombinant proteins can be manufactured in bacterial culture, cell culture, or yeast culture (Gomez & Robinson, 2018). Eagle Medium, Medium 199, and Minimum Essential Medium, are common media used to grow bacteria for vaccine production (VKP, 2022). Viruses only grow in cell lines, so it is necessary to have the suitable cell line to culture the viruses. Some viral cultures for vaccines may be enriched with bovine serum derived from cow or calf blood (The Immunization Advisory Center, New Zealand (IAC), 2017). Cell lines used in vaccine viral culture may be of human or animal origin. Viruses and their antigens that only develop in human cells, like varicella zoster, are grown in human cell lines. Cell lines currently in use are Wistar Institute line 38 (WI-38), and the Medical Research Council cell strain 5 (MRC-5) (Genzel, 2015), which were taken from lung cells of two legally aborted fetuses agreed to by the mothers but not initially intended for vaccine production (VKP, 2022). Additionally, the Human Embryonic Kidney 293 (HEK-293) cell line is used (Genzel, 2015; Dumont et al, 2015). HEK-293 was derived from the kidney (Genzel, 2021) of a legally aborted fetus in 1973 (VKP, 2022).

Animal viruses are usually grown in animal cell lines. Vero cell line is a common line used to grow these viruses. This line was initially sourced from kidney cells of an African green monkey in 1962 (Genzel, 2015). BHK21 from hamster kidney, MDCK from dog kidney, and CEF from chicken embryonic fibroblasts are other common animal cell lines used (Genzel, 2015).

Antibiotics: Trace amounts of antibiotics may be added to vaccine cultures to prevent bacterial contamination during the manufacturing process. Neomycin is commonly used (Aşi Içeriği, 2018). It is a broad-spectrum drug which works against a number Gram-positive and Gram-negative bacteria (Scholar, 2007). It could be added in several micrograms (µg) per dose, or trace amounts per gram. Kanamycin, streptomycin, (FDA, 2019; CDC, 2022e), polymyxin B, and gentamycin (FDA, 2019), are also be used. Some vaccines contain a combination of antibiotics (Aşi Içeriği,

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2018). Antibiotics, such as penicillins, cephalosporins and sulfonamides, which generate higher rates of allergy in the host, are not used in producing vaccines (FDA, 2019). Steps must be taken to prevent a reaction and those allergic to an antibiotic must be observed carefully if they are certified to use the vaccine.

Preservatives: Preservatives are added to the vaccine to keep it sterile and to prolong its shelf life (Finn & Egan, 2012; Gomez & Robinson, 2018). Antibiotics such as erythromycin and kanamycin may be used as preservatives (Aşi Içeriği, 2018). Generally, preservatives are not used in single-dose vaccines which are more commonly used, because they will be used at once but are used in multidose vaccines (Finn & Egan, 2012; Gomez & Robinson, 2018). Commonly used preservatives include thiomersal, phenol, 2-phenoxyethanol, benzethonium-and-formaldehyde (Gomez & Robinson, 2018), and glutaraldehyde (Mahler, 2022). Preservatives must be nontoxic and are added in trace amounts. The preservatives used are discussed in ensuing subheadings.

(a) Thiomersal: Also known as thimerosal in the US, it is a popular ethyl-mercury antimicrobial and preservative added in minute quantities to vaccines (Aşi Içeriği, 2018; WHO, 2022a). Although, there has been no evidence of toxicity caused by thiomersal, there are skeptics against its use due to its mercury content (WHO, 2022c). Sometimes, mild reactions like swelling at injection site and redness are recorded after thiomersal use (FDA, 2018; CDC, 2022f). Controversies surround the use of thiomersal in vaccines, as it was suspected to cause autism in children (VKP, 2022). Although this was disproved by research, public skepticism gave rise to a ban on thiomersal in several countries. Thiomersal-containing vaccines are not used in the European Union, UK, New Zealand, or in children's vaccines in the United States (except the flu vaccine) (VKP, 2022).

(b) Formaldehyde: It is used to inactivate viruses, for example, in the inactivated polio vaccine (IPV), and to detoxify bacterial toxins, such as the toxins used to make diphtheria and tetanus vaccines (Escudero et al, 2022). Before the vaccine is released, it goes through a purification process, during which most of the formaldehyde is removed (Gomez & Robinson, 2018). This leaves a relatively tolerable quantity. The human body produces formaldehyde as part of its metabolism. It can be found in the bloodstream but the quantity in vaccines is small in comparison. A pear contains about twenty to twenty-five times the amount of formaldehyde found in any vaccine (Powell et al, 2022).

(c) Gluteraldehyde: It is a similar compound to formaldehyde, may be used instead of formaldehyde to inactivate bacterial toxins when producing vaccines using bacterial antigens (Gomez, 2018).

(d) Phenol: The antibacterial properties of phenol (carbolic acid) are exploited in vaccine production (Gomez & Robinson, 2018).

Stabilizers: These are additives that prevent other ingredients from going through chemical reactions, sticking together, or adhering to the container (Aşi Içeriği, 2018, WHO 2020). These reactions, if not stopped, can cause the ingredients to change form and lose effectiveness in storage. For example, hydrolysis or aggregation of polymeric molecules can affect a vaccine's configuration and effectiveness. Temperature changes could also affect the constituents and potency of a vaccine because vaccines are not thermostable (Cardoso et al, 2017). Stabilizers work by lowering the surface tension of the liquid. Examples of vaccine stabilizers include:

(a) Gelatin: It is derived from pigs and thoroughly processed by hydrolysis. It is a key component in the lyophilization of LAVs (Cardoso et al, 2017). It is used to protect LAVs against the effects of temperature (Kang et al, 2010). It is generally well-tolerated and the rate of allergy is only about 1 case per 2 million doses (Cardoso et al, 2017).

(b) Human Serum Albumin (HSA): It is the commonest protein found in human blood, accounting for at least 50% of the protein content in the human blood plasma, corresponding to about 35 to 40g/L in the blood (Belew et al, 2022). Hence, it is derived from donated blood. Although the blood is properly screened for infection before use, there are concerns about the spread of infection, leading to calls to substitute HSA with a recombinant albumin of non-animal sources or by a mixture of amino acids (Cardoso et al, 2017).

(c) Recombinant Human Serum Albumin (RHSA): It is made by introducing the gene for the production of the human serum into microorganisms, for example, a recombinant *Pichia pastoris* yeast (Chuang & Otagiri, 2007; Belew et al, 2022). These organisms then serve as mini factories to produce the serum in large quantities. RHSA can also be derived from bovine serum and gelatin, or partially hydrolyzed bovine or porcine collagen.

(d) Sorbitol: It is a type of sugar alcohol with a sweet taste. It occurs naturally in the human body and in numerous plants like apples, pears, prunes, peaches, potatoes, apricots, dates, figs, nectarines, plums, raisins, and other plants and confectioneries. It is used as a sweetener in victuals and medicine (Liauw et al, 2019) and as a taste improver in vaccines. Up to 15 mg of sorbitol can be added to vaccines (VKP, 2022). The body metabolizes sorbitol slowly by passive diffusion in the small intestine (Islam & Sakaguchi, 2006). Therefore, excessive consumption of sorbitol can have a laxative effect in addition to abdominal cramps and bloating (Liauw et al, 2019). This is not a major concern when used as a vaccine additive, given the minute amount added per dose.

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(e) Others: Other ingredients used as stabilizers include but not limited to sucrose (common table sugar), lactose (a double sugar common in milk), mannitol (a sugar alcohol), glycerol, Medium 199 (which contains amino acids, vitamins, and mineral salts), monosodium glutamate (a common seasoning), urea, arginine hydrochloride (VKP, 2022), gelatin, glycine (WHO 2020), and $MgCl_2$ (Mukhopadhyay et al, 2022).

Genetically Engineered Organisms: The yeast cells modified to produce human serum are examples of genetically engineered organisms employed in vaccine production. Another example of such GEOs can be found in the formulation of Fluenz, a nasal flu vaccine. In creating this vaccine, two strains of the flu virus are injected into a developing chicken egg and their genomes are allowed to interact so as to create new strains of the virus (VKP, 2022). The new strains are then screened for the right antigens for the vaccines they intend to create and are used to make new vaccines (VKP, 2022).

Taste Improvers: Sugar and other good-tasting substances can be used as taste-improvers.

Emulsifiers: Emulsifiers hold the different ingredients together. Polysorbate 80 is a common emulsifier, stabilizer, and surfactant in vaccines, cosmetics, and other pharmaceutical product (Sampath et al, 2021).

Acidity-Regulators: Viruses and bacteria need to be kept at the right pH. Some acidity-regulators are:

(a) Salts Based on Potassium Phosphate and Sodium Phosphate: These are common and harmless. As well as keeping the pH balance, they keep the fragments of the active ingredient suspended in the water, so that they do not settle out. Hanks' Salts, which contains these and other salts, is sometimes used (Naini et al, 2022; Schmidt et al, 2022).

(b) Disodium Adipate: Also used as a food additive, it is added to vaccines (Naini et al, 2022).

(c) Succinic Acid: It is involved in several chemical processes in the body. It is used in creating vaccines against diseases, as well as anti-intoxicant vaccines, which help fight drug addiction by promoting antibody production against the active ingredient of the drug (Kosten et al, 2013).

(d) Sodium Hydroxide and Hydrochloric Acid: When these are used, they react to form water and harmless salts, and so do not appear in the final vaccine in their original form.

(e) Histidine: An amino acid found in most proteins in the human body, is also used as an acidity regulator in vaccines (VKP, 2022).

(f) Sodium Borate (Borax): A few µg may remain in vaccines such as the hepatitis B vaccine (HBVaxPro) and the HPV vaccine (Gardasil) (VKP, 2022). Such quantity is normally too small to cause any harm.

(g) Trometamol: It is a painkiller in addition to being an acidity regulator.

Adjuvants: Adjuvants are used to enhance and prolong the immune response to a vaccine (Pulendran et al, 2021; Fan et al, 2022). The word "adjuvant" was derived from the Latin word "adjuvare", meaning "to help" or "to aid" (Awate et al, 2013). The use of adjuvants reduces the quantity of the vaccine per dose required, and sometimes the number of doses. They have been in use for many years and were first described in 1924 (Ramon, 1924). Some mechanisms of action of adjuvants have been proposed in previous studies. The oldest known is to keep a reservoir of antigens at the site of injection, known as the "depot effect", so that the antigens can be readily accessed by immune cells (Awate et al, 2013). They are believed to upregulate chemokines and cytokines; they increase antigen binding and presentation to antigen-presenting cells (APCs); they could activate mature APCs and migration of APCs to the draining lymph nodes; and they are believed to activate inflammosomes (Hoebe et al, 2004; Fraser et al, 2007; Awate et al, 2013). Adjuvants used in licensed vaccines can be made from different materials. Mineral compounds such as aluminum salt or calcium salt can be used as adjuvants (Fan et al, 2022). Microbial by-products such as flagellin, Bacillus Calmette-Guérin, lipopolysaccharide, or cholera toxin, and emulsions like montanides, TiterMax, can be used as well (Fan et al, 2022). Emulsion adjuvants are made from substances such as squalene, vitamin E, or from lipids from the *Quillaja saponaria* tree or *Salmonella minnesota* bacterium. MF59 and AS03 are two common oil-based emulsion adjuvants (Tetsuani et al, 2012). MF59 comprises of squalene and two surfactants, Span 85, and Tween 80 or the citric acid buffer (Calabro et al, 2013; Ko & Kang, 2018). Squalene is a naturally occurring oil many species including humans. It is synthesized in the human liver and is a direct precursor to cholesterol and steroid hormones (Calabro et al, 2013). Nucleotide adjuvants are synthesized molecules mimicking patterns of bacterial DNA molecules that accentuate an immune response. Aluminum salts, in small amounts, have been added to some vaccines as adjuvants for more than 90 years (HogenEsch et al, 2018; Principi & Esposito, 2018). Albeit no evidence exists that they cause any serious or long-term adverse effects when used in vaccines due to their small concentration (HogenEsch, 2002; HogenEsch et al, 2018; Principi & Esposito, 2018; Goullé & Grangeot-Keros, 2020). The aluminum content in vaccines is significantly less than that received from food, inhaled in the air, absorbed through skin, or from medications such as some antacids (Goullé & Grangeot-Keros, 2020). Although aluminum increases immunogenicity, the presence of

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aluminum salts in intramuscular vaccines may trigger local reactions at the injection site after vaccination (Verdier et al, 2004). Cutaneous reactions (Rosenblatt & Stein, 2015) and subcutaneous nodules (Avcin et al, 2008) are also reported around the injection site due to reaction to aluminum.

Adjuvants can also be made from particulate substances like imidazoquinolines, liposomes, virus-like particles/ virosomes, polymeric nanoparticle, glycosphingolipids, and polysaccharides (Fan et al, 2022). Tesoactive substances like saponin, and proteases like papain, are also utilized (Fan et al, 2022). In addition to the known adjuvants, researchers have discovered at least 41 food additives that can be added to the influenza vaccine to enhance its immunogenicity in mouse models (Feng et al, 2019). Of these 41, 18 were novel additives (Feng et al, 2019).

Diluents: A diluent is a sterile liquid provided separately and used to dilute a vaccine to the proper concentration prior to administration. Sterile water, sodium chloride solution, or a combination of water and other constituents such as calcium carbonate and xanthan are common diluents (Immunization Action Coalition, 2020).

Trace of the Culture Medium: There usually are residues of the medium used to culture the pathogen. For example, if the pathogen is cultured using a developing egg embryo, then there could be egg proteins or ovalbumin in it, such as in influenza vaccines (Chung, 2014; Domachowske, 2020). Egg allergy is the commonest food allergy, with a 50% allergy rate (Allen et al, 2009). Egg-free flu vaccines have been manufactured to prevent these allergies (Lajeunesse et al, 2009; CDC 2022e). These are the Flublok Quadrivalent and the Flucelvax Quadrivalent, both recombinant flu vaccines (CDC 2022e). Most children with egg allergies are tolerant to vaccines containing egg proteins because the egg content in them is too low to cause a reaction (CDC, 2022g). Exceptions are given for children with severe anaphylaxis on first contact with the vaccines, and those who are allergic even to trace amounts of egg content. Similarly, if the vaccine is cultured using human cell lines, it could contain traces of the cell lines. Traces of other growing media or their components, for example, animal cell lines, bovine serum, antibiotics, proteins, vitamins, and minerals may also be found. Traces of yeast protein may be found in vaccines in which the antigen was grown in yeast, but cases of allergic reaction in those who are allergic to yeast are rare (Aytekin et al, 2021). In over 180,000 negative reactions to vaccines, only 15 cases (about 0.008%) were attributed to possible anaphylaxis of patients with yeast allergies after vaccination (Aytekin et al, 2021).

Latex: Latex (natural rubber) is used in the packaging of some vaccines. For example, the needle tip of the syringe may be protected with latex (Russell et al, 2004). This is a risk for people who have a severe allergy to latex that causes an anaphylactic reaction, and hypersensitivity reactions have been recorded to latex from the needle or syringe (Russell et al, 2004). People who have less severe latex allergies, for example, a history of contact allergy to latex gloves, are not at risk from latex in vaccine packaging.

Constituents of COVID-19 Vaccines

As stated earlier, several approved COVID-19 vaccines are not traditional vaccines. They are RVVs and NAVs. Traditional vaccines employ the canonical antigen-antibody recognition mechanism. The difference in the working principle thus reflects in their ingredients. More than thirty COVID-19 vaccines are licensed for use, under trials, or awaiting license in their respective countries or regions. However, we show the complete list of ingredients of only the COVID-19 vaccines that have received the WHO emergency use approval as of December 2022. Eleven vaccines make the list. They go by the trade names Comirnaty, Convidecia, Coronavac, Covaxin, COVILO, Covishield, Covovax, Jcovden, Nuvaxovid, Spikevax, and Vaxzevria (WHO, 2022d; VIPER Group, 2022). Comirnaty Original/Omicron BA.1 is also authorized for emergency use as a booster shot while the original Comirnaty is not authorized for booster shots (www.drugs.com, 2022). Both contain the same ingredients, except that the bivalent Comirnaty contains additional mRNA from the Omicron variant of the SARS-CoV-2 in addition to the Alpha strain.

Each COVID-19 vaccine has its active substance. Moreover, they may contain water to help with injection, and food salts such as NaCl, potassium chloride, and potassium dihydrogen phosphate to regulate acid content. Lipids such as cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine and 2[polyethylene glycol-2000]-N,N-ditetradecylacetamide1,2-distearoyl-sn-glycero-3-phosphocholine help deliver the nucleic acid into the cells. Some contain adjuvants such as aluminum hydroxide and L-histidine (which also balances the pH) to strengthen immune response (table 1). Disodium edetate dihydrate is used to chelate metal ions and minimize vaccine toxicity by metals (table 1). Preservatives and stabilizers e.g, sucrose, and citric acid (a common component in citrus fruits and vitamin C and several other edibles) are added to increase the shelf life and prevent changing of ingredients in storage. Ethanol, NaCl, and 2 hydroxypropyl-β-cyclodextrin are other examples of preservatives used in the approved COVID-19 vaccines. Emulsifiers (e.g, ethanol or polysorbate 80) help dissolve other ingredients in a vaccine mix. Human cell lines like HEK-293 are used to culture the antigen. By and large, COVID-19 vaccines do not contain significantly different ingredients from other vaccines. They are normally well-tolerated and nontoxic and are administered in small quantities (table 1).

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Table 1: Ingredients of COVID-19 vaccines approved by WHO for emergency use as of December 2022

S/N	Manufacturer	Trade name	Antigen type	Age group	Ingredients	References
1	Pfizer (USA) & BioNTech (Germany)	Comirnaty	mRNA	≥6 months	Nucleoside-modified mRNA encoding the SARS-CoV-2 viral spike (S) glycoprotein; 1,2-distearoyl-sn-glycero-3-phosphocholine; 2[polyethylene glycol-2000]-N,N-ditetradecylacetamide; 1,2-distearoyl-sn-glycero-3-phosphocholine; cholesterol; NaCl; dibasic sodium phosphate dihydrate; potassium chloride; sucrose; water	CDC, 2022c
2	CanSinoBIO (China)	Convidencia	RVV	18-59 years	Replication-defective Ad5 vectors expressing the full-length spike gene of wild-type SARS-CoV-2, Wuhan-Hu-1, stored at 2-8° C	Wu et al, 2021; WHO, 2022e
3	Sinovac Biotech (China)	Coronavac	WIV	3-59 years	Inactivated SARS-CoV-2 Virus (CZ02 strain); aluminum hydroxide; disodium hydrogen phosphate; sodium dihydrogen phosphate; sodium chloride; water	WHO, 2021a; WHO, 2022f
4	Bharat Biotech (India)/ Indian Council of Medical Research-National Institute of Virology (India)	Covaxin	WIV	≥18 years	Whole-virion inactivated SARSCoV-2 antigen (Strain: NIV-2020-770); aluminum hydroxide gel; TLR 7/8 agonist (imidazoquinolinone); 2-phenoxyethanol; phosphate buffer saline	Bharat Biotech International, No Date; WHO 2021b
5	Sinopharm (China)	COVILO	WIV	≥18 years	Inactivated SARS-CoV-2 antigen; aluminum hydroxide; disodium hydrogen phosphate; sodium dihydrogen phosphate; sodium chloride	Pan American Health Organization, 2022
6	Formulated by: University of Oxford (UK)/AstraZeneca (UK/Sweden) Produced by: SIIL (India)	Covishield	RVV	≥18 years	Recombinant, replication-deficient chimpanzee adenovirus vector encoding the SARS-CoV-2 Spike (S) glycoprotein; L-Histidine; L-Histidine hydrochloride monohydrate; magnesium chloride hexahydrate, polysorbate 80, ethanol, sucrose, sodium chloride, disodium edetate dihydrate, water	Serum Inst. of India LTD (SIIL), No Date; SIIL, 2021
7	SIIL (India)/ Coalition for Epidemic Preparedness Innovations (International)	Covovax	Protein subunit	≥6 months	SARS-CoV-2 recombinant spike protein; cholesterol; phosphatidylcholine; Fraction-A and Fraction-C of Quillaja saponaria Molina extract; disodium hydrogen phosphate heptahydrate; disodium hydrogen phosphate dihydrate; polysorbate-80; potassium chloride; potassium dihydrogen phosphate; sodium chloride; sodium dihydrogen phosphate monohydrate; sodium hydroxide or hydrochloric acid; water	CDC, 2022c
8	Johnson & Johnson (USA)/ Janssen (Belgium)	Jcovden	RVV	≥18 years	Recombinant, replication-incompetent Ad26 vector, encoding a stabilized variant of the SARS-CoV-2 Spike (S) protein; Polysorbate-80; 2-hydroxypropyl-β-cyclodextrin; trisodium citrate dihydrate; sodium chloride; citric acid monohydrate; ethanol	CDC, 2022c

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9	Novavax (USA)	Nuvaxovid	Protein subunit	≥18 years	SARS-CoV-2 recombinant spike protein; cholesterol; phosphatidylcholine; Fraction-A and Fraction-C of *Quillaja saponaria* Molina extract; disodium hydrogen phosphate heptahydrate; disodium hydrogen phosphate dihydrate; polysorbate-80; potassium chloride; potassium dihydrogen phosphate; sodium chloride; sodium dihydrogen phosphate monohydrate; sodium hydroxide or hydrochloric acid; water	WHO, 2021; CDC, 2022c
10	Moderna (USA)	Spikevax	mRNA	≥6 months	Nucleoside-modified mRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2; PEG2000-DMG: 1,2-dimyristoyl-rac-glycerol, methoxypolyethylene glycol; 1,2-distearoyl-sn-glycero-3-phosphocholine; BotaniChol (non-animal origin cholesterol); SM-102: heptadecane-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino) octanoate; sodium acetate; sucrose; tromethamine; tromethamine hydrochloride; acetic acid	CDC, 2022c
11	AstraZeneca (British-Swedish)	Vaxzevria	RVV	≥18 years	Recombinant, replication-deficient chimpanzee adenovirus vector encoding the SARS-CoV-2 Spike (S) glycoprotein; genetically modified HEK-293 cells; L-Histidine; L-Histidine hydrochloride monohydrate; magnesium chloride hexahydrate; polysorbate 80; ethanol; sucrose; sodium chloride; disodium edetate dihydrate; water	WHO, 2021d

Vaccine Production Requirements and Steps

Three main steps precede vaccine manufacture for public use. These are: research and development (R&D); manufacturing scale-up; and regulatory approval (Aars et al, 2021). Several stages are required in R&D. First, preclinical studies are carried out. These involve laboratory experiments in which candidate antigens and other products are studied for potential use in vaccines. Some studies begin in vitro and move to in vivo studies. Some studies are directly in vivo. Animal models are often used in preclinical trials. Success of the preclinical study could lead to filing a patent. Successful obtainment of the patent enables the developer to monopolize manufacture, sales, or other processes, for a limited time (Aars et al, 2021). Preclinical experiments may involve the use of already patented molecules or procedures. The analyst must carefully understand updated regulations and exemptions of using these patents for studies (Russo & Johnson, 2015). When the potential for use is ascertained from animal models, phase I human clinical trials are carried out to test the safety and correct dosage in humans (Aars et al, 2021). Phase II tests follow, in which the immunogenicity and effectiveness are studied (Aars et al, 2021). Phase III clinical trials are carried on a larger human sample size to test the safety and efficacy (Aars et al, 2021). If phase III is successful, the manufacturer can apply for license to manufacture and register the vaccine. Phase IV is for pharmacovigilance—observing for negative effects at the different stages of use (Ahmad et al, 2019; Thomas & Klika, 2019). Manufacturing scale-up begins in phase I clinical trials (Aars et al, 2021). At this stage, developers determine the right steps and amounts that will be needed to meet market demand. Product contents and quality are improved reciprocally to findings from the clinical trials. The process of quality upgrade continues even after the product hits the market. The regulatory phase is where the relevant Bodies determine through comprehensive tests that the product meets the necessary manufacturing, safety, and quality standards. Recommendations are made to adjust deficiencies and more studies may be required in some cases. Approval may be at the national level, regional level (such as the EU), or at the global level (such as approvals issued by WHO), and each level has its own requirements and standards.

The vaccine production procedure must adhere strictly to the highest standards of hygiene, sterility, quality control, and packaging at all stages. The product and environment must be protected from contamination and spillage (figure 1). Moreover, the personnel working in the facility must always be protected from all hazards. This includes the use

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of all necessary personal protective equipment (figure 1). As much of the process as possible is automated to minimize interference and errors.

The actual production of a vaccine can be divided into the following five steps:

Generation of the Antigen: The first step is to generate the active component of the vaccine. Using methods described previously, the antigen is produced in large quantities in its raw form. For this purpose, the pathogen's proteins or DNA need to be grown and harvested using the following mechanisms: viruses are grown in cell cultures that can be primary cells such as chicken fibroblasts for yellow fever vaccine, or continuous cell lines previously described (Gomez & Robinson 2018). Bacteria, yeast, or cell culture is used to produce recombinant proteins. A genetic sequence is inserted into a self-replicating vector and put into a controlled reactor to synthesize the mRNA (AstraZeneca, 2021). The generation process commences when the Master Seed Bank (MSB)—a collection of vialed cells or viral load that forms the starter culture for all future productions—is released into the medium or bioreactor (Gomez & Robinson 2018). The MSB can be expanded to create individual culture batches (Robinson, 2016).

Release and Isolation of the Antigen: In this step, as much of the antigen as possible is sequestered from the medium and other components used to culture them.

Purification: The antigen needs to be purified to remove impurities that may have been left behind from the previous step. High purity is needed to maximize the stability of the vaccine and convert it to a format that permits efficient delivery and distribution (Gomez & Robinson 2018). Filtration can be done to remove unwanted residual culture constituents, followed by membrane chromatography that allows the remainder to bind to a surface (AstraZeneca, 2021). Finally, ultrafiltration is done to buffer the vaccine to control the pH (AstraZeneca, 2021). Column chromatography and ultrafiltration are employed for recombinant proteins (Gomez & Robinson 2018). Inactivated vaccine antigens may be attenuated right away at this stage without further purification (Gomez & Robinson 2018).

Vaccine Formulation: This is the stage where the antigen is combined in a single vessel with other ingredients like the antibiotics, adjuvants, stabilizers, and preservatives, to form the final vaccine preparation (Gomez & Robinson 2018). When all the components are added, they are properly mixed to create uniform composition. Proper formulation is critical to effectiveness, shelf life, and safety of the vaccine.

Figure 1: Inside a human LAV production facility (Copyright © IDT Biologika)

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Packaging and Storage: The vaccine is stored in the appropriate sterile container, usually a small vial or syringe, and sealed with a sterile stopper. The vial is then kept according to the requirements of the vaccine it contains. Filled vials may be lyophilized to increase stability (Robinson, 2016; Gomez, 2018). While lyophilizing, special stoppers are inserted in the vials during drying to enable moisture escape, and the cap is fully fitted after drying (Robinson, 2016). The optimal storage method that prolongs the shelf life for the longest period is employed. Some extra volume may be added during formulation to make up for some ingredients that degrade during storage.

Benefits, Challenges, and Limitations of Vaccines

Benefits of Vaccines

The following are some of the benefits that are derived from vaccines:

(i) They are cheaper to research, produce, and purchase than other pharmaceuticals (Régnier & Huels, 2013), despite recording greater success.

(ii) Vaccines have specific measurements, and they are only administered by healthcare workers. Hence, it is hard to overdose on them compared to easily accessible chemotherapeutics.

(iii) They have been important in eradicating smallpox, minimizing infectious disease burden, and curtailing pandemics that otherwise kill, deform, scar, or upset populations and economies.

(iv) Unlike other chemotherapeutics that cure the sick but do not protect against reinfection, vaccines provide memory against diseases in case of future infection.

(v) Herd immunity against an infection will prevent bioterrorism of the population with the pathogen. For example, *Bacillus anthracis*, the causal organism of anthrax, is a likely weapon for bioterrorists (CDC 2020b). Today, anthrax vaccines are administered across the world, giving herd immunity in different populations against bioterrorist anthrax attacks. The same is applicable to many other infectious pathogens that can be vaccinated against.

(vi) Vaccines provide jobs to researchers, manufacturers, health workers, courier companies, and everyone involved in the supply chain. Manufacturers of vaccine-accompanying items like syringes and packaging, are not left out.

(vii) Vaccines reduce infection rates, provide an alternative to antimicrobials, and minimize the need for them. In so doing, they slow down the rate of antimicrobial resistance.

(viii) They improve life expectancy (Rappuoli et al, 2014), economic development and recovery, and standard of living in vaccinated populations by minimizing disease burden (United Nations Development Program (UNDP), 2021). Lower disease burden leads to less treatment costs and more productive time.

Challenges and Limitations of Vaccines

(i) Injection Pain: Local pain and tenderness are associated with vaccine injections (Nahm et al, 2012; Taddio et al, 2014; Taddio et al, 2015; Shah et al, 2015). Injection pain is the highest cause of iatrogenic pain in children (Taddio et al, 2014) and adults (Nahm et al, 2012) and contributes significantly to vaccine hesitancy. More than two-thirds of children are afraid of needles and one-tenth are non-compliant with vaccination due to the fear of injections (Taddio et al, 2014). Pain interventions are rarely provided, and it results in vaccinees suffering from unnecessary needle pain (Taddio et al, 2014). One of the reasons why the oral route is a preferred method of vaccine administration is that vaccines are easier to administer orally (Vela Ramirez et al, 2017). However, not all vaccines can be given orally if they will function optimally. Moreover, oral vaccines are difficult to formulate and must successfully go through the harsh gastrointestinal environment in order to function. (Vela Ramirez et al, 2017). Due to these challenges, only a limited number of oral vaccines are licensed for use (Marasini et al, 2014). Until pain-free injections are invented, or all vaccines are optimized for oral use, the challenge of painful vaccines looks likely to continue for the foreseeable future.

(ii) Beliefs and Vaccine Hesitancy: Negative beliefs about vaccines were the strongest predictor of opposition to pro-vaccine policies in a study (Stecula et al, 2020). In the United States for example, parents hold numerous beliefs which prevent them from vaccinating their children. This leads to outbreaks of vaccine-preventable diseases. In descending order, the most commonly held personal beliefs about vaccines in the USA were that: (i) vaccines cause illnesses; (ii) a child's immune system can be overwhelmed if it receives too many vaccines at once; (iii) vaccines contain harmful ingredients; (iv) younger children are more prone to vaccine adverse effects than adults; (v) vaccines are only manufactured for profit-making; and (vi) innate immunity is better than acquired immunity (Gidengil et al, 2019).

Similarly, religious beliefs convey strong implications for the acceptance of chemotherapeutic remedies (Gatrad & Sheikh, 2001; Kuru et al, 2022; Feizollah et al, 2022). Insisting on a healthcare provider of the same gender; modesty of the professional; refusal to expose body parts

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to the healthcare giver; and misconceptions about what causes some illnesses, are some of the beliefs quoted by some Muslims to reject vaccines and medical treatments in general (Attum et al, 2022). Some Muslims believe that receiving vaccines or intravenous fluids during a fast will break the fast (Attum et al, 2022). The use of vaccines containing gelatin sourced from pigs or animals that were not slaughtered in a manner regarded as *halal* (acceptable) is another anti-vaccine argument from the Islamic population (Ahmed et al, 2018; Maravia, 2021). Opponents of such vaccines argue that oral or intranasal use of vaccines containing gelatin is similar to consuming pork, and thus the vaccines are unclean (Maravia, 2021). Some Islamic scholars argue against the use of vaccine for infants, insisting that vaccines contain substances toxic to infants, and that only natural remedies such as plants and breast milk are optimal for a child's immune development (Maravia, 2021). Accordingly, outbreaks of vaccine-preventable diseases are usually recorded in Muslim majority communities and countries including Pakistan, Malaysia, Egypt, northern Nigeria, Nepal, Cameroon, Guinea, and South Sudan (Ahmed et al, 2018). Sects of the Jewish religion, classified as ultra-Orthodox, Orthodox, Conservative, and Reform, also have differing interpretations of the Torah, the Jewish Holy Book, as regards vaccine acceptance (Muravsky et al, 2021). While the more traditional groups argue against the use of vaccines containing pork and other substances prohibited by religious beluefs and medical equipment such as porcine valves, more liberal groups adopt a more favorable stance (Muravsky et al, 2021).

Similar challenges are encountered with Christians. The Catholic Church earlier declared that it is right to abstain from vaccines made with aborted fetuses unless children and the general population is subjected to significant health risks (Pontifical Academy for Life, 2006). No yardstick was given to define "significant health risks". Hence, the statement is open to individual interpretation, giving rise to divergent opinions over their use. An update to this declaration was made by the Catholic Church in the middle of the COVID-19 pandemic, stating, "*where ethically irreproachable COVID-19 vaccines are not available…it is morally acceptable to receive COVID-19 vaccines that have cell lines from aborted fetuses in their research and production process*" (Ladaria, 2020). In the United States, which has about 20% self-admitting Christians, ardent Christianity, including Evangelical Christianity, is associated with lower levels of vaccine acceptance and lower trust of scientific research (Gerend & Shepherd, 2011; Guidry et al, 2022). A pre-COVID-19 study (Whitehead & Perry, 2020) showed that after race, Christian nationalism—belief in Christianity as the sole authority in morality in the United States—was the highest driver of popular anti-vaccine beliefs. Christian nationalists carried the belief well into the COVID-19 pandemic, asserting their belief in the supernatural protection of God for the people of America against the infection, provided they upheld their identity as a Christian nation and lived according to the Bible's dictates (Whitehead and Perry, 2020b).

Adherents of other religions and denominations like Hinduism, Sikhism, and Amish, have questioned the moral and ethical uprightness of the COVID-19 vaccine (Feizollah et al, 2022; Volet et al, 2022), posing a barrier to not only the COVID-19 eradication, but the achievement of total vaccination against other diseases found all over the world.

(iii)Vaccine Side Effects: Side effects vary for different vaccines. Table 2 shows the side effects of some vaccines administered in the United States and COVID-19 vaccines administered internationally. Some side effects are mild while others can be very serious. Chances are low to develop serious side effects like seizures, encephalitis, and swelling of an extremity after receiving a vaccine. Advice is given to patients and measures are put in place to minimize and treat side effects. In addition to the listed side effects, a remote chance always exists of an allergic reaction to a component in any of these vaccines (CDC, 2020). While most signs and symptoms resolve themselves naturally, others need to be treated symptomatically or in extreme cases, by specialists. All through the care, the highest standards of hygiene and sterility must be observed to prevent transmission of other pathogens. While a general list of side effects for COVID-1v vaccines is given, each vaccine may have its own unique side effects. Myocarditis and pericarditis are possible side effects linked to Comirnaty, for example.

(iv)Challenging Production Process: The production process of vaccines is slow, expensive, and systematic (Kennedy et al, 2020). It requires the cooperation of divergent groups, including researchers, public health professionals, physicians, governments, and the general public. Bottlenecks, miscommunication, and bureaucracy among these groups will perturb the production process and increase the waiting time from R&D to public use. Transition from laboratory studies to clinical trials is a major hurdle for scientists due to the unpredictability and variability of microbes, which are life-like entities and not inanimate moieties injected into human subjects (Heaton, 2020). Therefore, these organisms must first be grown to the right titers at high purity and without contamination, and the conditions must be optimized to give maximum

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Table 2: Possible side effects of some vaccines administered in the USA

S/N	Vaccine	Side effects (Any of the following can be observed)	References
1	COVID-19 first shot (all ages)	Pain/swelling/redness at injection site, swollen lymph nodes, irritability or crying, sleepiness, inappetence, fatigue, muscle or joint pain, chills, headache, Bell's palsy	Obermann et al, 2021; CDC, 2022h
2	COVID-19 booster	Pain at injection site, fatigue, headache, fever	CDC, 2020a
3	DTaP	Pain/swelling at the injection site, fatigue, vomiting, irritability, seizures, inappetence, high fever (over 40.56 C), swelling in entire arm or leg	CDC 2020a
4	Hep A	Pain/swelling at injection site, headache, fever, fatigue, inappetence, dizziness	CDC 2020a
5	Hep B	Pain at injection site, dizziness	CDC 2020a
6	Hib	Pain/hotness at injection site, fever dizziness	CDC 2020a
7	HPV-Gardasil-9	Pain/swelling at injection site, fever, headache, dizziness	CDC 2020a
8	Influenza LAV	Wheezing, nasal congestion, runny nose, headache, vomiting, fever, muscle aches, coughing, sore throat, Bell's palsy	WHO, 2002; CDC 2020a
9	MMR	Pain/redness at site of injection, temporary pain and stiffness in joints, mild rash, swelling of the glands in cheeks or neck, temporary low platelet count that can cause unusual bleeding, seizures, dizziness	CDC 2020a
10	MMRV (MMR + rubella)	Pain/redness at injection site, mild rash, temporary pain and stiffness in joints, swelling of cheek or neck glands, seizures, low platelet count that can cause unusual bleeding, possible development of herpes zoster years later, fainting, dizziness	CDC 2020a
11	Meningococcal ACWY vaccine (against serotypes A, C, W, and Y)	Pain at injection site, muscle pain, fatigue, muscle pain, dizziness, fainting, ringing ears, impaired vision	CDC 2020a
12	Meningococcal B	Pain/swelling at injection site, fatigue, fever, nausea, headache, joint or muscle pain, chills, diarrhea, dizziness, ringing ears, impaired vision	CDC 2020a
13	PCV (pneumococcal conjugate vaccine)	Pain/swelling at injection site, inappetence, irritability, headache, chills, joint pain, muscle pain, fatigue, fever, dizziness	CDC 2020a
14	PPSV23 (pneumococcal polysaccharide V23)	Pain/redness at injection site, muscle pain, fever, fatigue, dizziness, ringing ears, vision impairment	CDC 2020a
15	Polio	Pain/redness at injection site, dizziness, fainting, ringing ears, vision impairment	CDC 2020a
16	Rabies	Pain/swelling/redness/itching at injection site, nausea, headache, hives, dizziness, joint pain, fever, Guillain-Barré Syndrome (GBS), dizziness, fainting, ringing ears, vision impairment	CDC 2020a
17	Rotavirus	Mild diarrhea, irritability, vomiting, intussusception	CDC 2020a
18	Td (adult tetanus and diphtheria)	Pain/swelling at injection site, diarrhea, vomiting, headache, stomachache, nausea, mild fever, fatigue, dizziness, fainting	CDC 2020a
19	Tdap (tetanus, diphtheria, acellular pertussis)	Pain/redness/swelling at injection site, fatigue, headache, stomachache, vomiting, diarrhea, mild fever, dizziness, fainting	CDC 2020a
20	Varicella (chickenpox)	Pain/rash/redness at injection site, fever, pneumonia, encephalitis, meningitis, seizures, rash, possible development of shingles, ringing ears, vision impairment, dizziness, fainting	CDC 2021b
21	Yellow fever	Pain/redness/swelling at injection site, headache, muscle pain, fever, encephalitis, meningitis, GBS, organ dysfunction or failure, dizziness, fainting	CDC 2020a
22	Zoster (shingles), and recombinant zoster vaccine (RZV)	Pain/swelling/redness at injection site, stomachache, nausea, fatigue, nausea, chills, muscle pain, GBS, dizziness, fainting	CDC 2020a
23	Adenovirus	Diarrhea, cough, sore throat, upper respiratory tract infection, stuffy nose, joint pain, abdominal pain, headache, nausea, fever, blood in urine or stool, stomach and intestinal inflammation, pneumonia	CDC 2020a
24	Anthrax	Pain/redness/itching/lump/bruise at injection site, headache, fatigue, muscle ache, short-term trouble with arm mobility, dizziness, ringing in ears, vision impairment, fainting	CDC 2020a
25	Cholera	Vomiting, nausea, inappetence, fatigue, headache, abdominal pain	CDC 2020a
26	Japanese encephalitis	Pain/tenderness/swelling/redness at injection site, fever, headache, muscle pain, dizziness, fainting, ringing ears, impaired vision	CDC 2020a
27	Typhoid	Pain/redness/swelling at injection site, general discomfort, diarrhea, fever, vomiting, nausea, headache, fever, dizziness, fainting, vision impairment, ringing ears	CDC 2020a

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yield. The formulation in which to suspend the antigen and keep it fully functional is also made. It is challenging to go through all these processes and get the mix just right and can take several years to complete (Heaton, 2020). After production, the immune response is gauged by clinical laboratory assays to measure antibody quantity and quality and other measures of immunological response like CD8+ T cell stimulation (Heaton, 2020). Another challenge in the vaccine production process is that, as with other chemotherapeutics, large clinical trials with several thousand subjects are required to ascertain safety and efficiency. And this safety is monitored long after administration of the vaccine and deep into public vaccine administration. All of these make it cumbersome to produce a vaccine.

(v) Microbial Mutation, Variation, and Evolution: We discussed in section 3 that with LAVs, there is the risk that an attenuated pathogen reverts to its virulent form, and this is a huge challenge. WIVs have a risk for virulence only if the attenuating treatment is not thorough enough. Genetic variability among pathogens of the same group also makes it challenging to make a vaccine to cover infections from all members of the group. For example, there are more than 160 pathogenic strains of rhinovirus, and they have significant genetic diversity, which makes it challenging to produce a rhinovirus vaccine that elicits cross-protective immunity (Poland & Barry, 2009). Furthermore, antigenic drift and antigenic shift make it difficult to make long-term vaccines against pathogens such as influenza viruses. Antigenic drift occurs when there is a change in the surface protein, hemagglutinin, and neuraminidase of the pathogen, caused by minor but consequential genetic changes. In antigenic shift, the pathogen combines genetic material with another pathogen of the same or different species, leading to the development of a mutant strain having genetic properties of both strains. Mutation can occur in the genetic sequence of any living organism or viral particle, and this can pose a challenge. Some, such as HIV, and the aforementioned influenza viruses mutate faster than others. This necessitates the production of new vaccines against new strains from time to time. Moreover, as living organisms, pathogens have their various adaptation mechanisms which can make it daunting to target them with vaccines. An example is *Plasmodium falciparum* which has varied developmental stages that necessitate different kinds of immune responses rather than the one-size-fits-all approach of vaccines (Kennedy et al, 2020). As part of their survival mechanisms, pathogens adopt reciprocal defense mechanisms to every method devised to destroy them. These mechanisms have been found against vaccines as well, as vaccine-induced pressure from the heptavalent vaccine has been associated with serotype changes (Hanage et al, 2020).

(vi)Challenges Arising From Global Demand: Vaccines have specific maintenance requirements that may not be met in resource-deprived settings and communities with poor maintenance culture. For instance, societies with unstable power supply may not guarantee constant refrigeration of LAVs, which need constant refrigeration. This will affect the effectiveness of the vaccines. In contrast, many other chemotherapeutic tablets and suspensions are unperturbed at room temperature, giving them an advantage over vaccines in this regard. Likewise, providing vaccines for resource-deprived settings is a burden on the global vaccination agenda. This lack of access to vaccines by resource-deprived communities causes a relapse in vaccine success in countries with access to vaccines (UNDP, 2021). And the high demand for vaccines as their importance is being realized further pressures an already challenging production process.

Discussion and Conclusion

Disease pathogens cause many infections and cancer (Sokefun & Akinnola, 2020). Mortality rates due to infectious disease were much higher before antibiotics were discovered than after. But antibiotics were only discovered in the 20th century. Therefore, man relied mostly on natural and unstandardized remedies to fight pathogens for thousands of years in the pre-antibiotic era, and especially before vaccination became a standard public health requirement. We can only imagine with a shudder how prone society was in contracting and transmitting deleterious infections at that point in history. Concerted global vaccination efforts helped to eradicate smallpox, a disease with such grievousness that the twenty-first century man can barely imagine. Vaccines have helped to significantly reduce disease burden and make the world safer from an epidemiological standpoint and their use ought to be promoted. Increased access of developing countries to vaccines and wider reach of vaccines to developing societies will further minimize the risk of infection and mortality rates, especially of susceptible members in a population. And it will stop drawing back vaccine efficiency in well-vaccinated societies. On the other hand, the sudden emergence of the COVID-19 pandemic shook up the world and crippled day-to-day life. This led to the rapid production and approval of vaccines to save lives. But the speed at which the vaccines were manufactured and approved, coupled with other sketchy events surrounding the COVID-19 generated a lot of controversy and conspiracy theories about the COVID-19 origins and the vaccines produced. Although the vaccines helped in minimizing the spread and destruction of the disease, these feelings persisted. We showed in this review that vaccines have existed for thousands of years and

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have been administered globally since the 19th century. We described aspects of the vaccine production process that may not be well-publicized, and the ingredients in vaccines. We discussed the classes of vaccines and their production steps. Before vaccines are approved for use, they go through rigorous safety tests, and quality control and improvement continue at all stages of production and beyond. Furthermore, we showed some benefits and challenges of vaccines. Vaccines prevent 3.5 to 5 million deaths from vaccine-preventable diseases annually. They are second only to clean drinking water in reducing infectious disease worldwide (Plotkin, 2009). They are the cheapest and fastest way to generate communal and global immunity to disease, as shown in the curbing of the COVID-19. Not only do they help to prevent a disease in the present, but also the memory that they give the body in recognizing the pathogen and preventing the same infection in the future distinguishes them from other drugs. Though they have some disadvantages and challenges, but their advantages far outweigh the disadvantages. Think for instance how having a clinical COVID-19 infection would compare with the sting of an injection, or how paralysis from poliomyelitis would compare with a short fever from the polio vaccine. In conclusion, we strongly recommend continuous and all-inclusive vaccination as a way to minimize and potentially eradicate infectious diseases.

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