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Chapter

The Silver Lining of the COVID-19 Pandemic: Fast-Tracked Vaccine Production and Approval

Wilson Lewis Mandala

Abstract

From the time when the smallpox vaccine was successfully produced in 1798, vaccines have proven to be the most reliable means for preventing and controlling most infectious diseases because they significantly reduce morbidity and mortality associated with life-threatening infectious diseases. During the pre-COVID-19 era, the development, testing, and final approval for vaccines would take as long as thirty years and this was regarded as a normal procedure by most regulatory bodies. However, the devastating COVID-19 pandemic witnessed the development and approval of several vaccines in just six months from when the first SARS-CoV-2 case was reported in Wuhan, China. The speed and apparent ease with which the COVID-19 vaccines have been produced and approved has introduced a paradigm shift in the vaccinology field, creating an environment within which the production of vaccines for most infectious disease now seems possible. This chapter delves into the vaccine production and approval process and discusses the benefits of vaccines, the types of vaccines, and how they work. It also explores how lessons from the COVID-19 pandemic can contribute toward the expedited development, trial, and approval of vaccines against other devastating diseases of equally high, if not higher, mortality rates such as HIV/AIDS, TB, and malaria.

Keywords: vaccines, COVID-19, HIV/AIDS, tuberculosis, malaria

1. Introduction

Over the years, vaccines have proven to be one of the most reliable means for preventing, controlling, and, in some cases, eliminating a number of infectious diseases. Where they have been used appropriately and administered at the right age and stage, both morbidity and mortality associated with the disease against which individuals have been vaccinated have been reduced or even eliminated [1]. Prior to the COVID-19 pandemic era, the development, testing, and ultimate approval of vaccines would take as many as 10 or even 30 years [2, 3]. However, the sudden advent of the COVID-19 pandemic witnessed the development of over a hundred vaccines against the viral disease (Table 1) some of which have already been approved (refer to Section 7.1) for use and have successfully saved millions of lives. More importantly,
the COVID-19 pandemic also experienced an astronomically expedited approval process for the new vaccines with some, such as the Pfizer COVID-19 vaccine, approved for use globally just after 6 months (Figure 1) from when the first SARS-CoV-2 case was officially detected and reported in Wuhan, China [3]. The speed at which these COVID-19 vaccines have been produced and approved has brought about a paradigm shift in the vaccinology world which some scientists and policymakers feel has completely revolutionized the vaccine development field. However, this watershed moment also raises some pertinent questions such as: are there any short-term and/or long-term effects on individuals who take such “seemingly” fast-tracked vaccines? Why have the vaccine-producing Pharmaceutical companies not been able to produce vaccines for other equally important and devastating infectious diseases such as HIV/AIDS, TB, and malaria in the past at an equally fast pace? Are there lessons or emerging innovative ways from the COVID-19 vaccine production platforms that could be used in an attempt to expedite the production of vaccines for these other infectious diseases?

![Figure 1](image)

**Figure 1.** Estimate duration (in years) from the time of establishing the causative link between a pathogen and the related disease to the time when a fully developed and tried vaccine is approved and licensed for use (adapted from Ball [4]).

<table>
<thead>
<tr>
<th>Vaccine platform</th>
<th>Number of vaccine candidates</th>
<th>% Total candidates</th>
</tr>
</thead>
<tbody>
<tr>
<td>1  Protein subunit</td>
<td>43</td>
<td>34</td>
</tr>
<tr>
<td>2  Viral vector (non-replicating)</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>3  DNA</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>4  Inactivated virus</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>5  RNA</td>
<td>21</td>
<td>17</td>
</tr>
<tr>
<td>6  Viral vector (replicating)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>7  Virus-like particle</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>8  rVV + APC</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>9  Live attenuated virus</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>10 nrVV + APC</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

**Table 1.** Number (and percentage of the total) of different COVID-19 vaccines categorized based on the platform used to produce them (rVV = replicating viral vector, nrVV = non-replicating viral vector, APC = antigen-presenting cell).
diseases that have been around for much longer than COVID-19? This chapter looks into the vaccine development world and highlights what can be adapted from the manner and speed at which the COVID-19-specific vaccines have been produced and approved.

2. History of vaccines

Vaccines are biological agents that can be used to safely induce an immune response against a specific antigen that is either derived from an infectious disease-causing pathogen or that is artificially manufactured [5]. Once the immune system is successfully and safely stimulated to respond to a vaccine, the vaccination process confers protection against infection or disease on subsequent exposure to that specific pathogen [5]. Edward Jenner is credited to have developed the very first vaccine in 1796–1798 using cowpox to inoculate humans against smallpox [6]. Prior to that, variolation, which was the ancient practice of inoculating human beings with biological material from an infectious disease-causing agent, was already in practice in various countries such as India, Turkey, and China centuries before Jenner’s groundbreaking experiments [6].

Although Jenner’s smallpox vaccine ended up being successfully used in various countries, the actual vaccination then was done from person to person with the biological material collected from one already vaccinated individual used to vaccinate others who were yet to be vaccinated [7]. The modern mode of vaccinating individuals was eventually developed by Louis Pasteur who developed vaccines by using agents extracted from disease-causing pathogens such that the effective vaccines against chicken cholera and human rabies in 1885 are accredited to him [7].

The next major innovation was the development of vaccines based on killed pathogens, which was done by two American scientists Daniel Elmer Salmon and Theobald Smith [6, 7]. This landmark was then followed by the vaccine development against typhoid, human cholera, and plague just before the end of the nineteenth century. Since then, many more vaccines have been developed as outlined in Figure 2.

During the twentieth century, vaccines against infectious diseases such as influenza and rotavirus were developed and these were either live attenuated, whole killed pathogens, or subunit vaccines that contained antigens such as protein, polysaccharides, or conjugated without the rest of the pathogen. In 1986, the first genetically engineered vaccine was developed and this was against Hepatitis B [7].

3. General composition of vaccines

The sole aim of vaccinating an otherwise healthy individual is to stimulate, pre-arm, and prepare the immune system in readiness for subsequent infections or diseases [5]. As such, the composition of each vaccine is essential as each primary ingredient is meant to be identified, recognized, responded to, and remembered by the highly developed and evolved human immune system during subsequent infections by the pathogen vaccinated against [7]. This being the case, the primary components of essentially all vaccines are protein antigens (with the exception of a few especially the polysaccharide vaccines) that are derived from the pathogenic organism that causes the infection one is being vaccinated against or synthetic antigens that
resemble components of the pathogens that are manufactured [8]. In addition, vac-
cines would normally have natural or added adjuvants, which assist in boosting the
immune response to the vaccine (immunogenicity).

Whereas the antigenic component of the vaccine directly induces the adaptive
immune response toward a specific pathogen, in turn the adjuvants interact with the
innate immune system through the pattern recognition receptors (PRRs) that recog-
nize pathogen-associated molecular patterns (PAMPs) [9]. They would also contain
stabilizers that maintain the stability and effectiveness of the vaccine after vaccine
manufacture and during the storage period, some antibiotics aimed at preventing
contamination during manufacturing stage, and emulsifiers such as polysorbate 80
and preservatives which protect any bacterial or fungal growth in the vaccine during
the manufacturing and storage stages [8]. Various other products that are used during
the vaccine manufacturing process sometimes end up as trace components of the
vaccine and these include egg or yeast proteins, formaldehyde, and acidity regulators
among other things [5].

4. How vaccines work

Vaccination, which is synonymous with vaccine administration, is the process
whereby a biological product (natural or manufactured) from a known pathogenic
organism is deliberately introduced into the body of an otherwise healthy human
being with the aim of inducing the individual’s immune response so as to confer pro-
tection against subsequent infections or disease caused by the specific pathogen [5, 8].

Once a vaccine is introduced into the body, its antigens are recognized by the
host’s antigen-presenting cells (APCs) such as dendritic cells (DCs), macrophages,
Langerhans cells, and B cells. Antigen recognition is mediated in part by a set
of proteins known as pathogen-associated molecular patterns (PAMPs) that are
recognized by cognate proteins such toll-like receptors (TLRs) on the APCs’
surfaces known as pattern recognition receptors (PRRs) [8]. While the antigen
directs the specificity of the adaptive immune response against a specific pathogen,
the adjuvants stimulate the innate immune response through the interaction of the
PRRs and the PAMPs [9].

Once phagocytosed, internalized antigens are processed (digested) into peptide
fragments and displayed on a major histocompatibility complex (MHC) either Class I
(for CD8+ T cells) or Class II (for CD4+ T cells). Vaccine antigens that are produced in
or enter the cytoplasm, such as live-attenuated viruses, are displayed on MHC Class I
in a process known as the endogenous antigen-processing pathway. MHC-Class
I-displayed antigens are recognized by the T cell receptors (TCRs) for CD8+ T cells.
In contrast, antigens that enter cells via a process of phagocytosis such as antigens introduced from killed or inactivated vaccines or recombinant proteins, or antigens that are secreted from infected cells, are displayed on MHC-II by the exogenous antigen processing pathway and are recognized by T-helper (CD4+) cells [5, 10].

The resulting activated APCs that are now presenting vaccine antigens on MHCs migrate to secondary lymphoid organs (SLOs) such as the draining lymph nodes, and spleen where they encounter naïve T cells in the T cell zones [11]. Interaction between antigen-presenting APCs and T cells through MHC/TCR binding leads to the differentiation and proliferation of naïve T cells into effector cells. In response to MHC-II/TCR binding, ligand-receptor interaction, and environmental support from cytokines, CD4+ T-helper (T\(_{\text{H}}\)) cells differentiate into T\(_{\text{H}}\)1, T\(_{\text{H}}\)2, T\(_{\text{H}}\)17, or Regulatory T cells. Of these, T\(_{\text{H}}\)1 cells secrete IFN-\(\gamma\), which in turn stimulate the activation and expansion of cytotoxic T cells, whereas T\(_{\text{H}}\)2 predominantly secrete other cytokines such as IL-10, IL-4, IL-5, and IL-13 [5].

In contrast, following TCR/MHC-I interaction and help from T\(_{\text{H}}\)1 cells through INF-\(\gamma\), CD8+ T cells differentiate into cytotoxic cells, which serve in part to recognize and eliminate infected cells thereby protecting the host against intracellular pathogens such as viruses. In addition to the effector cells that are generated in response to the presentation and recognition of vaccine antigens, both CD4+ and CD8+ cells also differentiate into memory cells such as central memory and effector memory among others. The memory cells are essential in responding and expanding the clonal pool upon antigen re-stimulation or subsequent encounter with the pathogen [12].

In addition to IFN-\(\gamma\) production, T\(_{\text{H}}\)1 cells are also involved in the production of IgG\(_1\) and IgG\(_3\) antibodies by different B cell subsets [5], whereas T\(_{\text{H}}\)2 cells secrete IL-4, IL-5, and IL-13, which promote the development, maturation, and differentiation of B cells into memory B cells (MBCs) and antibody-secreting plasma cells (PCs). The two other subsets of T cells, follicular T helper (T\(_{\text{F}}\)H) and T\(_{\text{H}}\)17, are essential for the generation of high-affinity antibodies and mucosal immunity, respectively. T\(_{\text{F}}\)H regulates B cell affinity maturation, selection of high-affinity germinal center (GC) B cells, and the duration of GC reaction [13, 14]. In turn, durable GC reaction favors the differentiation of GC B cells into high-affinity MBCs and antibody-secreting long-lived PCs (LLPCs) [5, 13].

MBCs are fundamental in vaccine-induced immunity since they can rapidly expand and differentiate into antibody-secreting plasma cells (ASPCs) upon re-encountering antigen thereby rapidly providing robust protection against disease-causing pathogen from where the antigen originated [5, 10]. LLPCs move from the draining lymph nodes (dLNs) germinal centers to the bone marrow to produce antibodies over a period ranging from few months to decades [12]. In addition, these LLPCs are terminally differentiated and, in contrast to MBCs, do not require reactivation or antigen re-encounter for them to produce antibodies. It is the high levels of neutralizing antibodies produced by LLPCs, which protects an individual against reinfection [5]. B cells, acting as APCs, are capable of recognizing and responding to vaccine antigen prior to engaging with T\(_{\text{H}}\)1 cells in what is known as T cell-dependent B cell activation. Just as is the case with the classical APCs, following vaccine administration, B cells recognize and internalize antigens and upon pattern recognition receptors (PRRs) activation differentiate into short-lived antibody-secreting cells, plasmablasts, that produce the first wave of antibodies. However, in the absence of help from T\(_{\text{H}}\)1 cells, B cells do not proceed to a stage of class switching into high-affinity antibody IgG secreting cells but instead will continue to secrete low-affinity IgM [8].
5. Types of vaccines

There are different ways of grouping vaccines depending on which characteristics are used. They can either be categorized as already licensed vaccines or those that are still being researched [8]. They can also be classified based on their ability to continue replicating once administered to the host such that some would be referred to as live vaccines and others as dead vaccines [5]. Vaccines can also be classified based on the technology platform utilized in producing them. Using this third criterion, vaccines can therefore be divided into the following types with some falling under the so-called Conventional Group and the others regarded as the so-called Next-Generation Vaccines (Figure 3) [8].

5.1 Conventional vaccine technologies

5.1.1 Live-attenuated vaccines

Live-attenuated vaccines, which are also known as replication-competent-attenuated vaccines, are prepared from weakened pathogens the virulence of which has been significantly reduced. The main feature of attenuated pathogens is that they characteristically mimic natural infection as they still maintain the intrinsic ability to infect host cells and replicate further within the host [15]. The main distinguishing feature of this type of vaccine is its ability to maintain the pathogen's replication potential without causing disease or attaining reversion to virulence.

Improved immunogenicity of live-attenuated vaccines is usually achieved through the activation of molecular sensors of the innate immune cells coupled with sustained antigen expression and presentation. Activation of pattern recognition receptors (PRRs) on classical antigen-presenting cells (APCs) such as dendritic cells (DCs) induces the upregulation of costimulatory molecules [16], and increases in the expression of various cytokines which, in turn, results in the differentiation and activation of the T<sub>H1</sub> cells thereby providing more potent cellular immune responses [10]. Most attenuated vaccines, like the one against smallpox which is now also being used in some countries against monkeypox, do not need an adjuvant and a single dose is sufficient to confer lifelong immunity [16]. However, the main disadvantage of these types of vaccines pertains to their potential to cause disease either in normal but most likely in immunocompromised individuals such as those infected with HIV. Although this type of vaccine is labor intensive in its production, they have been used successfully against such viral diseases as Polio and measles for decades (Figure 3).

5.1.2 Whole-inactivated (killed) vaccines

Although usually used interchangeably, the term “killed vaccines” is generally used in reference to vaccines for bacterial diseases, whereas “inactivated vaccines” relates to vaccines meant for viral infections [10]. These types of vaccines are derived from a killed form of virulent pathogens and typically stimulates a humoral-mediated immune response with the killing or inactivation process usually mediated by physical or chemical methods or a combination of the two.

These types of vaccines are comparably safer than the attenuated type since the inactivation or killing prevents any subsequent intra-host pathogen replication and potential gain of function mutations that could lead to reversion to virulence [8, 17].
In addition, these vaccines generate a much broader immune response against multiple targets since the whole pathogen is used during the immunization process. They are also less expensive to produce and because they are more thermostable, they can
be stored for relatively long duration [7]. The main disadvantage of these types of vaccines is that they have limited ability to trigger cellular immune responses against intracellular pathogens. Furthermore, relatively large doses and regular booster injections are required for long-lasting protection due to lower immunogenicity. Although less expensive to produce, these higher doses and regular administration increase potential adverse events and manufacturing costs and reduce vaccine compliance. However, the efficacy of these vaccines can be substantially boosted by increasing the dose or the addition of an adjuvant in the formulation [10]. This type of vaccine has been used against diseases such as Hepatitis A, Zika virus, Poliovirus, Japanese Encephalitis virus, Diphtheria, and Tetanus [17].

5.1.3 Virus-like particles vaccines

Virus-like particles (VLPs) are macromolecular assemblies that are designed to mimic the morphology of a native virus in features such as size, shape, and surface proteins. VLPs can further be divided into two groups based on the presence or absence of a lipid envelope and the number of protein layers forming the capsid [18]. VLP-based vaccines are designed to target B cells and induce potent antibody responses following antigen presentation on MHC-II and activation of $\text{T}_\text{H}1$ cells. The process commences with VLPs being internalized by either classical or follicular dendritic cells or sub-capsular macrophages or B cells. The multivalent epitopes on the VLPs’ surface are then displayed, which facilitate interaction with and crosslinking of B cell receptors (BCR).

Compared with other traditional vaccines, the high potency of this vaccine technology is associated with the multivalent interaction (increased avidity) with cells of the innate immune system, which results in their activation. In the past, this technology has been used to develop the human papillomavirus vaccine and is currently being used to develop vaccines against the Chikungunya, Zika [8], and SARS-CoV-2 viruses [19].

5.1.4 Synthetic peptide vaccines

Peptide-based synthetic vaccines, which are also known as epitope vaccines, are subunit vaccines which are manufactured from peptides. In turn, these peptides mimic the epitopes of the antigen that triggers direct or potent immune responses [20]. These peptide-based synthetic vaccines are relatively safer than live-attenuated or killed vaccines and have demonstrated efficacy against infectious diseases such as Hepatitis C, Influenza and recently COVID-19 [21]. In addition, the vaccines do not have any biological contamination since they are chemically synthesized and the peptides can be accurately designed for specificity. Furthermore, being synthetic, it is possible to design a single peptide vaccine that has multiple epitopes thereby generating immune responses for several diseases simultaneously. However, some of the main disadvantages of these types of vaccines include their poor immunogenicity and their instability once they are intracellular [20, 21].

5.1.5 Toxoid vaccines

Some pathogens, such as bacteria and not viruses, cause disease by secreting an exotoxin, which is responsible for the disease and not the pathogen itself. Examples of these pathogens include those responsible for causing diseases such as tetanus,
diphtheria, botulism, cholera, and pseudomembranous colitis [10]. Toxoid vaccines, which are also known as fractional inactivated vaccines, are derived from the inactivation of such toxins and these vaccines generate an immune response against the disease-causing toxins. Inactivation of the toxin to convert it to a vaccine can be achieved by subjecting the toxins to chemicals such as formaldehyde, which results in altering either the structure of specific amino acids or in inducing minor conformational changes in the toxin structure. This in turn prevents and neutralizes any potential pathologic effects of the toxins on human tissues and also indirectly minimizes the invasiveness of the pathogen thereby rendering it harmless [22].

Since antitoxin responses typically do not target the actual bacterium, vaccine-mediated elimination of the disease-causing bacteria is not achieved. Instead, the bacteria are decolonized either through the normal immune response (with both the innate and adaptive arms involved) or through the use of appropriate antibiotics or via natural competition between the bacterial pathogen and the normal microbiota or a combination of any of these. Toxoid-specific T cell responses are mainly based on T\textsubscript{H}1 cells [23], which then bridge the activation and differentiation of B cells into antibody-producing plasma cells and memory B cells that are essential during secondary infections. The addition of an adjuvant usually improves the efficacy and the longevity of the immune protection of this type of vaccine [23].

5.1.6 Polysaccharide and polysaccharide conjugate vaccines

When early bacteriological studies revealed that many pathogens were surrounded by a polysaccharide capsule and that specific antibodies against this capsule resulted in enhanced phagocytosis of the pathogen, the polysaccharide capsule was therefore considered a potential vaccine candidate [24]. Bacteria with a polysaccharide capsule include \textit{Haemophilus influenzae}, \textit{Neisseria meningitidis}, and \textit{Streptococcus pneumoniae} and these cause infections such as meningitis, sepsis, and pneumonia, which are life-threatening [25]. Polysaccharide vaccines therefore are those that are derived from carbohydrate-based polymers such as peptidoglycans and glycoproteins that form the capsular structure of these pathogenic bacteria.

One drawback of this type of vaccine is that although they are extremely efficacious in adults generating high titers of serum antibodies, polysaccharide vaccines induce very low or have no immunogenicity in children aged less than 2 years [21]. This is the case because polysaccharides, unlike protein segments, are not processed and displayed on MHC molecules but remains T cell-independent [8]. The reason why only adults produce antibodies against these molecules is that a particular subtype of B cells, the marginal zone CD21 + B cells (MZB), which are found in the spleen, is critical in the detection and binding of naked or complement-coated polysaccharide antigens and this type of B cells is not found in infants below 2 years old [26].

This limitation of polysaccharide vaccines is overcome by adding adjuvants and forming glycoconjugates, which successfully results in inducing T cell response and improving their immunogenicity [8]. Polysaccharide conjugates are produced by covalent attachment of the polysaccharide with a carrier protein such as diphtheria or tetanus toxoids with the aim of boosting the vaccine immunogenicity and improving protection in infants and children [27]. With the polysaccharide chain conjugated to a protein, both of these molecules are presented on MHC Class II and this results in the recognition of the antigens by TCR and activation of the T\textsubscript{H} response. The subsequent interaction between T\textsubscript{H} cells and B cells improves titers and the quality of antibodies as well as B cell memory [27].
5.2 Next-generation (modern) vaccine technologies

Although the conventional vaccine platforms have proven to be so successful in the development of some extremely effective vaccines over the past decades, their production and testing process normally takes years (Figure 1). As such, using those classical platforms for developing vaccines against emerging pathogens that have pandemic potential such as SARS-CoV-2 is usually not feasible due to associated manufacturing limitations [28]. In light of this, there has always been a need to develop more modern platforms that could potentially be used to respond rapidly to pandemic threats. Such platforms also need to be versatile enough to be deployed in different parts of the world and can easily be scaled up for industrial production. This is where the so-called next-generation vaccine platforms perform better than the conventional ones. The following are some of these modern vaccine platforms.

5.2.1 Bacterial vectored vaccines

Recently, genetically attenuated microorganisms, pathogenic, and commensal bacteria have been engineered to safely deliver recombinant heterologous antigens to stimulate the host immune system without causing any disease. The main characteristic of these live vectors is their capacity to stimulate humoral and/or cellular systemic immunity as well as mucosal immunity in some cases. As such, the use of this type of vaccines prevents pathogen colonization of mucosal tissues, which is the first point of contact for many infectious pathogens. In addition, delivery of DNA vaccines (refer to Section 5.2.3) and other immune system stimulatory molecules, such as cytokines, can be achieved using these special vectors, whose adjuvant properties and, sometimes, invasive capacities boost the immune response [28].

A good example is the use of live bacterial cells as carriers as one way of producing new vaccines [29]. Bacterial carriers can either be considered as non-pathogenic or pathogenic but attenuated carriers. Since most bacteria utilize the mucous membranes to gain entry into the human body for infection, using them as carriers makes it ideal for the administration of vaccines in the mucosal tissues thereby inducing mucosal immunity. However, one major disadvantage of this type of vaccines, especially when attenuated pathogenic bacteria are used, is the risk of infection, especially in children, the elderly, and immunocompromised individuals such as those infected with HIV. Therefore, non-pathogenic bacteria such as *Lactobacillus* species are considered to be better suited as vaccine vectors [30]. However, genetic engineering has made it possible to identify and delete specific genes responsible for bacterial virulence, which then allows for the attenuation of pathogenic bacteria such as *Yersinia pestis* to be used as vectors that cannot regain virulence [31]. Furthermore, as one way of improving antigen presentation for this type of vaccine, simultaneous expression and secretion of cytokines have been incorporated and this has improved the vaccine-induced immune response by both the innate and adaptive immune systems and also boosted immunological memory [32].

5.2.2 Viral vector-based vaccines

Viral vector-based vaccines are derived from viruses, which are genetically engineered to encode genes for one or several antigens cloned into the vector backbone. Viral vectors can either be engineered to be replication-deficient (replication incompetent), but still maintain their ability to infect cells and express
the encoded antigen. On the other hand, replication-competent vectors are still capable of replicating and as such, they are considered to be similar to the classical live-attenuated vaccines [8].

This type of vaccine mimics natural infection to generate potent humoral and cellular (both T_H and T_C cells) responses [33]. In addition to being highly immunogenic, viral vector-based vaccines are easier to manufacture, and in some cases, safer in comparison with the inactivated, live-attenuated, and recombinant protein technologies. They are designed either for single administration or as a component of a mix-and-match heterologous vaccine regimen due to the strong immune response that they induce [34].

The main challenges with these vaccines include pre-existing immunity to the viral vector and reduced efficacy of subsequent administrations due to antivector immunity. In the case of SARS-CoV-2, vaccines were developed using vectors with low seroprevalence such as human adenovirus serotype 26 (Ad.26) used by Janssen/Johnson & Johnson and chimpanzee adenovirus (ChAd) vector used by Oxford/AstraZeneca. The vaccines were well tolerated and demonstrated an overall efficacy of 66% and 75% respectively in preventing symptomatic COVID-19 disease [35–38].

5.2.3 Synthetic DNA vaccines

DNA vaccines are relatively larger than mRNA, which tend to be polyanionic and sensitive to nuclease characterized by lower efficiency of passive entry into cells. Previous work has shown that synthetic DNA (SynDNA) that is delivered into the muscle is capable of transfecting different cell types including myocytes, keratinocytes, and tissue-resident APCs [39, 40]. Once it is internalized, DNA is translocated into the nucleus and transcribed into messenger RNA (mRNA), and the mRNA is then exported back into the nucleus for protein translation with the aid of ribosomes [21] and it is this nascent protein that serves as an antigen. Just as with exogenous antigen, this internally generated antigen can be presented on both MHC-I and II, which in part triggers a robust T cell response.

Tissue-resident APCs expressing the antigen of interest can move directly to the draining lymph node to initiate immune responses. In contrast, antigen expression on myocytes may generate immune responses by translation and secretion of the antigen into the local environment. This promotes the uptake and MHC class II-related cross-presentation by un-transfected APCs. B cells may also recognize secreted or shed protein, leading to their T cell-independent activation [40]. Irrespective of being secreted or shed, the soluble antigen can drain to lymph nodes, extending antigen presentation locally and in distal tissues, resulting in improved germinal center reactions and re-expansion of lymph-node primed CD4+ and CD8+ T cells. Transfected myocytes upregulate MHC-I and other co-stimulatory molecules such as CD80, and may contribute to T cell responses by priming naïve CD8+ T cells [41].

The fact that synDNA vaccines can induce both humoral and the cellular components of the immune responses is one special characteristic that improves their efficacy from that of the conventional vaccine technologies. Compared with the conventional inactivated, attenuated, and recombinant subunit vaccine platforms, synDNA vaccines are faster, cheaper, and easier to manufacture [42] and this makes this platform, as well as the mRNA one (Refer to Section 5.2.4), ideal for use in developing a vaccine in a pandemic setting. In addition, they can easily be lyophilized and are thermostable exhibiting much higher pharmaceutical stability than conventional inactivated or attenuated vaccines attributes that make them ideal for long-term
storage under field conditions [8]. Although earlier studies raised some safety concerns with the persistence of synthetic DNA in the nucleus with an enhanced probability of integrating into genomic DNA (gDNA), recent experimental data suggest that this risk is extremely minimal. Despite positive clinical data, no DNA-based vaccine is licensed for human use as yet against any disease most likely because the generation of robust B and T cell responses requires at least a prime, and two or three boosters. However, about 14 DNA vaccine candidates for COVID-19 are currently under clinical trials (Table 1).

5.2.4 mRNA-based vaccines

The concept of mRNA-based therapeutics is not new since over three decades ago some researchers [43–45] successfully showed that mRNA extracted from cells and in vitro transcribed (IVT) mRNA could be delivered to cells and animals for protein expression. Despite encouraging results from subsequent studies, major limitations such as potent inflammation and reduced in vivo translation due to mRNA’s short half-life were quickly recognized. Once these challenges were overcome, the platform improved enabling the successful development of mRNA vaccines and/or adjuvants, which elicited both antigen-specific cytotoxic T (Tc) cell and humoral responses [46].

mRNA vaccines can be divided into three major categories: conventional mRNA, self-amplifying mRNA (SAM), and circular RNA (circRNA). Conventional in vitro transcribed (IVT) mRNAs are relatively simple in their architecture and manufactured at a high yield using a cell-free template-directed enzymatic synthesis [47]. Depending upon the use of nucleoside modifications during manufacturing and synthesis, the conventional mRNA vaccine platform can be further divided into nucleoside-modified or non-modified mRNA. Nucleoside modifications have proven essential in successful clinical application of conventional mRNA vaccines. The significance of nucleoside modifications in ensuring the success of this platform was indicated by data for the COVID-19 vaccine from CureVac that showed disappointing results (47% protection compared to over 94% with the Pfizer/BioNTech and Moderna’s vaccines). This significant difference in efficacy has been attributed to CureVac using unmodified mRNA, which has higher innate immunogenicity than nucleoside-modified mRNA [48].

As the name suggests, self-amplifying mRNA is engineered to include viral-derived molecular machinery such as alphavirus-derived replicases and conserved sequence elements (CSEs) to enable intracellular amplification of the mRNA sequence once it is administered [49]. The presence of replicate enzymes facilitates replication of the mRNA vaccine in the cytoplasm, resulting in efficient and long-lived transcription and protein expression. Since SAMs are relatively larger in size, their manufacturing is more complex and challenging compared with the conventional mRNA vaccines due to low yield, difficulty in purification, and susceptibility to autocatalysis and physical degradation. circRNA is a class of non-coding single-stranded RNAs generated through a non-canonical splicing event known as backsplicing in eukaryotic cells [50]. Some [51] have shown that circRNA generates potent antigen-specific CD4+ and CD8+ cellular and humoral immune responses in mice against SARS-CoV-2 and its emerging variants, therefore providing proof of concept for vaccine applications.

Immune responses to the mRNA vaccines are heavily dependent on the delivery system used [47], the immunogenicity of the encoded antigen, and the longevity and subcellular localization of antigen expression. This being the case, if these vaccines
are delivered intramuscularly or intradermally, they tend to be highly immunogenic with the additional benefit of inducing local cytokine and chemokine production that initiates prompt recruitment of neutrophils, monocytes, and other cells to prime the immune responses. In contrast to synDNA, mRNA vaccines are directly translated into the cytoplasm, and the ensuing proteins are processed and presented in MHC class I and class II, followed by the presentation to CD8+ (T<sup>C</sup>) cells and CD4+ (helper) T cells in the draining lymph nodes. Compared with DNA vaccines, the expression kinetics of mRNA vaccines is much faster, with the onset typically peaking 4 h after administration and this is the case because mRNA does not need to enter the nucleus. In comparison with viral and synDNA vaccine platforms, mRNA presents virtually no risk of integration into the genomic DNA, is more cost-effective, and is relatively easy to manufacture. That is what makes this platform so ideal for rapid vaccine production during a pandemic setting.

6. Vaccines production, testing, and approval process

6.1 Production

Different types of vaccines as highlighted in Section 5 are produced in different ways. However, the general outline of vaccine manufacturing generally comprises several basic steps that result in the finished product [52]. The first step is the generation of the antigen which is supposed to induce an immune response. This step includes the generation of the pathogen itself (for subsequent inactivation or isolation of a subunit) or the generation of a recombinant protein derived from the pathogen. In the case of viral vaccines, the viruses are grown in cells, which can be either primary cells, such as chicken fibroblasts (a good example is that of yellow fever vaccine), or continuous cell lines. In contrast, bacterial pathogens are grown in bioreactors using a medium developed to optimize the yield of the antigen while maintaining its integrity. Recombinant proteins can be manufactured in bacteria, yeast, or cell culture. The viral and bacterial seed cultures and the cell lines used for viral production are carefully controlled, stored, characterized, and, often, protected. The first step in manufacture is the establishment of a “master cell bank.” From this bank, working cell banks are prepared that are used as the routine starting culture for production lots. The final vaccine is a direct function of its starting materials, and a change in this seed can be as complicated as initiating a new product development altogether [52].

The next step aims at releasing the antigen from the substrate and isolates it from the bulk of the environment used in its growth. This can be the isolation of free virus or of secreted proteins from cells or of cells containing the antigen from the spent medium and this is followed by the purification of the antigen [52]. For vaccines that are composed of recombinant proteins, antigen purification may involve many unit operations of column chromatography and ultrafiltration. For an inactivated viral vaccine, there may simply be the inactivation of viral isolate with no further purification. The formulation of the vaccine is designed to maximize its stability while delivering it in a format that allows efficient distribution. The formulated vaccine may include an adjuvant to enhance the immune response, stabilizers to prolong shelf life, and even preservatives to allow multidose vials to be delivered [53].

The formulation consists of combining all components that constitute the final vaccine and uniformly mixing them in a single vessel and this is done in a highly controlled environment to avoid contamination. During this phase, individual, thoroughly
cleaned, depyrogenated, single-dose, or multidose containers are filled with vaccine and sealed with sterile stoppers or plungers. If the vaccine is to be lyophilized, the vial stoppers are only partially inserted so that moisture can escape during the lyophilization process, and the vials are moved to a lyophilization chamber. All vials receive outer caps over the stopper for container closure integrity [54]. In order to eliminate the introduction of extraneous viable and nonviable contamination, all filling operations are usually done in a highly controlled environment where people, equipment, and components are introduced into the critical area in a controlled manner. After filling, all containers are inspected using semiautomated or automated equipment designed to detect any minute cosmetic and physical defects. As with the formulation phase of the vaccine manufacturing operation, extensive control and monitoring of the environment and critical surfaces are conducted during operations. Quality control testing at this stage also consists of safety, potency, purity, sterility, and other assays that may be specific to the product. Storage at very low temperatures within the manufacturing supply chain may be used to reduce potency loss during storage [55].

6.2 Testing, approval and post-approval regulation

Vaccines are developed, tested, and regulated in a similar manner to other drugs based on stringent guidelines set by various regulatory bodies including the World Health Organization (WHO), the European Medicines Agency (EMA), and the United States Food and Drug Administration (USFDA) to name a few. However, in most cases vaccines are even more thoroughly tested than non-vaccine commodities firstly because the number of human subjects in vaccine clinical trials is usually greater and secondly because vaccines are normally administered to individuals who are not ill at the time of vaccination. The process of testing and approving new vaccines is generally divided into various stages but most regulatory agencies across the world usually divide it into preclinical (involving in vitro and in vivo testing in animals and generally exploratory in nature) and clinical (which involved clinical trials in human participants) stages (refer to Figure 4). However, regulation and oversight increase as the candidate vaccine gradually progresses through the process [57–61].

6.2.1 First stage: laboratory and animal studies

6.2.1.1 Exploratory stage

This stage involves basic laboratory research and often lasts 2–4 years (Figure 4). At this stage, scientists identify natural or synthetic antigens that could help prevent or treat a disease. These antigens may include virus-like particles, weakened viruses or bacteria, weakened bacterial toxins, or other substances derived from pathogens [58].

6.2.1.2 Preclinical stage

Preclinical studies use tissue-culture or cell-culture systems and animal testing to assess the safety of the candidate vaccine and its immunogenicity, or ability to provoke an immune response (Figure 4). Animal subjects may include mice and monkeys. These studies give researchers an idea of the cellular responses they might expect in humans. They may also suggest a safe starting dose for the next phase of research, as well as a safe method of administering the vaccine [58–60]. Researchers may adapt or modify the candidate vaccine during the preclinical state to try to make
it more effective. They may also do some challenge studies on the animals by vaccinating the animals and then infecting them with the target pathogen. Many candidate vaccines never progress beyond this stage, because they fail to produce the desired immune response. The preclinical stages often last 1–2 years and usually involve researchers in both private and public industries.

6.2.1.3 Investigational New Drug (IND) application

Under this stage, a sponsor, usually a private company, submits an application for an Investigational New Drug (IND) to a respective regulatory body such as the U.S. Food and Drug Administration. The sponsor describes the manufacturing and testing processes, summarizes the laboratory reports, and describes the proposed study. An institutional review board, representing an institution where the clinical trial will be conducted, must approve the clinical protocol [61]. Once the IND application has been approved, the vaccine is subject to three phases of testing.

6.2.2 Second stage: clinical studies with human subjects

6.2.2.1 Phase I vaccine trials

This first attempt to assess the candidate vaccine in humans involves a small group of adults, usually between 20 and 80 subjects. If the vaccine is intended for children, researchers will first test adults and then gradually step down the age of the test subjects until they reach their targeted age group. Phase I trials may be non-blinded (also known as open-label in that the researchers and perhaps subjects know whether a vaccine or placebo is used).
The main goals of Phase I testing are to assess the safety of the candidate vaccine and determine the type and extent of immune response that the vaccine provokes. In a small minority of Phase I vaccine trials, researchers may use the challenge model, attempting to infect participants with the pathogen after the experimental group has been vaccinated. The participants in these studies are carefully monitored, and conditions are carefully controlled. In some cases, an attenuated, or modified, version of the pathogen is used for the challenge. A promising Phase I trial vaccine candidate will progress to the next stage [58–60].

6.2.2.2 Phase II vaccine trials

A larger group of several hundred individuals participates in Phase II testing. Some individuals may belong to groups at risk of acquiring the disease. These trials are randomized and well controlled, and include a placebo group. The goals of Phase II testing are to study the candidate vaccine's safety, immunogenicity, proposed doses, schedule of immunizations, and method of delivery [58–60].

6.2.2.3 Phase III vaccine trials

Successful Phase II candidate vaccines move on to larger trials, involving thousands to tens of thousands of people. These Phase III tests are randomized and double-blind, and involve the experimental vaccine being tested against a placebo. One of Phase III's goals is to assess vaccine safety in a large group of people. Certain rare side effects might not surface in the smaller groups of subjects tested in earlier phases. A good example is that an adverse event related to a candidate vaccine could occur in 1 of every 10,000 people. To detect a significant difference for a low-frequency event, the trial would have to include 60,000 subjects, half of them in the placebo group [62].

Vaccine efficacy is also tested and the factors tested could include whether the candidate vaccine can prevent infection from the pathogen of interest and whether the infection leads to full-blown disease. More importantly, this stage also checks if the vaccine candidate leads to the production of antibodies or other types of protective immune responses related to the pathogen.

6.2.3 Third stage: approval and licensure

After a successful Phase III trial, the vaccine developer is expected to submit a Biologics License Application (BLA) to an appropriate regulatory body such as the USFDA, EMA, or WHO, which would then inspect the factory where the vaccine will be made and approve the labeling of the vaccine. After licensure, the regulatory body will continue to monitor the production of the vaccine, including inspecting facilities and reviewing the manufacturer's tests of lots of vaccines for potency, safety, and purity. The regulatory body has the right to conduct its own testing of manufacturers' vaccines [58–60].

6.2.4 Fourth stage: post-licensure monitoring of vaccines

A variety of systems monitor vaccines after they have been approved. They include Phase IV trials, the Vaccine Adverse Event Reporting System (VAERS), and the Vaccine Safety Datalink.
6.2.4.1 Phase IV trials

Phase IV trials are optional studies that drug companies may conduct after a vaccine is released. The manufacturer may continue to test the vaccine for safety, efficacy, and other potential uses.

6.2.4.2 VAERS

EMA (as well as individual EU member countries), USFDA and other regulatory bodies have established the Vaccine Adverse Event Reporting System (VAERS) with the aim of “detecting possible signals of adverse events associated with vaccines.” A signal is regarded as evidence of a possible adverse event that emerges in the data collected being collected after a vaccine has been approved for us. Roughly, close to 30,000 events are reported each year to VAERS globally and as many as 15% of these reports describe serious medical events that lead to hospitalization, life-threatening illness, disability, or death [58–60].

VAERS is a voluntary reporting system such that anyone, including parents or friends of a patient or newly vaccinated individual or health care workers who suspects an association between a vaccination and an adverse event, may report that event and information about it to VAERS. The respective regulatory body then investigates the event and tries to find out whether the vaccination actually caused the adverse event.

7. COVID-19 vaccines: a game changer?

As mentioned earlier, the production of conventional vaccines is essentially based on reproducing the entire or part of the pathogen in some form either as an inactivated, live-but-attenuated, or as a subunit like a recombinant protein [63]. Although these modalities have worked successfully in the past against a number of pathogens such as measles and smallpox, they have had their own limitations. Over the years, advances in technology, immunology, vaccinology, structural biology of pathogens, and new vaccine platforms have contributed to the revolution in the vaccine development world. The success story of the COVID-19 pandemic has been greatly dependent on the earlier discovery that the virus’ spike is the primary surface feature on coronavirus virions responsible for both attachment and entry into target cells [64].

Once the full sequence of SARS-CoV-2 was released, the race was on to develop a vaccine based on the virus’s spike that could elicit the production of high titers of neutralizing antibodies efficaciously enough to control severe COVID-19 disease, hospitalization, and mortality. Currently, over three hundred COVID-19 vaccine candidates are at different stages of development and being tried (Table 1) with the following having already been approved for use by different regulatory bodies; the Pfizer-BioNTech BNT162b2 mRNA vaccine that has a reported efficacy of 95% [65, 66], the Moderna-US National Institutes of Health (NIH) mRNA-1273 vaccine with an efficacy of 94% [66, 67], the AstraZeneca-Oxford ChAdOx1 nCov-19 vaccine that originally had an efficacy of 67% [68], the Gamaleya GamCovidVac [Sputnik V] vaccine with a 91% efficacy [69], and the Johnson & Johnson [J&J] Ad26 COV2.S vaccine with 67% efficacy [66].
7.1 Types of COVID-19 vaccines and related platforms used

As of June 2022, a total of 320 vaccine candidates were in clinical (125) and preclinical (195) development stages globally with different developers using different platforms to manufacture their COVID-19 vaccines (Table 1). Based on history (refer to Figure 1), the fastest any vaccine had been developed in the past from pathogen sampling and identification to vaccine approval was the vaccine against mumps which took 4 years [4, 70]. However, for SARS-CoV-2, which was initially reported in Wuhan China in November 2019, by December 2, 2020, a period of less than a year (Figure 1), the Pfizer-BioNTech BNT162b2 mRNA vaccine with reported efficacy of 95% became the first fully-tested immunization to be approved for emergency use [65]. Within days, a few more vaccines were approved for emergency use. A number of factors have contributed to the speed at which these vaccines have been developed, fast-tracked through clinical trials, and approved for use.

One of the reasons for the rapid vaccine production was the knowledge and expertise gained through research conducted over the past years in vaccine production technology, which has largely benefitted from the advances in viral immunology, pathogen structural biology, and the availability of novel vaccine platforms listed in Table 1. For years, researchers had been working on related coronaviruses like the one that causes severe acute respiratory syndrome (SARS) and the ones responsible for the Middle East respiratory syndrome (MERS). Such work had enabled the researchers to gain vast amounts of knowledge on the viruses’ structure, which in turn provided a basis for the development of possible vaccine candidates using various vaccine platforms. As such, by the time COVID-19 was finally declared to be a global pandemic by the World Health Organization (WHO) on March 11, 2020, biomedical and pharmaceutical research and development companies in the USA alone had well over 70 potential SARS-CoV-2 vaccine candidates and vaccine technologies [3].

Funding is the main factor that facilitates and supports all this work. It is well known that the slowest component of the vaccine development process is not actually finding the promising vaccine candidates but testing such candidates, which usually takes years. However, it is not just the availability of funds alone that is fundamental, how such funds are used and the prioritized activities being funded are just as important. Such tests would normally start with trying the vaccine candidates in animals before shifting to the three-phase clinical trials in humans and all this requires huge amounts of money. The billions of dollars that were promptly made available by world governments and international organizations made it possible for most pharmaceutical companies to expedite the process in some cases, as was the case with Pfizer/BioNTech, conducting their Phase 3 efficacy trials in 150 sites in USA, Argentina, Brazil, South Africa, Germany, and Turkey [65].

The third factor is somehow linked to funding but is mainly based on the global response to previous epidemics such as Ebola. Some have argued that most wealthy countries, pharmaceutical companies, and international organizations only made the billion-dollars funding available to combat COVID-19 when they realized that their own economies were at risk of being severely devastated if the pandemic could be protracted [4]. This argument is supported by the observed country-based development of COVID-19 vaccines, which included the work of Sinovac and Sinopharm groups in China, India’s Covaxin from Bharat Biotech, and the Russian Gamaleya rAd vaccine [3]. This observation, therefore, could be one of the main reasons why vaccine development for diseases such as malaria, TB, and HIV, which do not pose too much of a problem to wealthy country economies, may not be a priority for funding globally.
The fourth factor is the provision of a conducive environment for the development and approval of any promising vaccine candidates. The US government expedited the formation of public-private partnerships to safely and effectively accelerate the clinical development of the most promising vaccine candidates and also speedily put in place measures that could facilitate conducting of placebo-controlled efficacy and clinical trials of such vaccine candidates in line with the key endpoints and adherence to FDA protocols and guidelines [71, 72].

8. Current vaccine status for other diseases of interest

8.1 HIV/AIDS

Although the first cases of HIV/AIDS were detected in the USA in 1981, it took decades before any promising vaccine was even tried. Although HIV/AIDS has now been around for close to five decades, there have been no approved vaccines for the infection and the only HIV vaccine candidate, the RV144 which was investigated in the Thai clinical trial, has shown some promising results with an efficacy of 31% [73]. Although a number of mRNA vaccine candidates did show some promising results as an alternative to those produced through conventional methods, their further development and potential use have been restricted due to high intrinsic immunogenicity, easy degradation, and inefficacious in vivo delivery [74, 75].

Just as is the case with the various COVID-19 vaccines, an ideal HIV vaccine is expected to induce cell-mediated and humoral immunity. Antibodies that neutralize the virus would provide the first layer of defense, preventing infection of host cells upon virus entry into the body [65]. However, in the event that some virions succeed in evading the neutralizing antibodies, cytotoxic CD8+ T cells should then provide a secondary layer of defense, eliminating the earliest infected cells and preventing the establishment of a latent reservoir of HIV-infected. However, such a vaccine has so far proven to be elusive.

8.2 Malaria

A safe and protective antimalarial vaccine made up of irradiated \textit{P. falciparum} sporozoites was first successfully administered to humans in the year 1973 [76], nearly five decades ago. Due to the complex life cycle of the parasite, three distinct vaccine development approaches that are currently being explored are based on the three distinct stages in the parasite life cycle essentially focusing on delivering antigen-specific vaccines as opposed to attenuated vaccines from live virus isolate [77].

8.2.1 Pre-erythrocytic vaccines candidates

These are designed to elicit a robust immune response that would prevent the sporozoites from invading and destroying infected hepatocytes [77, 78]. To date, the RTS,S/ has proven to be the most successful candidate among these vaccine candidates. The radiated circumsporozoite protein (CS) fused with a Hepatitis B surface antigen has been shown to be immunogenic conferring some protection, especially in children aged five or younger and subsequent trials in three African countries, including Malawi, have so far yielded very promising results [79, 80].
Although RTS,S has shown an efficacy of 55.8% in clinical trials in Africa [80], a new anti-malarial circumsporozoite protein-based vaccine, R21 with a Matrix-M™ (MM) adjuvant, has recently reported as high as 77% efficacy at high-dose adjuvant groups in preliminary clinical trials conducted in Burkina Faso [81]. If subsequent trials currently underway replicate such promising results, the introduction of the R21/MM vaccine could prove to be the turning point in the fight against malaria.

The recent success stories of mRNA-based vaccines against SARS-CoV-2 have prompted some investigators to explore if similar approaches could prove to be equally successful against malaria. A recent study [82] has shown some very promising results with an mRNA-based vaccine, which, similar to RTS,S, relies on *P. falciparum* circumsporozoite protein (PfCSP) to generate an immune response. However, unlike RTS,S, instead of administering a version of the protein directly, this vaccine introduces the mRNA specific for the PfCSP, which the instructs the cells to synthesize their own circumsporozoite protein that triggers a protective response against malaria [82]. Since this approach interrupts the malaria infection at a stage before the parasite reaches the RBCs, results in the mice models show that mRNA confers sterile protection against *P. berghei* making it a very promising vaccine candidate for humans.

### 8.3 Erythrocytic vaccine candidates

These blood-stage vaccine candidates, including PfRH5, are designed to block the rapid invasion of RBCs by the parasites and their fast asexual reproduction once they are in RBCs. Since the blood stage is the stage when malaria-related symptoms manifest, with over 40,000 merozoites released for each infected hepatocyte, this is an important stage to disrupt. An ideal blood-stage vaccine should therefore aim to reduce the number of merozoites infecting RBCs rather than completely block their replication [80]. This being the case, currently there are no blood-stage vaccine candidates that have been as successful as the RTS,S vaccine.

### 8.4 Transmission blocking vaccine (TBV)

These vaccine candidates target the sexual reproduction stages in the mosquito gut to stop the parasite from spreading further. This is an indirect approach to a vaccine since the individual who gets vaccinated is not protected but rather prevents subsequent infections [79, 80]. The Pf25-EPA vaccine candidate is designed on the basis that those vaccinated will produce specific antibodies against the specific antigen so that if a mosquito feeds on this person it will take up some of these antibodies into its stomach. Once they are in the mosquito’s stomach, the antibodies will encounter the antigen, enabling them to interfere with the parasite’s development and ultimately kill the parasite such that when the mosquito has its next blood meal it will not introduce any infectious parasites into the injected person [80].

### 8.5 Tuberculosis (TB)

#### 8.5.1 BCG

*Mycobacterium tuberculosis* (Mtb) is associated with the highest annual mortality globally than any other infectious pathogen, but to date, there is only one licensed vaccine, Bacille Calmette Guerin (BCG) against the disease, and this vaccine has been in use for nearly hundred years. Unfortunately, BCG efficacy wanes in adolescents [83] and is
known to offer little or no protection at all against adult-type pulmonary TB [84]. This being the case, despite universal infant BCG vaccination in all TB-endemic countries, close to 10 million people develop TB annually and of these, 1.6 million die from the infection [85]. As such, a more effective vaccine against TB is urgently needed.

8.5.2 mRNA TB vaccine

In 2004, a mRNA vaccine candidate that encodes the MPT83 antigen was reportedly successful in inducing protective cell-mediated and humoral immune responses against Mycobacterium Tb infection in mice models [86]. The protection was rather modest and was observed to be lower than that conferred by BCG and lasted for only 6 months. Unfortunately, this work has not been followed up since then probably due to the possible difficulties and costly process of developing the vaccine candidate.

8.5.3 DNA TB vaccine candidate

From 1996, well over 60 mycobacterial antigens have been identified as potential vaccine candidates. Subsequent immunization trials in mice using plasmid DNA encoding mycobacterial antigens have successfully triggered a robust T_{H}1 immune response characterized by high levels of IL-2 and IFN-γ [87]. The promising candidates include those based on cfp-10 antigen and ESAT-6 antigen. These vaccine candidates have the advantage that their use poses no risk of infection to the host, allows for antigen presentation to both MHC Class I and class II molecules, which could potentially trigger a much stronger and more robust immune response, are stable during storage, and can potentially elicit long-term immune responses [88]. However, since much of the work on these promising vaccine candidates has only been done on mice models, it is crucial that further research work should be done to determine their efficacy and graduate the most promising candidates to human clinical trials.

9. Conclusion

Vaccines still feature highly as the most effective means of reducing morbidity and mortality of most infectious diseases. In this COVID-19 pandemic era, they have once again proven to be the most reliable means of control against highly transmissible infectious diseases. The unexpected emergence of a previously unknown but highly contagious respiratory pathogen as the cause of a global pandemic has proven to be a blessing in disguise in terms of the global approach to vaccine development and approval. The speed at which these vaccines have been made available for use has been unprecedented and marks a watershed moment in the vaccinology world. However, the question still remains as to whether the same urgency with which COVID-19 vaccines were developed can be switched to the development of equally efficacious vaccines against other infectious diseases such as malaria, TB, and HIV, which have been around for much longer than COVID-19. One can understand why a vaccine for malaria, a disease caused by a protozoan, and for TB, a bacterial infection, might be harder to develop due to the more complex life cycles of the pathogens, but a vaccine against HIV, another viral infection, could be developed from some of recently tried and perfected vaccine platforms that have proven to be very successful in developing hundreds of effective vaccines against one viral disease. This is probably the best time to intensify the search for the most effective vaccines against these diseases although
priority still seems to be focused on global preparedness for pathogen X in the future. The recent monkeypox outbreak, which has now been declared a “global health emergency” by the WHO [89], could serve as a justification for investing just as heavily in developing very effective vaccines against diseases that so far seem to be only prevalent in very few developing countries. The recent developments in the use of DNA and mRNA vaccines provide a great opportunity to fast-track the development and production of new and more efficacious vaccines for diseases that have been in existence for years such as TB and malaria. The recent establishment of the mRNA Vaccine Technology Transfer hub in South Africa [90] is a good example of how this technology can be fully utilized for new vaccine development and testing in countries where the diseases of interest are more prevalent and economically relevant thereby eliminating the recently observed vaccine equity during a pandemic setting [90, 91].

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Conflict of interest

The author declares no conflict of interest.

Notes/thanks/other declarations

None.
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