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Vaccine Production, Safety, and Efficacy

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Glossary

Adjuvant A substance that enhances the body's immune response to an antigen.
Clinical trial A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.
Correlate of protection Correlates of immunity/protection to a virus or other infectious pathogen are measurable signs that a person is immune, in the sense of being protected against becoming infected and/or developing disease. For many viruses, antibodies serve as a correlate of immunity.
Herpes zoster Shingles, also known as zoster or herpes zoster, is a viral disease characterized by a painful skin rash with blisters in a localized area. Shingles is due to a reactivation of varicella-zoster virus (VZV) in a person's body. The disease chickenpox is caused by the initial infection with VZV.
Immunization The action of making a person or animal immune to infection, typically by inoculation with a nonpathogenic version of the infectious agent. Synonymous with vaccination.
Regulatory authority National regulatory agencies responsible for ensuring that products released for public distribution (normally pharmaceuticals and biological products, such as vaccines) are evaluated properly and meet international standards of quality and safety.

Introduction

The development of vaccines is closely linked to the need to protect increasingly larger populations. This started with the transition from populations consisting of hunter-gatherers to agricultural settlements. It went on when urbanization made man even more vulnerable to contagious diseases. Presently about 55% of the world population lives in cities, a situation that is only sustainable with vaccination. Stopping vaccination would result in epidemics. The medical need to prevent (viral) infections is still the major incentive for vaccine development. But whether a vaccine will be developed is also heavily influenced by commercial considerations.

The first vaccine against smallpox ended a disease that in the century before its eradication killed 500 million people (**Fig. 1**). Thanks to vaccination, the average life expectancy has gone up in many countries from about 40 years in 1900 to more than 80 years today. **Table 1** gives an overview of available viral vaccines for human use. Additionally, many vaccines for animals have been licensed. Thanks to vaccination, smallpox was eradicated by 1977. Rinderpest, a disease that killed up to 100% of cattle during outbreaks was eradicated by 2010 and polio is very close to eradication. Despite of these successes additional vaccines are needed, some urgently. **Table 1** lists these vaccines.

Although there have been several "golden ages of vaccines" with important scientific and technical advances bringing vaccine development from a trial-and-error approach to "reverse vaccinology" (Delany *et al.*, 2014), development times of vaccines have only increased. This is especially worrying when we have to develop vaccines against new viral diseases, where pre-existing immunity is completely absent. This article aims to provide an overview of the history, current status, and future of viral vaccine development and use. A full description of all aspects of viral vaccines would require many hundreds of pages (Plotkin *et al.*, 2018; Plotkin, 2011). We have selected some recently developed vaccines to demonstrate the general principles of vaccine development and provide an overview of the long road from vaccine candidates towards market entry. Lastly, several new technologies and opportunities are discussed that are expected to change the vaccine development process for the better, especially by shortening development times.

The History of Vaccination

The realization that victims of a severe infectious disease remain immune to the same disease for the rest of their lives was the basis of the first vaccine against smallpox. Actually, a similar approach was already used from about 1570 in China (Plotkin, 2011). The procedure is called variolation and entailed introducing minute amounts of virus-containing pox material into the nostril of a child. This resulted in a light form of the disease. Already, in those times, the balance between efficacy and adverse effects was evaluated. Up to 1% of variolated children died. This was considered acceptable considering the larger risk of contracting smallpox.

Vaccination differs fundamentally from variolation in that vaccines are composed of viral antigens that produce protective immunity and immune memory without causing disease. There are three classes of licensed viral vaccines: (1) Live-attenuated

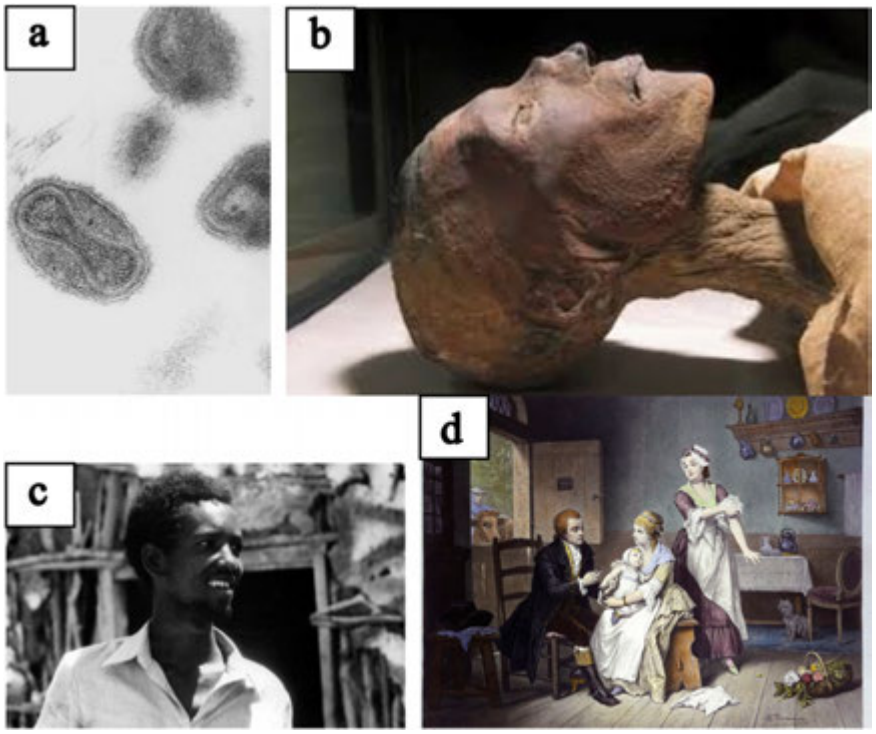

Fig. 1 Conquering smallpox. The smallpox virus (a) has been responsible for hundreds of millions of deaths. The virus was already present in ancient Egypt (b). It spread, by trade routes, wars and colonization, to all continents. Typically, 3 out of 10 people who got the disease died. Survivors were left with scars; some became blind. An eradication program organized by the WHO was successful by 1977 with the last case of naturally acquired smallpox (c). The virus is now confined to two laboratories. Eradication was possible with a vaccine discovered by Edward Jenner in 1796 (d). Sources: (a) CDC PHIL #1849, (b) and (c) WHO, (d) Wellcome Library no. 546000i.

Table 1 Overview of licensed viral vaccines and vaccines under development

Licensed vaccines (Year of market introduction)	*Vaccines that are needed (Estimated global death toll /year)*
Smallpox (1796)	HIV (770,000)
Rabies (1885)	Broadly protecting influenza vaccine (720,000)
Yellow fever (1930)	Hepatitis C (399,000)
Japanese encephalitis (1930)	Norovirus (200,000)
Influenza (1938) (efficacy 40%–60%)	Epstein-Barr (143,000)
Polio (1954)	Human respiratory syncytial virus (120,000)
Adenovirus (1956)	Hepatitis E (44,000)
Measles (1963)	Cytomegalovirus (N/A)
Mumps (1967)	Improved dengue vaccine (N/A)
Rubella (1969)	Herpes simplex
Varicella (1970)	Human metapneumovirus (N/A)
Hepatitis B (1981)	
Hepatitis A (1991)	
Rotavirus (2006)	
HPV (2006)	
Herpes Zoster (2006)	
Dengue (2015) (efficacy 44%, adverse events)	
Ebola (2019)	

vaccines, (2) Inactivated vaccines and (3) Non-replicating protein vaccines produced by recombinant DNA technology. An advantage of live-attenuated vaccines is that production is inexpensive and no adjuvants to boost immune responses are needed. Disadvantages are more adverse effects. These are usually mild, in rare cases severe. For example, smallpox and yellow fever vaccines result in respectively 1–8 and 1–2 deaths per million vaccinations. Another risk is that mutations may lead to regained virulence. This has been a problem for the oral polio vaccine (Amanna and Slifka, 2009). Inactivated and non-replicating vaccines

are very safe, but a downside is that alone they are often unable to generate robust immunity. These vaccines require adjuvants, substances added to vaccines to enhance the immunogenicity (Di Pasquale *et al.*, 2015). Traditionally aluminum salts, with a strong safety record, were used as adjuvant. Scientific advances have led to additional, more potent, adjuvants with a smaller safety database.

What has Happened When Vaccine Reaches the Market? The Development of Shingrix

Shingrix is the herpes zoster (shingles) vaccine. It was licensed in October 2017 in the USA and in 2018 in Europe and Japan. Licensing was based on two large clinical trials with almost 28,000 participants (Maltz and Fidler, 2019; Levin and Weinberg, 2020). Shingrix was the second herpes zoster vaccine. It addressed several limitations of Zostavax, the first vaccine. These limitations included limited protection, especially in individuals over 70 years old, a limited duration of protection, and safety risks for immunocompromised individuals (Dooling *et al.*, 2018).

The history of this successful vaccine dates back to basic research in the early 1990s. Researchers looked for promising viral antigens for a new vaccine. They opted for antigens that could induce cell-mediated immunity in addition to virus neutralizing antibodies elicited by Zostavax. Viral glycoprotein E (gE) was selected as the most suitable candidate (Vafai, 1993; Haumont *et al.*, 1996). Thus, at least 24 years passed between the beginning of research into this vaccine and its licensing.

Phases and Timelines in Vaccine Development: From Discovery to Product

A development time of several decades is typical for vaccine development which consists of separate phases that can only be carried out after each other. **Fig. 2** summarizes this step-wise process.

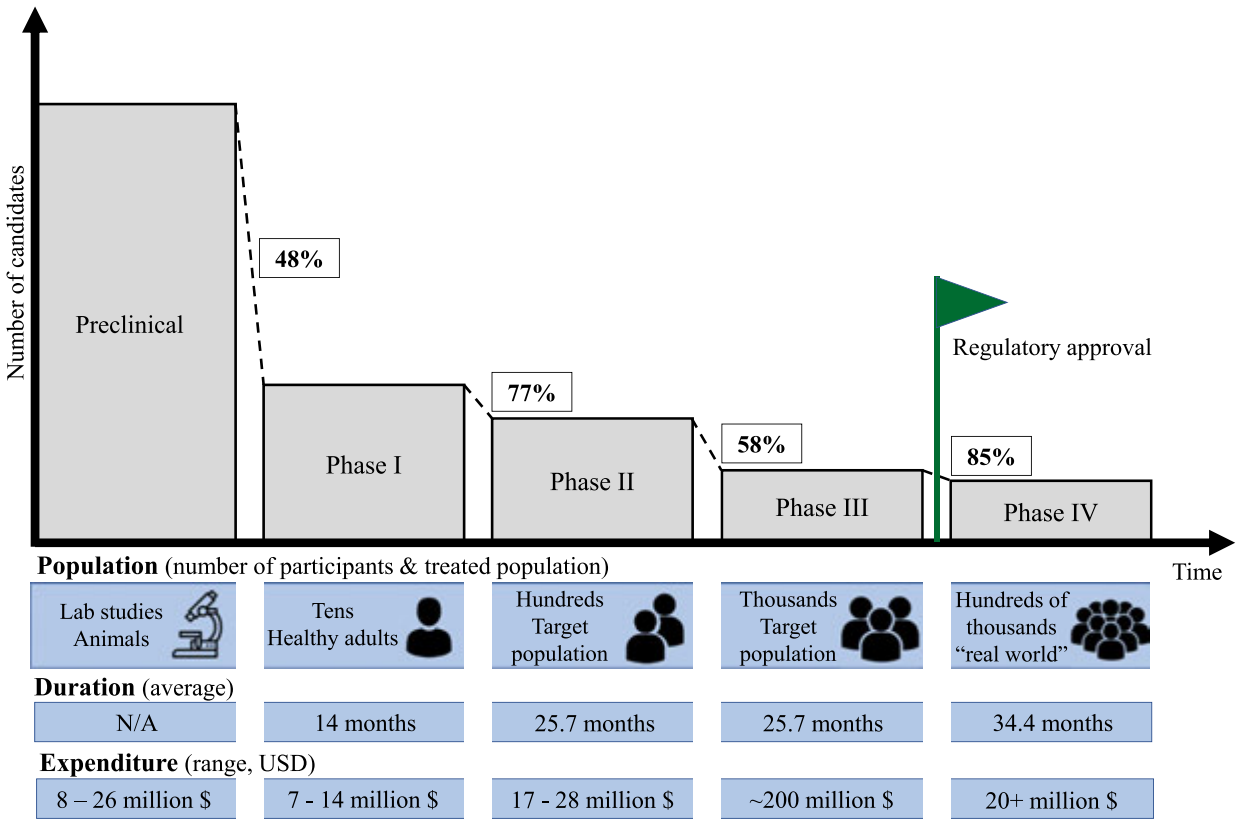

Fig. 2 Timelines and success rates in vaccine development. The transition successes between the clinical phases are from (Wong, C.H., Siah, K.W., LO, A.W., 2019. Estimation of clinical trial success rates and related parameters. Biostatistics 20, 273–286). The data on duration from (Dimasi, J.A., Florez, M.I., Stergiopoulos, S., *et al.*, 2020. Development times and approval success rates for drugs to treat infectious diseases. Clinical Pharmacology & Therapeutics 107, 324–332) and the cost estimate up to phase 2 from (Gouglas, D., Le, T.T., Henderson, K., *et al.*, 2018. Estimating the cost of vaccine development against epidemic infectious diseases: A cost minimisation study. The Lancet Global Health 6, (e1386–e1396)).

Preclinical Studies

The starting point for vaccine development is the medical need to prevent disease. The development begins with basic research to identify the virus responsible for the diseases and, if possible, the antigen(s) that elicit a protective immune response. In addition, attempts are made to determine which immune responses are protective (antibodies, T cells, for example). This is all carried out in the laboratory. Blood samples are often used to study immune responses ex vivo. In those cases where an animal model is available, candidate vaccines can be tested for protection after challenge with virulent virus. Finally, toxicity data are collected. The preclinical stage ends with the establishment of a production process.

In Human Studies

After the preclinical studies have come to a satisfactory end, the vaccine is tested in humans (or animals for veterinary vaccines). 'First-in-human' studies and all other clinical studies are subject to strict rules to protect study participants and ensure quality. Clinical trials in humans are classified into three phases: phase I, phase II and phase III. Phase I studies are carried out on limited numbers, for example, 20+ healthy adults and are primarily concerned with safety. Phase II studies involve larger numbers of persons belonging to the target population with the aim of getting preliminary information about efficacy, usually immunogenicity and additional safety data.

Together, phase I and II trials should give sufficient confidence that a vaccine is efficacious and safe. The real test comes from phase III trials in which a vaccinated population is compared with a control group for protection against the target diseases, resulting in an estimate of vaccine effectiveness. Depending on the prevalence of the disease these studies may require 10,000 or more participants. After the completion of the phase III studies, all results are summarized in a dossier. This dossier also includes data on a consistent manufacturing process and assays to monitor the production and its end products. This dossier is submitted to the regulatory authorities (The Federal Drug Administration in the USA and the European Medicine Agency). After the regulatory authorities have decided that the vaccine is safe and effective, it is licensed and can be released to the market.

Exceptionally, a vaccine fails in the phase III stage. This happened in the 1960s with a vaccine against disease caused by respiratory syncytial virus. This vaccine was not efficacious and even unsafe, killing two participants of the trial (Hurwitz, 2011). Other problems that popped up in the past were due to the limited number of participants in the phase III trials. As a consequence, rare adverse effects e.g., occurring 1 in 100,000 times will not be detected. Therefore, post-licensure safety surveillance (phase IV studies) is needed to detect adverse effects following immunization (AEFI).

Phase IV studies revealed that a rotavirus vaccine caused intussusception in one or two cases per 10,000 infants vaccinated. This vaccine was withdrawn from the market. Newer rotavirus vaccines are 10-fold safer, but not completely without AEFI (Di Pasquale *et al.*, 2016). Narcolepsy, a sleeping disorder, was identified as a possible AEFI associated with the AS03-adjuvanted influenza vaccine Pandemrix. Although there is a clear association between the receipt of Pandemrix and the development of narcolepsy the causality remains unproven. This incident has shown that there is a need for an internationally coordinated vaccine safety structure that can monitor the safety of the many doses of pandemic vaccines administered in a short period (Edwards *et al.*, 2019).

Costs and Duration of Vaccine Development

The exact data on the development of Shingrix are confidential to the developer and producer GlaxoSmithKline. Clinical studies are responsible for the major costs of vaccine development. Thus, costs will vary depending on the complexity of these studies. Estimates of vaccine development expenditure vary from 135 to more than 1000 million USD (Plotkin *et al.*, 2017; DiMasi *et al.*, 2016). An analysis reported a breakdown of the costs of the separate steps in vaccine development (Gouglas *et al.*, 2018). Analysis of databases with clinical trials on vaccines has yielded reliable data on the success rate of vaccine development. Two studies reported an identical success rate of vaccine development from phase I studies to licensing of 33% (DiMasi *et al.*, 2020; Wong *et al.*, 2019). A success rate of 48% in the transition from the preclinical phase to phase 1 studies (Davis *et al.*, 2011) results in a 16% overall success rate. Estimates for the median duration of phase I-III trials during vaccine development are 6.4–10.7 years (Davis *et al.*, 2011; Pronker *et al.*, 2013). A summary of the data is given in **Fig. 2**.

Vaccine Production

Coming back to the Shingrix example: this vaccine is produced by expression, via DNA-recombinant technology, of the antigen in Chinese hamster ovary (CHO) cells. The CHO cells are grown in bioreactors in dedicated production facilities. Typically, these production facilities contain stainless steel bioreactors controlled by sophisticated computer programs to ensure a reproducible production process. After this upstream processing the antigen has to be purified, usually, in various steps, a process called downstream processing. Assays are carried out to check (intermediate) products against the specifications (quality control [QC]) during all steps. At the same time, a quality assurance (QA) team follows the stream of accompanying documentation to ensure that all intended controls were carried out. Production, together with QC and QA, can be a long process of more than one year.

The decision to build production facilities is usually taken before the regulatory authorities approve the vaccine. This implies a considerable financial risk.

Shingrix is a successful vaccine and has reached blockbuster status with annual sales in 2019 of more than 1.5 billion USD. The demand was much higher than foreseen, resulting in the need to build additional production facilities. Since the production process is an integral part of the license, careful calibration of a new production facility and the demonstration of equivalence of the product are required. Alternatives for the traditional bioreactor-based production methods that can speed up production, are scalable and reduce costs are being intensively investigated. See Section "Emerging Viral Diseases".

More About Vaccine Development

Clinical studies are time-consuming and expensive. It would be much easier to measure an immune response that is predictive for protection. Such correlates of protection (CoP) are available for many viral vaccines (Plotkin, 2010). CoPs can be used to license newer vaccines, but also to evaluate existing and new vaccination schedules for protection. Systems vaccinology is a more advanced method to predict the immunogenicity of vaccines. In essence, this links host gene expression (molecular signatures) to protection by vaccines. This approach was very successful for the live attenuated yellow fever vaccine and is, in principle, also useful to predict adverse effects. But more work is needed to move it from 'promising' to a standard approach (Raeven *et al.*, 2019).

The Licensing of Influenza Vaccines Follows a Different Procedure

The current influenza vaccines are mostly produced from an egg-grown virus. The vaccines have to be matched every year to the predominantly circulating virus strains. This requires a special procedure. The production process is licensed with the possibility to insert the circulating viruses, selected in the Northern hemisphere in February-March by the WHO. The current production process is capable to make the vaccine available in October (Soema *et al.*, 2015).

The Vaccine Industry

Over the past decades, the number of vaccine suppliers has decreased considerably due to mergers and acquisitions of pharmaceutical companies. Presently about 90% of global vaccine sales come from four large multi-national corporations: GlaxoSmithKline, Merck, Pfizer and Sanofi Pasteur (Shen and Cooke, 2019). In the 1980s emerging market manufacturers started to enter the vaccine market and assumed a significant role since then. Emerging manufacturers, represented by the Developing Countries Vaccine Manufacturers Network, play a critical role in the supply of vaccines of developing countries. They now supply about half of UNICEF's vaccine procurement in a volume of doses, representing about 30% of the value of UNICEF's total vaccine procurement. Even including producers from developing countries, there are relatively few vaccine manufacturers that meet international standards of quality. Many vaccine markets are monopolies or oligopolies. The limited number of vaccine suppliers and production capacities leads to a tenuous balance between demand and supply in many individual vaccine markets and regularly to vaccine shortages.

Taking Stock

Due to vaccination, viral diseases remain under control. Two vaccines, hepatitis B and human papillomavirus protect against cancer. Thanks to a functional vaccine industry, vaccines remain available for a largely stable market. In addition, the research-based vaccine industry is innovative and develops new vaccines to answer unmet medical needs. This also applies to influenza vaccines with a new composition every year. However, problems exist with vaccines against new viral diseases to combat epidemics. The duration of these epidemics is unknown and usually, there is no commercially attractive market. Market forces fail, but vaccines are urgently needed. This will be the topic of the second part of this article.

The Challenge of Emerging Viral Diseases

In March 2003, the WHO issued a global alert about a new viral disease, severe acute respiratory syndrome (SARS). In retrospect, the SARS epidemic started in 2002 in China. In several months, SARS spread to 37 countries where it caused 8098 cases with 774 deaths before it came under control. SARS coronavirus (SARS-CoV), the causative agent of the syndrome, was traced back to an intermediate host, the civet cat, which originated as a virus of the horseshoe bat. Small mutations in the viral genome expanded the host range to humans.

A new viral disease in an immune naïve population could cause a catastrophe with many fatalities. It is worrying that there are many animal viruses with unknown pandemic potential. The SARS epidemic was the first wake-up call.

The 2007 World Health Report of the WHO was dedicated to Emerging viral diseases (EVD) and stated that "It would be extremely naive and complacent to assume that there will not be another disease like AIDS, another Ebola, or another SARS, sooner or later" (WHO, 2007). The real wake-up call came only in 2013 after an outbreak of Ebola in West Africa (Guinea, Liberia and Sierra Leone). Ebolavirus had been discovered in 1976. Between 1976 and 2013 it regularly spilled over from its animal reservoir to humans. There were several outbreaks, but these remained small and were contained. In the 2013 outbreak, about 28,000 persons were infected and 11,000 died. In addition, there was transmission to other countries and loss in GDP in the three affected countries. Many discussions in the aftermath of the Ebola outbreak led to the conclusion that more investments in R&D to counter EVD were needed, together with a more active role involving the WHO. As a result, the WHO Blueprint for Action to Prevent Epidemics was developed. The 2018 Blueprint list of priority diseases contains the following viral diseases:

- Crimean-Congo hemorrhagic fever
- Ebola virus disease and Marburg virus disease
- Lassa fever
- Middle East respiratory syndrome (MERS-CoV) and SARS
- Nipah and henipaviral diseases
- Rift Valley fever
- Zika
- Disease X (caused by a pathogen currently unknown)

The coordination and execution of R&D are in the hands of the Coalition for Epidemic Preparedness Innovations (CEPI). CEPI is a public-private partnership that was established during the World Economic Forum Annual Meeting of 2017.

CEPI acquired access to 755 million USD and used the money to support work on priority diseases (Lassa, Nipah, MERS, Rift Valley Fever and Chikungunya), selected with the aid of the WHO Blueprint. Two requests for proposals involved priority viruses. The aim is to bring vaccines through phase II studies and have vaccine stockpiles available for at least two pathogens by the end of 2022.

Another request for proposals involved platform technologies. Please see the CEPI Business Plan 2019–2022 for more details. Platform technologies have the potential to speed up development and production drastically. The common property of platforms is that they can be used for multiple vaccine antigens. The safety of the platform is known, the only variable is the inserted antigen. This will save time and may lead to regulatory streamlining, comparable to the procedure for influenza virus vaccines. Based on reduced development and production times, the most promising platforms are DNA and RNA vaccines and neutralizing antibodies, as discussed below.

DNA vaccines date back to the early 1990s when it was discovered that plasmid DNA, delivered in muscle or skin induces an antibody response to the encoded protein. The DNA has to cross the membranes of the cell and the nucleus. Subsequently, the antigen is synthesized. The initial excitement diminished somewhat after it appeared that immune responses in man were weaker than in mice. However, this problem has been solved by more efficient systems for the delivery and formulations that protect DNA against degradation. In addition to antibodies, DNA vaccines elicit $CD4^+$ and $CD8^+$ T cells. Logistically DNA vaccines have many advantages, such as fast, inexpensive and scalable production and short development times. Also, no handling of infectious virus is required during vaccine development. This makes these vaccines ideal as protection against emerging viral diseases (Rauch *et al.*, 2018). Presently vaccine development against various diseases, including Ebola, MERS and Zika, is ongoing (Rauch *et al.*, 2018). A (theoretical) disadvantage of DNA vaccines is that they may integrate into the human genome and lead to undesired gene activation. Presently (2019) no DNA vaccines have been licensed for human use.

RNA vaccines consist of mRNA. They have the same advantages as DNA vaccines, but since mRNA has to cross only one membrane, immune responses are stronger. In addition to conventional mRNA, self-amplifying mRNA can be used. mRNA is extremely sensitive to degradation by endonucleases. Therefore, a formulation, e.g., liposomes, which protect the RNA is used. Many vaccines are presently under development and also in clinical trials. But although RNA vaccines are very promising, their development is still at an early stage (Maruggi *et al.*, 2019).

Neutralizing antibodies offer an alternative treatment for viral infections. This is what is referred to as passive immunization and was successful in the treatment of Ebola (Saphire *et al.*, 2018). Another new development is the use of broadly neutralizing antibodies directed against conserved viral structures. These antibodies are promising both for prophylaxis and therapy for a range of viruses (Walker and Burton, 2018).

Looking Forward

Existing vaccines will continue to play a key role in controlling (viral) diseases. Many vaccines come as a combination vaccine and it will be complicated and very expensive to modify these vaccines. Newly developed vaccines will probably be made using novel approaches (Mascola and Fauci, 2020). We expect that the establishment of CEPI will contribute to these innovations. Paving a regulatory path to the first registration of DNA and RNA vaccines for infectious diseases will be a

challenge. But nucleic acid vaccines are also a promising approach for the immunotherapy of cancer. This may help in paving this path.

Another challenge is the design of clinical trials to test EVD. During the 2013 Ebola outbreak, there was disagreement about the design of clinical studies, particularly on ethical aspects of a placebo group. However, without a placebo group, it is impossible to measure the safety and efficacy of a vaccine. During these discussions the incidence of the disease declined, making it more difficult to carry out the phase III study. Choices about the design of clinical studies have to be made before outbreaks.

The Development of COVID-19 Vaccines

Shortly after the completion of the manuscript for this chapter, SARS-CoV-2 was discovered. Its global spread led to an overburdening of health systems and a death toll of about 1.6 million by December 13, 2020. Measures aimed at controlling the disease disrupted daily activities. A widespread hope is that immunity provided by vaccination will be the key to a return to 'normal life'. The first vaccine, an mRNA vaccine, developed and produced by Pfizer/BioNTech has been approved by now in several countries and vaccination has begun or will so shortly. The approval of a second mRNA vaccine developed by Moderna is expected in January 2021. Vaccine development started on January 11, 2020 when the genomic sequence of the virus, determined by Chinese scientists, became available. According to the WHO, 214 vaccines were under development on December 10, 2020, of which 13 in phase III clinical trials. The approval of more vaccines is expected in the first months of 2021. Estimated efficacies of vaccines are high, more than 90%. Adverse effects are present. But they are of short duration and not categorized as serious. Three vaccine platforms contributed to the most promising COVID-19 vaccines: (1) mRNA vaccines, (2) Adenovirus-based vaccines and (3) Vaccines consisting of inactivated virus. In addition, there are promising results from protein subunit vaccines. The use of these platforms significantly cut the development timelines. Further factors were an abundance of funding, tight collaborations between vaccine developers, governments and regulatory agencies, and the parallelization of activities. Especially the construction of manufacturing facilities parallel to the clinical development saved a lot of time. Several new platforms and procedures were adopted in the development of the COVID-19 vaccines. Licensing of these vaccines will pave the way for more vaccines based on these technologies. This could lead to considerable changes in the development and production of future vaccines.

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