Pharmacology of anti Covid-19 Vaccines in Clinical use globally: A Review

Abstract.
A worldwide effort to develop a vaccine against the coronavirus was commenced, in view of the seriousness of the disease, the high rate of transmission, and the high demand for health service by infected patients. Several technologies are used to produce vaccines against SARS-CoV-2 and at an incredible pace . Any serious, undesirable or unexpected sign or symptom manifested in an individual who has received any type of immunological and biological product is considered adverse events following immunization (AEFI) and can be caused by several factors related to the components of the immunological and biological product, the vaccination process, or the person already vaccinated. As at June 14, 2021, the Center for Disease Control and prevention (CDC) have recorded more than 3500 reports of side effects from people in the USA who have received covid-19 vaccines. The CDC data also revealed hospitalizations of those receiving covid-19 vaccines. Summaries of their symptoms include heart palpitations, severe abdominal pain, seizures, and almost stroke-like symptoms". Several people have also reported that they could not breathe after receiving the shot.
According to the CDC, since April 2021, more than one thousand (1000) cases of myocarditis and pericarditis have been reported to the Vaccine Adverse Event Reporting System (VAERS) after mRNA-based covid-19 vaccination (Pfizer-BioNtech, Moderna) in the United States of America (USA).

Keywords: coronavirus vaccine, SARS-COV2, immunology, disease, adverse event

Introduction.

The overall impact of COVID-19 pandemic on the social determinants of health globally has been far-reaching and grossly debilitating. The world was clearly cut unawares by this scourge which was completely strange to the present world population. With the passage of time, it was clear that victory over this pandemic can only be achieved through mass vaccination of the population (1). Vaccination against infectious diseases such as SARS-CoV-2 is the most efficient and affordable public health intervention worldwide. In addition to individual immunization, the achievement of collective protection (so-called community immunity) for the majority of vaccine preventable infections is also crucial to protect vulnerable groups in the population who, for various reasons, cannot be vaccinated (2).

The currently available vaccines against SARS-CoV-2 are manufactured by one of the following technologies: (a) mRNA-based vaccines, (b) viral vector-based vaccines, (c) protein subunit vaccines, and (d) whole virus or inactivated virus vaccines (3). In consequence, the European Medicines Agency (EMA) has approved vaccines that only belong to the first two technologies (mRNA-based and viral vector-based vaccines), which aim to produce spike protein-specific antibodies (4).

The mRNA-based technology is relatively novel in vaccine industry, and it employs molecular templates of messenger RNA (mRNA) to deliver the genetic information to produce the spike (S) glycoprotein antigen, not to deliver the antigen itself (5). The viral vector-based vaccines against SARS-CoV-2 use a non-replicating harmless version of adenovirus as a vehicle to deliver the genetic code of the S glycoprotein antigen, thus eliciting the targeted immune response (6). In Germany, a country with a population of around 84 million, 3,729,682 COVID-19 cases with 91,007 deaths were reported by 1 July 2021 (7).

To date, four COVID-19 vaccines had been approved in Germany; Pfizer-BioNTech (mRNA-based vaccine) approved since 21 December 2020, Moderna (mRNA-based vaccine) approved since 6 January 2021, AstraZeneca-Oxford (viral vector-based vaccine) approved since 29 January 2021, and Janssen (viral vector-based vaccine) approved since 11 March 2021 (8). On 1 July 2021, 926,463 vaccine doses were administered in Germany, leading to 31.487.487 people (37.9% of the total population) being fully vaccinated and 46,249,449 people (55.6%) receiving at least one vaccine dose. The German government imported -to date- 57,619,463 doses of Pfizer-BioNTech, 13,869,863 doses of AstraZeneca Oxford, 7,641,280 doses of Moderna, and 2,893,697 doses of Janssen. The Germany's vaccination strategy prioritized healthcare workers to receive the vaccine, especially those who worked in the frontlines and treated COVID-19 patients (9).

A world-wide effort to develop a vaccine against the coronavirus was commenced, in view of the seriousness of the disease, the high rate of transmission, and the high demand for health service by infected patients. Several technologies are used to produce vaccines against SARS-CoV-2 and at a surprising speed. In less than 6 months, different vaccine

candidates have reached the clinical stage. In Brazil, given the epidemiological emergency resulting from covid-19, the country established a temporary authorization for the emergency use of covid-19 vaccines on an experimental basis to face a public health emergency (10).

In a scenario of the introduction of a recent vaccine to the population, the pharmacovigilance of Adverse Events Following Immunization (AEFI) is extremely relevant12,13. Any serious, undesirable or unexpected sign or symptom manifested in an individual who has received any type of immunobiological is considered an AEFI and can be caused by several factors related to the components of the immunobiological, the vaccination process, or the person already vaccinated (10, 11).

The development of the vaccines started as soon as the virus genome was published in early January 2020 (12,13). As of April, 9 2020, there have been 186 vaccine candidates for COVID-19 and 87 of them have started human clinical trials (14). Many different vaccine technology platforms have been used to develop a safe and effective vaccine. Currently, 4 different vaccine platforms are approved for use. These comprise nucleic acid (mRNA) platforms, viral vector platforms, inactivated virus platforms and subunit vaccine platforms (15, 16, 17). Among these platforms, 11 vaccines showed promising results that allowed them to gain emergency approval for use in different parts of the world. The emergence of new variants of SARS-CoV-2 is another problem in vaccine development. Recently, 3 SARS-CoV-2 variants, B.1.1.7 (501Y.V1), B.1.351 (501Y.V2) and B.1.1.28.1 (P.1), have emerged in the United Kingdom, South Africa and Brazil, respectively (15).

Vaccine Names, Types and Manufacturer (Developer).

By 19th of June, 2021, seventy eight (78) vaccine candidates were in development in 201 different ongoing clinical trials. Among them, 12 vaccines were approved by the US FDA, the World Health Organization (WHO) and the European Medicines Agency (18). As the virus is spreading widely in the population and causing infections, many new variants are emerging. Researchers believe that Covid-19 vaccines currently being developed or already approved induce a broad immune response, so they are expected to give at least some protection against future viral strains. However, data are being collected to analyze the effectiveness of covid-19 vaccines on new variants (14).

Currently approved covid-19 vaccines by the World Health Organization (14) are as follows:

1. **mRNA-BNT 162b2-Comirnaty.**
   This vaccine was developed by Pfizer/BioNTech + Fosun Pharma in Germany and United states of America. The vaccine platform is mRNA-based.
2. **mRNA-1273.**
   This vaccine was developed by Moderna + National Institute of Allergy and Infectious Diseases (NIAID) in the United states of America (USA). The vaccine platform is mRNA.
3. **ChAdOxI-S-AZD1222.**
   Developed by Astrazeneca + University of Oxford in the United Kingdom and Sweden. The vaccine platform is non-replicating Viral Vector.

   Sputnik V

Developed by Gamaleya Research Institute + Health Ministry of the Russian Federation in Russia. The vaccine platform is non-replicating Viral Vector.

4. **Ad26 COV2S-JNJ 78436735.**
   This vaccine was developed by Johnson and Johnson + Janssen pharmaceuticals in Germany and United states of America (USA). The vaccine platform is Recombinant, replication-incompetent human adenovirus type 26 vector.
5. **Convidecia.**
   Developed by Cansino Biological Inc. + Janssen pharmaceutical in China. The vaccine platform is inactivated vaccine.
6. **BBIBP-CorV.**
   Developed by Sinopharm + China National Biotec Group company in China. The vaccine platform is inactivated vaccine.
7. **CoronaVac.**
   This vaccine was developed by Sinovac Research and Development company limited in China. The vaccine platform is inactivated vaccine.
8. **BBV152-Covaxin.**
   Developed by Bharat Biotech International limited in India. The vaccine platform is inactivated vaccine.
9. **NVX-Cov2373.**
   Developed by Novavax in United States of America (USA). The vaccine platform is subunit.
10. **EpiVacCorona.**
    Developed by the Federal Budgetary Research Institution State Research Center of Virology and Biotechnology 'Vector' in Russia. The vaccine platform is peptide vaccine.

11. **Covishield.**
    Developed by serum institute of India. It is an adenovirus vaccine.

Composition of Covid-19 Vaccines, Routes of Administration, and Efficacy (14).

1. **mRNA-BNT 162b2 – Comirnaty.**
   The vaccine is composed of mRNA vaccine encoding for the RBD of the SI protein. The vaccine contains single nucleoside incorporations of 1-methylpseudouridine. RBD antigen contains a T4 fibritin-derived fold-on trimerization domain. Encapsulated within an LNP. Efficacy of the vaccine is 95%.
2. **MRNA-1273.**
   Composed of mRNA vaccine encoding for the profusion form of the S-antigen that includes a transmembrane anchor and an intact S1-S2 cleavage site in its production form. Encapsulated with an LNP. Efficacy is 94.1%.
3. **ChAdOxl-S-AZDI222.**

Composed of adenovirus derived from chimpanzee with EI and E3 deletions, encoding for this full-length S protein with a tissue plasminogen activator signals peptide. Efficacy is 70.4%

4. **Sputrik V**

This vaccine is composed of adenovirus base combining 2 adenoviruses, Ads and Ad26. Efficacy is 91.6%.

5. Ad26 Cov2 S-JNJ-78436735.

Composed of recombinant, replication incompetent adenovirus serotype 26 (Ad26) vector encoding a full-length and stabilized SARS-Cov-2 spike (s) protein. The vaccine was derived from the clinical isolate of Wuhan Strain. Efficacy is 72%.

6. Convidecia.

Vaccine is composed of Ad5 with E1 and E3 deletions encoding for the full-length S protein. Gene was derived from the Wuhan-Hu-1 sequence for SARS-Cov2 and contains a tissue plasminogen activator signal peptide. Efficacy is 65.28%.

7. BBIBP-Cor V.

Composed of β-propionolactone inactivated vaccine of SARS-COv-2. Efficacy is 79.34%.

8. Coronavac.

Also composed of β-propionolactone inactivated vaccine of SARS-cov-2. Efficacy is 50.38% - 83.50%.

9. BBV152 – Covaxin

Vaccine is composed of a whole virion inactivated SARS- Cov-2 vaccine formulated with a Toll-like receptor 7/8 agonist molecule adsorbed to alum (Algel-IMDG) or Alum (Algel). Efficacy is 81.0%.

10. NVX-Cov2373.

Composed of stable profusion, full-length S protein made form VLP nanoparticle technology, given with saponin-based adjuvant, Matrix-M^{TM}. Efficacy is 96.4%.

11. Epivac Corona.

The vaccine contains small portions of viral proteins known as peptides. Efficacy is 100%

12. **Covishield** contains adenovirus. Efficacy is 70%.

All the vaccines are administered intramuscularly (i/m).

Table 1 : Covid-19 Vaccine Platforms, Attributes and Doses (14).

Platform	Attributes	Doses	Vaccine candidate (Manufacturer).
mRNA	Fast development speed, low-to-medium manufacturing scale.	2	BNT-162b2 (Pfizer, BioNTech mRNA-1273 (Moderna).
DNA	Fast development speed; low to medium manufacturing scale	2	INO-4800 (Inovio)
Viral vector	Medium to fast development;	1 or 2	AZD-1222Ad5 Cov

	high manufacturing scale		(Astrazeneca; Oxford University Ad26.Cov2.S (Johnson&Johnson)
Protein subunit	Medium-to-fast development, high manufacturing scale.	2	NVX-Cov2373 (Novavax)
Whole virion inactivated	Ability to quickly produce large amount of vaccine	2	Covaxin; BBV152 (Ocugen and Bharat Biotech).

Mechanism of Action of Covid-19 Vaccines.

A. mRNA Vaccines

BNT 162b2 is a lipid nanoparticle (LNP) formulated, nucleoside-modified messenger RNA (mRNA) vaccine which encodes the receptor binding domain (RBD) of the SI protein. The RBD is constructed on a T4- fibritin -derived fold on trimerization base, which helps to guide antigen folding into the native trimeric state. The N-methyl pseudo-uridine (m1ψ) nucleoside modification protects it from innate immunity. It is encapsulated with an LNP that protects it from enzymatic degradation and ensures efficient cellular uptake (15, 16 17). In the phase 1 clinical trial, BNT 162b2 elicited high SARS-Cov-2 neutralizing antibody titers with robust T cell responses.

B. Non-Replicative Vector Vaccines

ChAdOx1-S, Currently named as AZD1222, employs a different viral vector, an adenovirus derived from the chimpanzee. The use of a chimpanzee vector minimizes the possibility of interaction with preformed antibodies against adenoviruses while the EI deletion blocks the viral replication, the E3 deletion enables incorporation of larger genetic cargo into the viral vector. The added sequence encodes for the full-length S protein with a tissue plasminogen activator signal sequence. The S protein sequence is codon-optimized (Sharma et al., 2020; Chung et al, 2020; Lee et al., 2021). In the phase 1 clinical trial, the results showed no severe side effects with efficient humoral and cellular immune responses, (19,20).

C. Inactivated vaccines

BBIBP-CorV is a propionolactone inactivated SARS-Cov-2 vaccine. The inactivated virus was isolated from a patient in the Jinyintan Hospital in Wuhan (HBO2 Strain). The virus was cultivated in a qualified Vero cell line for propagation (Sharma et al., 2020, Chung et al., 2020; Lee et al., 2021). In the phase 1 and 2 clinical trials, a robust humoral response was observed in 100% of vaccine recipients (21).

D. Subunit Vaccines .

NVX-Cov 2373 is a recombinant SARS-Cov-2 (rSARS-Cov-2) nanoparticle vaccine constructed from the full-length (including the transmembrane domain) and wild-type SARS-COV-2 spike glycoprotein. The vaccine was designed with a special adjuvant called Matrix-M^{TM}.

Matrix-M™ an adjuvant based on saponin extracted from Quillaja saponaria Molina tree induces high and long-lasting levels of broadly reacting antibodies supported by a balanced THI and TH2 type of response. Although the mode of action of Matrix-M adjuvant has not been elucidated in detail, the adjuvant promotes rapid and profound effects on cellular drainage to local lymph nodes, creating a milieu of activating cells including T cells, B cells, Natural Killer cells, neutrophils, monocytes and dendritic cells. From the previous vaccine studies, it has shown a significant dose-sparing effect and an acceptable safety profile (15,16,17).

Adverse Effects of Covid-19 Vaccines.

In a scenario of the introduction of a recent vaccine to the population, the pharmacovigilance of adverse events following immunization (AEFI) is extremely relevant (Minsterio da Sauda (BR), 2020; Ministerio da Saude da Saude (BR), 2021). Any serious undesirable or unexpected sign or symptom manifested in an individual who has received any type of immunobiological is considered an AEFI and can be caused by several factors related to the component of the immunobiological, the vaccination process, or the person already vaccinated (10,14).

AEFI can be classified as a serious adverse events (SAE), which is an event that requires hospitalization, compromises the patient, that is, that causes risk of death and that requires immediate clinical intervention to prevent death, and that requires immediate clinical intervention to prevent death, causes significant dysfunction and/or permanent disability, results in congenital anomaly or causes death, or a non-serious adverse events (NSAE), which are all those events that do not meet the SAE criteria (10).

Immunization errors (IE) are adverse events caused by inadequate handling, prescriptions and/or administration and are preventable by personal training, adequate supply of equipment and supplies for vaccination, and supervision of services (14). In a study done by Roberta Barros da Silva (22), the occurrence of immunization errors was low and in particular, the number of immunization error (IE) with adverse events (AE) had a 0.74 IT per 100,000 doses, which can be considered as any preventable event that could cause or lead to inappropriate use of immunological and biological products or cause harm to the patient (10).

Immunization error can be classified as production error (non-compliance with good manufacturing practices that leads to quality deviation, such as potency changes and increased reactogenicity); error in the cold chain (vaccine transported or stored incorrectly); error in handling; and administration error (non-sterile injection, reconstitution error, injection in the wrong place, ignored contraindication, expired vaccine), which occur due to non-compliance with standards and techniques, which may result in an adverse event (19,24). The most common immunization errors in this study were extravasation and administration of the vaccine in pregnant women outside the priority group.

According to the center for disease control (CDC) report 2021 (25), during December 21, 2020 to January 10, 2021, the administration of 4,041396 first doses of Moderna covid-19 vaccine (2,465,411 to females (61%), 1,450,966 to males (36%) and 125019 to persons whose sex was not recorded (3%) was reported to CDC. During the same period, reports of 1266 (0.03%) adverse events after receipt of the first dose of Moderna covid-19 vaccine had been submitted to Vaccine Adverse Events Reporting System (VAERS). Among these, 108 case reports were identified for further review as possible cases of severe allergic reaction, including anaphylaxis, based on description of signs and symptoms; 10 of these reports all describing events in females,

met the Brighton collaboration case definition criteria for anaphylaxis, corresponding to an initial estimated rate of 2.5 anaphylaxis case per million first Moderna covid-19 vaccine dose administered (26).

Klugar et al (27) studied the side effects of mRNA-based and viral vector-based covid-19 vaccines among German healthcare workers. All local side effects related to the injection site were more prevalent in the mRNA-based vaccine group than the viral vector-based vaccine group. A total of 78.3% and 70.4% of mRNA-based vaccine recipients reported at least one local side effect (χ^2= 3.421, sig = 0.064), respectively. Overall, injection site pain (75.6%) was the most prevalent local side effect, followed by injection site swelling (18%) and injection site redness (10.4%). Injection site pain (77.4%) Vs 68.8%, respectively) was significantly more common in the mRNA-based vaccine group compared to the viral vector-based vaccine group (χ^2 = 3.993; Sig. 0.046).

On the contrary, all systemic side effects were more prevalent in the viral vector-based vaccine group than the MRNA-based vaccine group than the mRNA-based vaccine group. A total of 87.2% and 61% of viral vector-based vaccine and mRNA-based vaccine recipients reported at least one systemic side effect (χ^2 = 30.522; sig < 0.001), respectively. Overall, the most common systemic side effect was headache/fatigue (53.6%), followed by muscle pain (33.2%), malaise (25%), chills (23%), and joint pain 21.2%). (27,28)

The differences between the viral vector-based vaccine group and mRNA-based vaccine group were statistically significant (χ^2 97.782, 106,419, 27.506, 27.292, 63.907, 16.161 and 47.501, sig. < 0.001, < 0.001 and < 0.001, < 0.001 <0.001 and < 0.001, respectively), chills (57.6% vs 13.9%), headache/fatigue (74.4% vs 48.1%), joint pain (47.2% vs 14.3%), nausea (20.8% vs 8.2%) and malaise (48.8% vs 18.8%). The most prevalent oral side effect was vesicles (6.3%) then bleeding gingiva (4.3%), halitosis (3.7%) oral paranesthesia (2.2%) swollen mucosa (2.2%) and ulcers (2%). More than three fourths (75.6%) of oral side effects emerged within the first week after vaccination.

A total of 21 (3.5%) participants reported experiencing at least one skin-related side effect with 3% and 5.6% of mRNA-based vaccine and viral vector-based vaccine recipients being affected (sig = 0.171; 2-S Fisher's exact test) respectively. The most prevalent skin-related side effect was rash (2.8%) followed by urticaria (0.7%), and angioedema (0.7%). The most common affected sites were face (57.1%), followed by upper limb (38.1%), and lower limb (19%) (26,28,29).

As at June 14, 2021, the Center for Disease Control and prevention (CDC) have recorded more than 3500 reports of side effects from people in the USA who have received covid-19 vaccines. The CDC data also revealed hospitalizations of those receiving covid-19 vaccines (25). Summaries of their symptoms include heart palpitations, severe abdominal pain, seizures, and almost stroke-like symptoms". Several people have also reported that they could not breathe after receiving the shot (24,25).

According to the CDC, since April 2021, more than 1000 cases of myocarditis and pericarditis have been reported to the Vaccine Adverse Event Reporting System (VAERS) after mRNA-based covid-19 vaccination (i.e Pfizer-BioNtech, Moderna) in the USA (CDC, 2021). Moreover, on 25 June, 2021 the Food and Drug Administration (FDA) revised the patient and provider fact sheets regarding the suggested increased risks of myocarditis and pericarditis following vaccination (30).

Within 24 hours of the administration of the first dose of the Pfizer vaccine (authorized in the UK on the 2nd of December, 2020), 3 cases of suspected anaphylaxis and were treated with adrenaline. A single case report has confirmed that polyethylene glycol (PEG) can cause severe anaphylaxis to the Pfizer vaccine (30,31).

The Pfizer vaccine was given an emergency use authorization by the United States Federal Drug Administration (US FDA) on the 11th of December, 2020. Following the introduction of the Pfizer vaccine in the United States by December 2020, more than 1.8 million first doses were administered and 4393 adverse drug reactions had been submitted to the Vaccine Adverse Event Reporting System (VAERS). Twenty one reactions were classified as anaphylaxis according to Brighton collaboration criteria for reactions to vaccines. Six were limited to skin only (32,33).

Polysorbate 80 (PS80;Tween 80) is derived from polyethoxylated sorbitan and oleic acid. It is one of the excipients in the Astrazeneca vaccine. PEG and PS80 share an allergenic epitope, that is the repeating polymer domain. Immediate hypersensitivity to PEG 3350 with skin test cross-reactivity to PS80 has been reported (34,35,36,37).

Conclusion

Twelve vaccines have been approved worldwide by the World Health Organization, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). New variants of the coronavirus have continued to emerge s the virus continues to spread causing widespread mortality and morbidity. Some of the vaccines are formulated from nucleoside-modified mRNA while some are formulated from an adenovirus derived from the chimpanzee. Others are recombinant nanoparticle vaccines. Adverse reactions to the coronavirus vaccines can be due to immunization errors and components of the immunological and biological products. The adverse reactions include: injection site pains, fever, anaphylaxis, urticaria, myocarditis, pericarditis, thrombotic events and bleeding tendencies.

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