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REVIEW ARTICLE

New age in vaccinology: the impact of the COVID-19 pandemic on third-generation vaccine development

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Highlights
- An analysis of vaccine technologies is conducted in this study.
- A third generation vaccine has been developed with the COVID19 pandemic.
- The different platforms, immune characteristics and production processes are reviewed.

Abstract: The emergency caused by the COVID-19 pandemic required fast and effective vaccine development. Thus, third-generation vaccine technologies were pushed forward and, for the first time, obtained approval for human use. This review presents an analysis on the production, efficacy, and safety of different third-generation vaccines for infectious diseases. DNA, mRNA, and viral vector vaccines in phase III and IV clinical trials were explored here, with considerations and comparisons between them. Two databases of clinical trial vaccines were also analyzed, revealing that 7.9% of phase III and IV clinical trial studies are related to third-generation vaccines. Most of these studies started in 2020 (28.6%) and 2021 (63.1%). The target disease is primarily COVID-19 (92.9%), and most trials are concentrated in developed countries. Scientific, economic, and political factors influenced the rapid development of third-generation vaccines, marking the beginning of a new age in vaccinology. The knowledge obtained during this brief period will influence future vaccine development and treatment of infectious diseases.
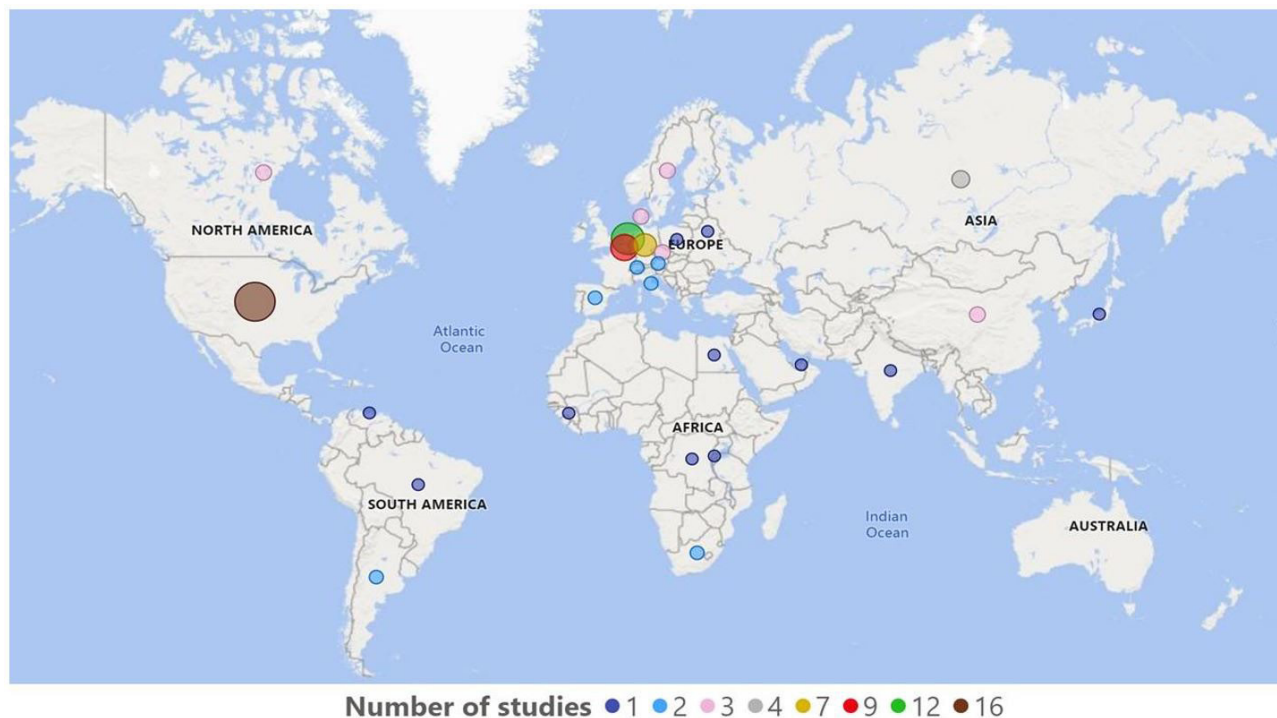
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Graphical abstract

Number of studies ●1 ●2 ●3 ●4 ●7 ●9 ●12 ●16

Map of the 28 countries conducting phase III and IV clinical trials of third-generation vaccines. The size of the bubbles represents the number of studies developed in each country. The USA has the largest number of studies.

Introduction

For many years, first-generation vaccines (attenuated and inactivated organisms) have successfully prevented and eradicated infectious diseases. However, they have some limitations when it comes to production and effectively inducing an immune response. Second-generation vaccines (subunit and recombinant) have advantages over first-generation ones in terms of facilitated production. However, they still have some limiting factors, such as requiring potent adjuvants to stimulate a protective immune response (Pushparajah et al., 2021; Rauch et al., 2018). In contrast, recent attention has favored the development of third-generation vaccines based on DNA or RNA, in which the host cell machinery produces the immunogenic antigen. The manipulation of these vaccines through genetic engineering can increase their efficacy, safety, and the possibility of combining different target antigens to induce immunity (Humphreys & Sebastian, 2018; Pushparajah et al., 2021).

In March 2020, the World Health Organization (WHO) declared a pandemic status for COVID-19 (World Health Organization, 2020). The infection spread rapidly around the world, requiring the fastest search for effective and safe vaccines ever documented in human history (World Health Organization, 2020; Ahmad, 2020; Crommelin et al., 2021). As a result, studies on genetic material-based vaccines began to develop quickly, and third-generation vaccines led the race for the vaccines against COVID-19. In December 2020, an Emergency Use Authorization (EUA) was granted by the Food and Drug Administration (FDA) for the first third-

generation COVID-19 vaccine, Pfizer-BioNTech (BNT162b2). Its clinical trial results showed considerable protection and allowed the beginning of COVID-19 immunization. Research on genetic material-based vaccines has been done since the 1990s. However, it was only during the COVID-19 pandemic that these vaccines began to be more explored in clinical trials (Amanpour, 2021; Golob et al., 2021).

Here we present a review on the current third-generation vaccines, the different platforms, immune characteristics, and production processes. We also searched for and reviewed the third-generation vaccines currently being used in phase III and IV clinical trials in the last five years. Two databases were searched: the Clinical Trial (CT) of the National Institute of Health (NIH) and the European Union Clinical Trial (EU Clinical Trial Register) of the European Medicine Agency (EMA). The term "vaccine" was searched in the infectious diseases category of the databases for studies published between June 1, 2016, and May 31, 2021. The data obtained will be discussed in the following sections of this review.

Third-generation vaccines

DNA

This vaccine consists of delivering a DNA plasmid to host cells. The genetic information will be used by the cells to produce immunogenic antigens. This approach induces the efficient cross-priming and presentation of antigens to CD4+ and CD8+ T cells, thus inducing humoral and cellular

immune responses (Silveira et al., 2021). DNA vaccines have a challenging delivery system as the genetic material must be delivered to the nucleus of host cells. Electroporation and pyro-drive jet injection are used for this purpose. This first consists of brief electric pulses that create reversible membrane pores and allow plasmid internalization. Pyro-drive jet injection propels plasmids into the skin by applying short, controlled combustion reactions. The delivery system could affect the overall vaccine efficacy (Batty et al., 2021). AG0302-COVID19 is the only DNA vaccine currently in phase II/III trials. It is being tested for COVID-19 and encodes the full length of the SARS-CoV-2 spike (S) protein. The protein sequence was optimized to accelerate its expression in human cells. The AG0302-COVID19 vaccine-induced antibodies that neutralized the S protein (Nishikawa et al., 2021). A circular pDNA is usually engineered as the cloning vector to be expressed in bacteria (Figure 1).

The major components of the plasmid are the origin of replication, a promoter, a gene of interest, and commonly an antibiotic resistance gene. *Escherichia coli* is used as a host cell and grown in bioreactors from 10-500 L. Fermentation lasts less than two days (Lee et al., 2018). Then, cells go through lysis by alkaline or thermal treatments followed by downstream processes to eliminate impurities, such as proteins, RNA, chromosomal DNA, and endotoxins. The most common purification steps are precipitation, ultrafiltration, and centrifugation. Chromatography is also used as an efficient method for protein-based pharmaceuticals and has the advantage of an easy scale-up. This large-scale DNA production is cost-effective, making the technology cheaper than traditional live or attenuated vaccines (Lee et al., 2018). These vaccines are produced quickly and are thermostable, not requiring a cold-chain system distribution, which could be an advantage compared to other third-generation vaccines.

mRNA

The technology is based on the delivery of transcriptional information in the form of mRNA into the cytoplasm of host cells. The cells recognize and translate the information into a target immunogenic protein. The platform is considered safe because there is no possibility of mutation in the host genome, and the anomalous RNA is degraded within a few days (Lin et al., 2020).

The mRNA vaccines can induce a cellular immune response composed mainly of CD8+ T cells, which are specialized in killing infected cells. Furthermore, CD4+ T cells and antigen-specific antibodies are also intensely produced (Lindgren et al., 2017). These vaccines are mainly formulated in lipid nanoparticles (LNP). For this approach, neutral or positively charged lipids balance the negative nucleic-acid charge, allowing the proper delivery of mRNA into the cytoplasm. The most common formulations are constructed with ionizable lipids, cholesterol, phosphatidylcholine, and PEGylated lipids (Batty et al., 2021).

BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (ModeRNA) are mRNA vaccines currently being used in phase III and IV clinical trials. They deliver a nucleoside-modified mRNA that encodes the SARS-CoV-2 prefusion S protein (Jackson et al., 2020; Polack et al., 2020). Thus, two proline mutations are substituted into S protein residues 986 and 987 to produce prefusion-stabilized SARS-CoV-2 S(2P) proteins, preventing the early intracellular activation of interferon-associated genes and allowing greater stability in the protein structure (Teo, 2021). The first clinical trials demonstrated 95% efficacy for BNT162b2 (Polack et al., 2020) and 94.5% for mRNA-1273 (Teo, 2021). The side effects of both vaccines were fever or chills in 40% to 60% of participants, and almost all participants reported some mild or moderate systemic symptoms (fatigue, fever, chills, and pain) after two doses (Lin et al., 2020). A practical challenge of these vaccines is the need for a second dose, as first-dose efficacy was 92.6% and 92.1% for BNT162b2 and mRNA-1273, respectively (Teo, 2021). CureVac CVnCoV is another mRNA COVID-19 vaccine being used in phase III trials. The mRNA has no chemical modifications and encodes the full-length S protein. However, this immunizer showed only 47% protection from symptomatic SARS-CoV-2 infection (Cromer et al., 2021).

The manufacturing of mRNA vaccines begins with the enzymatic *in vitro* transcription reaction (IVT) used to generate mRNA from the corresponding linear DNA template (Figure 1). The mRNA is produced in a cell-free system, which is safer as it reduces impurities and the likelihood of contamination. The reaction takes just a few hours, in contrast to the time-consuming processes used to make conventional vaccines. The yield is around milligrams of mRNA per mL of reaction. The mRNA capping can be performed during the IVT reaction by replacing part of the guanosine triphosphate substrate with a cap analog, or in a second enzymatic reaction, using the vaccinia capping enzyme and a methyl donor as substrate. Once the mRNA is produced, it must be isolated and purified to reach clinical purity standards through several purification steps. There are several options for purification, but chromatography is generally used as a common purification process widely accepted in the pharmaceutical industry. Ion-pair reversed-phase chromatography (IPC) has proven to be an excellent method for mRNA purification, but alternatives such as ion-exchange chromatography (IEC) and affinity-based chromatography are also applied. Then, small-size impurities can be removed during concentration or diafiltration of solutions by tangential flow filtration. The last step before the filling is the preparation of LNPs, which involves rapid mixing, whereby an organic phase containing the lipid components is mixed at diluted concentrations with an acidic aqueous solution containing the nucleic acid (Rosa et al., 2021).

The mRNA vaccine manufacturing process can be standardized by replacing only the initial linear DNA template. In this way, the platform is not dependent on the encoded antigen - that is why it is called "plug-and-play." From this perspective, the characteristics of the platform make it suitable to respond to pandemics (Baden et al., 2021). Finally, a challenge for these vaccines is that RNA is a less stable molecule than DNA or attenuated viruses, requiring cold-chain storage and transport at temperatures around -70 °C for BNT162b2 and -20 °C for mRNA-1273.

Viral vector

Viral vector vaccines use replicating or non-replicating viruses as vehicles for heterologous gene transport, allowing antigen production by the host cell (Lee et al., 2018).
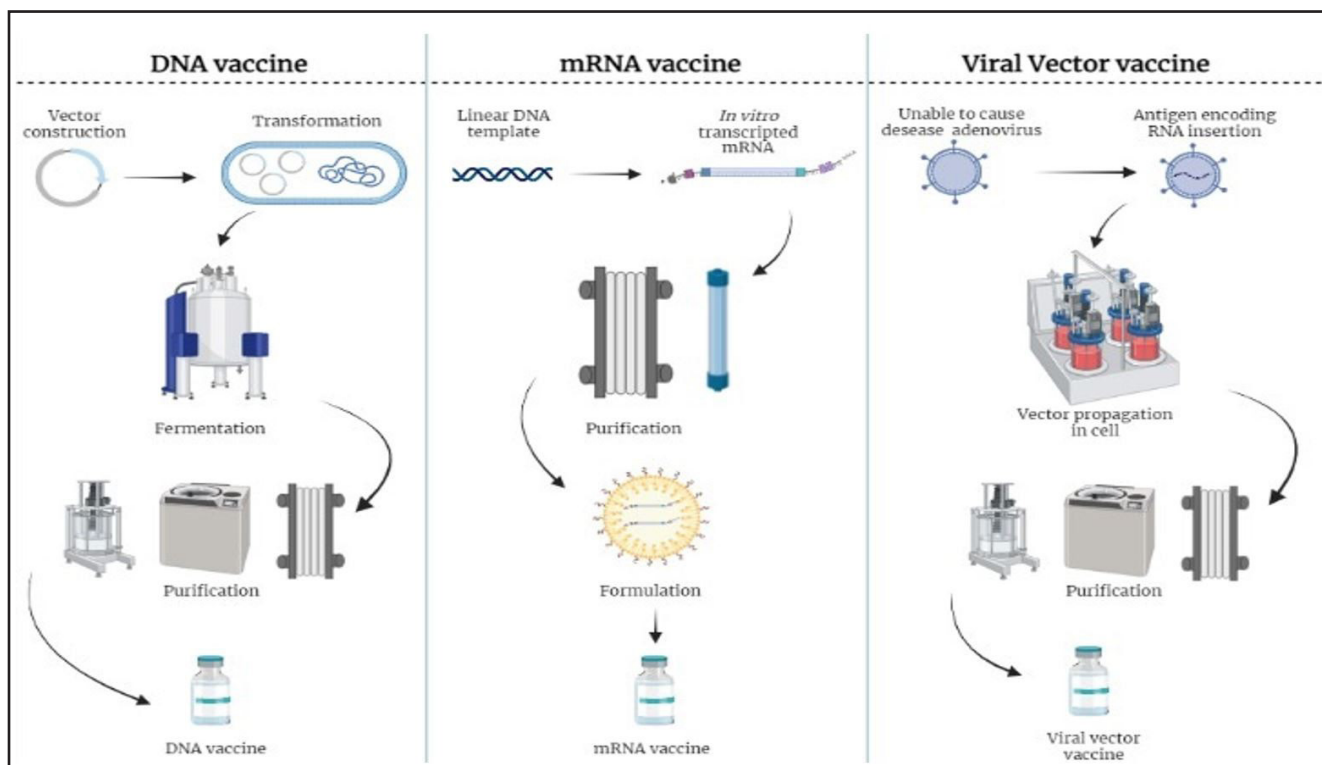
Figure 1. Illustrative representation of the manufacturing processes of third-generation vaccines. DNA vaccine production starts with vector construction, followed by host cell transformation. Subsequently, cells are grown in a bioreactor and purified. The purification includes precipitation, ultrafiltration, centrifugation, and chromatography. For RNA vaccines, the first step of production is *in vitro* transcription of the linear DNA template. Afterward, purification may include column chromatography and tangential flow filtration, followed by LNP formulation. Finally, viral vector vaccines are produced by initially inserting an antigen-encoding RNA into an adenovirus unable to cause disease. The virus is then propagated in cell culture, followed by purification. Purification steps include filtration, centrifugation, and chromatography. The image was created in BioRender (biorender.com).

The main vectors are adenoviruses due to their low and well-characterized pathogenic profile, enhancing the immune response during vaccination, especially by triggering the induction of CD8+ T cells. Additionally, this technique is highly stable and results in high yields, allowing industrial production at a low cost under good manufacturing practices (Daussy et al., 2021).

To construct an adenoviral vector, it is first necessary to identify a non-replicating adenovirus of low seroprevalence (Figure 1). Then, the antigen sequence selected from the pathogen will be inserted into the adenoviral genome and further transfected into cells (Gebre et al., 2021). Large suspension culture bioreactors using continuous cell lines can be used for large-scale production of the adenovirus. Clarification, concentration, purification, and polishing are usually common steps in the downstream process of adenovirus purification. Chromatography can be found in the last step, with anion exchange and size exclusion (van der Loo & Wright, 2016). With regard to storage, refrigeration (2-8 °C) is highly preferred over freezing (-20 °C). For viral vector vaccines, the COVID-19 vaccines cited here are usually stored in frozen liquid form at –20 ℃. However, in the short term, both can be successfully kept under non-frozen conditions. Zabdeno for Ebola virus can also be stored at temperatures between 2 and 8 °C (Crommelin et al., 2021).

Ten of the 14 vaccines used in the studies retrieved from the databases apply this technology (Table 1). Among these, the ChAdOx1 nCoV-19 (Oxford-AstraZeneca) and Ad26.COV2.S (Janssen) vaccines stand out as both use replication-incompetent vectors and deliver the genetic material into the host cell. ChAdOx1 nCoV-19 or AZD1222 (Oxford-AstraZeneca) is a ChAdOx1-based vaccine, a chimpanzee adenovirus that expresses the full-length prefusion S protein of SARS-CoV-2. This vector has been used in vaccines and demonstrated to be immunogenic in adults with no safety concerns, even in immunocompromised individuals (Coughlan et al., 2018). Moreover, it can be manufactured on a large scale, making the technology a good approach to an emergency COVID-19 vaccine. The ChAdOx1 vector of this vaccine contains the S protein with a tissue plasminogen activator leader sequence, expressing a codon-optimized coding sequence (Folegatti et al., 2020). The vaccine showed a T-cell response peak after 14 days of immunization and was boosted with a second dose. The overall efficacy of ChAdOx1 nCoV-19 was 70.4% (Voysey et al., 2021). Similarly, the Ad26.COV2.S vaccine expresses the same native conformation protein, but its viral vector is the adenovirus serotype 26 (Ad26), which has been proved to be safe in humans and to induce CD4+ and CD8+ T cell responses as well as binding and neutralizing antibodies (Anywaine et al., 2019; Barouch et al., 2018). The construction of the Ad26.COV2.S vaccine first evaluated

Table 1. Third-generation vaccines for infectious diseases under phase III and IV clinical trials between June 1, 2016 and May 31, 2021. A single clinical trial may assess more than one vaccine at a time.

Vaccine platform	Vaccine name	Delivery system	No. of studies
DNA	AG0302-COVID19	Pyro-drive jet injector	1
mRNA	Pfizer-BioNTech COVID-19 Vaccine (BNT162b2)	LNP	31
	Moderna COVID-19 Vaccine (mRNA-1273)	LNP	24
	CVnCoV Vaccine (CV07050101)	LNP	7
	Not specified (SARS-CoV-2 mRNA Vaccine)		1
Viral vector	Oxford-AstraZeneca COVID-19 Vaccine (ChAdOx1 nCoV-19)	ChAdOx1	10
	Janssen COVID-19 Vaccine (Ad26.COV2.S)	Ad26	8
	Sputnik V (Gam-COVID-Vac)/ Sputnik Light	Ad26	6
	Convidecea Vaccine (Ad5-nCoV)	Ad5	4
	GRAd-COV2 - COVITAR	GRAd	2
	Ad26.ZEBOV / MVA-BN-Filo	Ad26 / MVA	2
	GamEvac-Combi	Ad5	1
	Ad26.ZEBOV	Ad26	1
	Ad26.Mos4.HIV	Ad26	1
	ALVAC-HIV (vCP2438)	ALVAC	1

the design elements used for other coronavirus S protein-based vaccines, such as prefusion-stabilizing substitutions and heterologous signal peptides (Bos et al., 2020). Site mutations increased the ratio of neutralizing antibodies versus non-neutralizing antibodies, as shown by *in vitro* characterization. This suggested a prefusion conformation of the S protein. Additionally, a wild-type signal peptide was needed for a natively folded protein. Also, Ad26.COV2.S showed 66.9% efficacy with a single dose, protecting against SARS-CoV-2 infection, which was higher against critical cases (Sadoff et al., 2021).

The Ad26 vector has been studied for some years in the development of other vaccines, such as Ad26.ZEBOV and Ad26.Mos4.HIV for Ebola and HIV, respectively (Baden et al., 2021; Pollard et al., 2021). Ad26.ZEBOV, also called Zabdeno, is a monovalent vaccine that expresses a Zaire Ebola virus glycoprotein, which is given along with MVA-BN-Filo as the first dose. The second dose, MVA-BN-Filo (or Mvabea), is a Modified Vaccinia Ankara (MVA) vector-based vaccine encoding several glycoproteins, conferring protection against Ebola and other viruses. Zabdeno is given first, and Mvabea is administered around eight weeks later as a booster. The heterologous prime-boost vaccine demonstrated high efficacy and safety in phase II clinical trials (Pollard et al., 2021).

Former HIV vaccines being tested were bivalent and trivalent mosaics that have been shown to broaden the immune response in animals (Barouch et al., 2018). The vaccines presented in this study are the trivalent viral vector vaccine Ad26.Mos.HIV and the tetravalent Ad26.Mos4.HIV, both using the Ad26 vector. This mosaic technology uses complementary sequences of env, gag, and pol antigens to enhance the immune response against worldwide circulating HIV strains. Ad26 was chosen since it is well tolerated and elicits the immune response; also, both vaccines have the viral vector encoding the Mos1 and HIV-1 Gag and Pol protein, the Mos2 HIV-1 Gag and Pol protein, and the Mos1 HIV-1 Env protein. The tetravalent also has the Mos2 HIV-1 Env protein. Additionally, both have the recombinant trimeric glycoprotein gp140. All participants in the trial developed binding antibodies after the second vaccination, with higher titers for the tetravalent vaccine (Baden et al., 2021).

Scenario of phase III and IV clinical trials

This study only analyzed phase III and IV registered clinical trials, retrieving 1,064 vaccine studies, of which 84 (7.89%)

were third-generation vaccine studies. Only seven studies were registered from 2016 to 2019, followed by 24 in 2020 and 53 in 2021. In addition, the diseases involved in these studies were COVID-19, accounting for 92.86% (78), Ebola (4.76%), and HIV (2.38%). With regard to vaccine platforms, three are mRNA vaccines, ten are viral vector vaccines, and one is a DNA vaccine (Table 1).

The decision to develop and test a vaccine is influenced by scientific, economic, and political factors. The cost of a single-phase III clinical trial is estimated at U$19 million (Mullard, 2018), requiring a demand to justify the investment. Moreover, several factors influence the decision to advance a candidate vaccine from phase II to phase III trials. First, only vaccines with solid results from preclinical and phase I and II trials are considered to follow through. Moreover, a certain number of individuals should be exposed to the infectious agent in order to test and assess the efficacy of the vaccine (Gaba & Bhatt, 2020). This was possible during the COVID-19 pandemic as several populations were infected by SARS-CoV-2, allowing COVID-19 vaccines to move faster to the next phases. Nevertheless, many vaccines for other infectious diseases are held in phase II for the lack of exposed individuals, condensing clinical trial protocols. Furthermore, although the cost for the clinical trials of new technologies is the same as for well-established technologies, there is greater distrust around new vaccine platforms (Gouglas et al., 2018). However, the global scenario in 2020/21 was favorable for testing third-generation vaccines, which allowed them to advance to phase III and IV trials. As a result, the effectiveness of these platforms was validated, serving as a basis for future vaccine development (Bloom et al., 2021).

Most phase III and IV clinical trials with third-generation vaccines are concentrated in Europe and North America. All countries with more than three studies are developed nations, and the USA concentrates the largest number of studies. Furthermore, the countries responsible for developing third-generation vaccines have many phase III and IV clinical trials. These data point to a global disparity in terms of technology development across continents and nations. Also, certain countries are both developers and exporters, while others have become consumers of this technology. This scenario could be maintained even after the end of the COVID-19 pandemic.

A drawback of the present study is that it only considers data from The NIH Clinical Trial Database and the EU Clinical Trial Register However, these are the largest databases available, with the most extensive catalogs, thus providing a solid estimate of the third-generation vaccines being tested. Finally, it would be beneficial if these data were centralized in a single international database, simplifying the search for currently decentralized information.

Conflict of interests

The authors declare no conflict of interest.

Acknowledgements

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