Efficacy, Safety and Immune Reactions Associated with COVID-19 Vaccines

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Abstract: COVID-19 is a disease caused by the SARS-CoV-2 virus that has spread into an worldwide pandemic. Quick efforts into developing vaccines against SARS-CoV-2 took place, using both existing technologies or ones newly released to the public. Side effects observed upon administration of previous vaccines or the unknown associated with new vaccines have caused concern in large cohorts of population regarding their safety. In this paper, we look with detail into the ingredients of existing COVID-19 vaccines and their side effects, hoping to clear any concerns and claims that rose out of proportion. To obtain the presented data, we searched and analyzed online reports and databases from vaccine developers and clinicians alike, as well as research articles that covered the potential side effects of specific vaccine ingredients. Our research indicates that existing vaccines against COVID-19 are safe for most of the population, with very small percentages of severe side effects associated with it. The side effects of the vaccines largely outweigh the potential complications arising from SARS-CoV-2 infection. Long term clinical trials for safety and efficacy are currently underway to monitor any potential long term side effects.

1 INTRODUCTION

COVID-19 is a disease caused by the SARS-CoV-2 virus, that affects the respiratory system and a multitude of other organs. It has a mortality rate of around 2%, having caused about 4 million deaths worldwide, and 200 million infections as of July 2021. SARS-CoV-2 virus has a surface spike protein S that binds to the angiotensin converting enzyme II (ACE2) in human cells, allowing the virus particle to fuse with the host cell membrane and enter via endocytosis. Currently, there is no approved treatment that effectively reverses the course of disease. As such, vaccines became a strong bet in the fight against SARS-CoV-2. Several countries have rushed to manufacture vaccines against the virus in record times, starting in 2020 and as of July 2021, 20 vaccines against COVID-19 were approved worldwide in different countries and 900 million people have been vaccinated worldwide. (Vaccine Tracker.2021)

With the development of new vaccines—some with technology never used before in clinical settings—several concerns about its safety profile were raised. These concerns arise at times from unfounded or false information from less reliable sources, and leads to many individuals not taking the vaccine, potentially increasing the spread of the pandemic. In this article, we explored the possible side effects and allergic reactions based on single vaccine ingredients as well as complete vaccine formulations. We explore and compare the current vaccines against COVID-19, safety data, and potential for immune reactions based on their ingredients. These vaccines are described on Table 1, showing the technology used for development and their ingredients. In the following section, we describe the different types of vaccines that are developed against SARS-CoV-2.

2 COVID-19 VACCINE TYPES

2.1 Inactivated Virus Vaccines

Inactivated vaccines are developed by growing the virus in a controlled laboratory environment using a suitable cell culture as a host, and then deactivating it

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using a variety of biological, chemical, or physical methods. The inactivated virus offers a strong safety profile but it will still be recognized by the immune system, which makes antibodies against it. (Sanders, Koldijk, and Schuitemaker 2014) Inactivated virus vaccines have been used for a long time and other types include vaccines against polio, hepatitis A, rabies, influenza, tick-borne encephalitis, injected typhoid, cholera, plague, pertussis, among others. The viral material in inactivated vaccines does not replicate, making them virtually impossible to cause pathological effects due to infection.

2.2 Adenovirus Vector

Adenoviruses are originally nonenveloped double-stranded DNA viruses. They can be modified to deliver genetic material in human cells and as such have been used for decades in gene therapy research. Currently, there are several undergoing clinical or preclinical trials using adenoviruses for vaccines against different diseases and pathogens such as HIV, Ebola, influenza, rabies, dengue, plasmodium falciparum, mycobacterium tuberculosis. For COVID-19 vaccines, these viruses were modified to deliver DNA encoding the SARS-CoV-2 Spike protein.

The adenovirus used in the vaccine lacks replication because some genes necessary for replication have been removed. Following vaccination, the adenoviral vector enters the cell and releases its genes, which are transported to the nucleus, where the cellular machinery transcribes messenger ribonucleic acid (mRNA) and translates it into protein. Once released outside the cell, the protein induces an immune response to generate antibodies against it. (TATSIS, ERTL 2004)

2.3 mRNA Vaccines

mRNA molecules need to reach the cytoplasm or endoplasmic reticulum ribosomes and be translated into proteins, which is the concept of mRNA vaccines. mRNA molecules can be encapsulated in lipid nanoparticle (LNP) carriers to penetrate tissues to facilitate the transfer of genetic information in host cells, thereby initiating the synthesis of antigenic proteins. (JACKSON, KESTER, CASIMIRO 2020) In these vaccines, LNPs are used to protect RNA against degradation, since this type of biomolecule is more sensitive to degradation than DNA or proteins. mRNA vaccines are new vaccine types that were not tested before COVID-19. An advantage of these vaccines when compared to adenovirus vector ones, is that they can be produced in large scale more quickly and at lower costs, since RNA encapsulation in lipid nanoparticles is a more straight-forward process. (PARDI, HOGAN, PORTER 2018)

2.4 Subunit Vaccines

Subunit vaccines are based on the direct delivery of proteins, or parts of proteins, that mimic the ones in SARS-CoV-2 and trigger an immune response to these antigens. These vaccines are designed so that their antigens lack pathogen-associated molecular patterns (PAMPs) required by the host immune system to recognize the antigen, reducing the immunogenic potential of this vaccine approach. (NIH 2019)

A potential problem with subunit vaccines is the antigenic denaturation can occur, which can lead to the production of different antibodies that do not recognize the pathogen. This could potentially lead to the protein binding to a different antibody than to a specific antigen against the pathogen. Because the antigens themselves normally only elicit a weak immune response, when making this vaccine, non-immunogenic materials are usually incorporated into the vaccine formulation to improve the immune response and enhance the efficacy of the vaccine. These materials are called adjuvants.

Currently, a large number of protein subunit vaccine candidates for SARS-CoV-2 are in human clinical trials, with 2 on the market (see Table 1). These candidates use a different immunogen, either the whole Spike protein or a different form of its receptor binding domain (RBD). RBD is the S protein region that mediates the binding of the virus to the ACE2 receptor of the target host cell.

Table 1: Approved covid-19 vaccines (as of July).

Vaccine name	Country of origin	Trial Start Date
Inactivated virus vaccines		
CoronaVac	China	**2020-09-16**
BBIBP-CorV	China	**2020-4-29**
WIBP-CorV	China	**2020-04-11**
Minhai Biotechnology Co: SARS-CoV-2 Vaccine	China	**2020-10-07**
Covaxin	India	**2020-9-8**
KoviVac	Russia	**2020-9-21**
QazVac	Republic of Kazakhstan	**2020-8-28**
COVIran Barekat	Iran	**2021-3-13**
Adenovirus vector		
Ad26.COV2.S	United States	**2020-6-30**

AZD1222	United Kingdom	**2020-3-19**
Ad5-nCoV	China	**2020-9-26**
Sputnik V COVID-19 vaccine	Russia	**2020-6-18**
Sputnik Light	Russia	**2021-1-19**
Covishield	India	**2020-08-15**
mRNA vaccines		
mRNA-BNT162b2	United States	**2021-3-25**
mRNA-1273	United States	**2020-2-25**
Takeda: TAK-919	Japan	**2020-11-21**
Subunit vaccines		
ZF2001	China	**2020-08-16**
EpiVacCorona	Russia	**2020-8-26**
CIGB-66	Cuba	**2020-12-7**

3 SAFETY DATA

Initial clinical trials for the vaccines excluded volunteers with history of allergic reactions, diabetes, cancer, among other pathologies. Despite that, several volunteers suffered adverse reactions upon vaccine administration that resulted in temporary disability or even death, although in very low numbers. This prompted us to look at vaccine ingredients with a potential to cause adverse effects.

In the sections below, we describe the safety and efficacy data for some extensive used vaccines.

4 INACTIVATED VIRUS VACCINES

4.1 CoronaVac

CoronaVac is an inactivated vaccine candidate against COVID-19, From July 21 to December 16, 2020, Brazil recruited a total of 12,396 volunteers to receive CoronaVac and placebo in a phase 3 clinical trial. (PALACIOS, BATISTA, ALBUQUERQUE 2021) The most common adverse reactions in the vaccine group were pain at the injection site (60.3%), swelling (5.8%) and itching (4.2%); the most common systemic adverse reactions were headache (34.3%), fatigue (16.0%) and muscle pain (11.7%). Among the 4,953 people, 14 days after the second vaccination, 85 cases of symptomatic infection were detected; among 4870 people in the placebo group, 168 cases of symptomatic infection were observed. Therefore, the effective rate of Coronavac was determined to be 50.7%. Fourteen days after vaccination, the effective rate of preventing cases where minimal medical intervention was required is 83.7%, and the effective rate of preventing moderate to severe disease was determined to be 100%. All severe cases (6 cases) are in the placebo group. There are mainly three new coronavirus strains in Brazil, namely B.1.1.28, P.1 and P.2. The first one is wild type, and the latter two are variants. The main variant of the institute in the region is P.2 The neutralizing activity ratios of 45 volunteers' serum to B.1.1.28, P.1 and P.2 were 32 (71.1%) and 31 (68.9%), respectively. In 36 people (80.0%), the study found that the sera of the vaccinators had a consistent neutralizing effect on all these variants. Overall, Coronavac seems to be well tolerated.

4.2 BBIBP-CorV

BBIBP-CorV is a vaccine based on inactivated viral particles. This candidate vaccine was developed by Sinopharm Wuhan Institute of Biological Products and the China Center for Disease Control and Prevention. Two different SARS-CoV-2 strains, WIV04 and HB02, were isolated from a patient at the Jinyintan Hospital in Wuhan, China.

A large phase 3 clinical trial was conducted in Asia, covering more than a dozen countries including the United Arab Emirates (23.9%), India (14.0%), Bangladesh (10.4%), China (9.8%), Pakistan (9.1%), and others. The average age of volunteers was 36.1 years old, 84.4% were males, and 98.4% were 59 years old and below. Of the total 40,411 volunteers, 13,066 volunteers in WIV04 group, 13,086 volunteers in HB02 group, and 13,071 volunteers in placebo group completed two injections. Within 1 week after vaccination, 44.2% (WIV04 group), 41.7% (HB02 group), 46.5% (placebo group) had adverse reactions in each group, the most common of which was injection site pain (24.3%, 19.4%, 27.9% respectively) and headache (12.9%, 13.1%, 12.6% respectively). As of December 20, 2020, after the volunteers received the first injection (vaccine or placebo), there were a total of 962 suspected cases. After confirmation, there were 255 confirmed cases. Among them, outside the monitoring period (the first injection). In the 35th day afterwards, there were 113 confirmed cases, and within the monitoring period (14 days after the second injection), there were 142 confirmed cases overall. (AL KAABI, ZHANG, XIA 2021) Among these 142 cases, 95 cases were in the placebo group, 26 cases were in the WIV04 group, and 21 cases were in the HB02 group. The calculated

effective rate of the WIV04 vaccine is 72.8%, and the effective rate of the HB02 vaccine is 78.1%.

4.3 WIBP-CorV

WIBP-CorV is another inactivated virus COVID-19 vaccine also developed by Sinopharm, for which the viral particles were obtained from a different SARS-CoV-2 source. JAMA published the phase III clinical interim results of both BBIBP-CorV and WIBP-CorV at the same time. (AL KAABI, ZHANG, XIA 2021) Peer-reviewed results show WIBP-CorV is 72.8% effective against symptomatic cases and 100% against severe cases. The safety profile of the vaccine is similar to BBIPP-CorV.

4.4 COVAXIN

COVAXIN, also known as BBV152, is a COVID-19 vaccine developed by Bharat Biotech in India in collaboration with the Indian Medical Research Council (ICMR), part of the National Institute of Virology (NIV). The vaccine is manufactured using viral particles that were grown on Vero cells and subsequently inactivated. (Bharat Biotech 2021)

Phase 3 clinical trials of Covaxin were conducted in different locations across India. 24,419 individuals received two doses of BBV152 (n = 12,221) or placebo (n = 12,198). There were 24 infections in the vaccine group and 106 infections in the placebo group, reported at least 2 weeks after the second dose. The overall vaccine efficacy was 77.8%. The two-dose vaccine was also 93.4% effective in those with severe disease and 63% protective in those with asymptomatic infection. The preprint reveals that in those 60 years and older, the vaccine was 67.8% effective, while in younger people, the effectivity was determined to be 79.4%. Adverse events were below 1% in both groups, with the most frequent being headache, followed by fever, fatigue and myalgia.

5 ADENOVIRUS VECTOR

5.1 Ad26.COV2.S (Janssen)

The Janssen COVID-19 vaccine is a recombinant, replication-incompetent adenovirus serotype 26 (Ad26) vector vaccine that has been modified to contain the gene for making a protein found on SARS-CoV-2. Vaccination with the Janssen COVID-19 vaccine consists of a single 0.6 mL dose containing 5×10^{10} viral particles, administered intramuscularly. (LIVINGSTON, MALANI, CREECH 2021)

In the phase 3 clinical trial “ENSEMBLE” (clinicaltrials.gov accession number NCT04505722), the per-protocol population included 19,630 SARS-CoV-2–negative participants who received Ad26.COV2.S and 19,691 who received placebo. Three deaths reports occurred in the vaccine group but no case was related to covid-19 and not attributed to the vaccine, and 16 in the placebo group, 5 of which were determined to be caused to COVID-19. (SADOFF, GRAY, VANDEBOSCH 2021)

Vaccine recipients experienced a variety of adverse symptoms. However, most were mild to moderate and resolved 1–2 days after vaccination. These are more common in people aged 18-59 than in people over 60. Severe local or systemic reactogenic symptoms were more common among vaccine recipients (2.2%) than placebo recipients (0.7%). The FDA identified injection site pain, hypersensitivity, and systemic reactogenicity as three adverse events associated with vaccination. No specific security issues were found after analysis.

Out of more than 6.8 million doses administered, embolic and thrombotic events were observed, including six cases of a rare and severe type of blood clot in individuals following administration. (CDC 2021) (FDA 2021) Cerebral venous sinus thrombosis (CVST) was observed in combination with low levels of blood platelets (thrombocytopenia) in these cases. Medical and scientific teams at the FDA and CDC examined available data and determined these events were thrombosis-thrombocytopenia syndrome (TTS).

After a brief suspension, and following a safety review by the CDC’s Advisory Committee on Immunization Practices and the FDA have determined that use of Janssen vaccine would resume in the United States, effective April 23, 2021.

Ad26.COV2.S protected against moderate to severe–critical COVID-19 with onset at least 2 weeks after administration, where 116 cases in the vaccine group vs. 348 in the placebo group were observed, resulting in an efficacy of 66.9%. It was more effective against severe Covid-19, with an incidence of 76.7% at least 14 days after administration and 85.4% after 28 days .

Rare cases of the neurological disorder Guillain-Barré syndrome have also been reported following vaccination with the Janssen COVID-19 vaccine. Although the chances of developing the condition are low, they appear to be three to five times higher among recipients of the Johnson & Johnson vaccine than among the general population in the United

States, although a causal relationship has not been yet established. (VOYSEY, CLEMENS, MADHI 2021)

A single dose of Ad26.COV2.S protected against symptomatic COVID-19 and asymptomatic SARS-CoV-2 infection and was effective against severe–critical disease, including hospitalization and death.

5.2 AZD1222 Vaxzevria (Oxford-AstraZeneca)

The Oxford–AstraZeneca COVID-19 vaccine is a replication-deficient Simian adenovirus vector. Between April and November 2020, 23,848 participants were enrolled and 11,636 participants (7,548 in the UK, 4,088 in Brazil) were included in the primary efficacy analysis. (SCHULTZ, SØRVOLL, MICHELSEN 2021) In participants who received two standard doses, vaccine efficacy was 70.4%. From 21 days after the first dose, there were ten cases hospitalized for COVID-19, all of which in the placebo group; two were classified as severe COVID-19, including one death. 175 severe adverse events occurred in 168 participants, 84 events in the ChAdOx1 nCoV-19 group and 91 in the control group.

An article published on The New England Journal of Medicine reported five cases of severe venous thromboembolism in unusual sites and concomitant thrombocytopenia that occurred 7 to 10 days after vaccination with AZD1222. (EUROPEAN MEDICINES AGENCY 2021) Four of the patients had severe cerebral venous thrombosis with intracranial hemorrhage, and the outcome for three of them was fatal. Thrombotic thrombocytopenic purpura and immune thrombocytopenic purpura are not suspected because there was no hemolysis and the platelet transfusion response was normal. What all five patients have in common is high levels of PF4-polyanion complex antibodies. The researchers suggest that these cases represent vaccine-related variants of spontaneous heparin-induced thrombocytopenia, which they call vaccine-induced immune thrombotic thrombocytopenia (VITT).

After a period of suspension, AZD1222 Vaxzevria was authorized in the EU to prevent COVID-19 as the benefits of Vaxzevria outweigh its risks in adults of all age groups from adverse events including thrombosis in combination with TTS. The frequency of TTS events was observed to be very rare based on current reporting. (LOGUNOV, DOLZHIKOVA, SHCHEBLYAKOV 2021)

5.3 Sputnik V (Gam-COVID-Vac) COVID-19 vaccine

The Gam-COVID-Vac vaccine, also known as Sputnik V, was developed by a government-sponsored team of cell microbiologists at the Gamalaya Institute for Epidemiology and Microbiology in Russia. Gam-COVID-Vac is based on two human adenoviruses that contain a gene that encodes the full-length spike protein S of SARS-CoV-2 to stimulate an immune response.

In the Phase 3 trial, 21,977 adults were randomly assigned to the vaccine group (n = 16,501) or the placebo group (n = 5,476). From 21 days after the first dose of vaccine, the day on which dose 2 was administered, 16 (0.1%) participants in the vaccine group and 62 (1,3%) in the placebo group were confirmed to have COVID-19. Based on the second interim analysis of data obtained 28 days after administering the first dose, 7 days after the second dose, vaccine efficacy was determined to be over 95% 42 days after the first dose, no life-threatening adverse events were observed. (LOGUNOV, DOLZHIKOVA, SHCHEBLYAKOV 2021)

The vaccine induced robust humoral and cellular immune responses among individuals of all ages, indicating a strong potential to prevent severe disease in individuals over the age of 60.

An article published by Lancet claimed discrepancies and substandard reporting of data on the Sputnik V phase 3 trial. According to the trial data, 35,963 individuals were screened and 21,977 individuals were randomized, but there disclosure as to why 13,986 participants were excluded. The authors also claim inconsistencies in the numerical data related to vaccine efficacy. (BUCCI, BERKHOF, GILLIBERT 2021)

6 mRNA VACCINE

6.1 Pfizer–BioNTech COVID-19 Vaccine (BNT162b2)

The Pfizer-BioNTech COVID-19 vaccine is developed by the German company BioNTech, a novel type based on encapsulated mRNA, that encodes for the full SARS-CoV-2 Spike protein S.

In their press release issued on November 18 2020, Pfizer and BioNTech stated that the final interim analysis data was 95% effective against COVID-19 within a week of the candidate receiving both inoculations. (Pfizer 2020) This data is based on

the assessment of 43,448 participants, 170 of whom developed COVID-19 during the assessment period. Of these, 162 were in the placebo group and 8 were in the vaccine candidate group. Vaccine efficacy is consistent across age, gender, race, and ethnic demographics. In addition, the efficacy observed in the inoculated individuals over the age of 65 was over 94%. With regard to the safety of BNT162b2, no serious safety issues have been reported. The more frequent event compared to the placebo group is fatigue. Based on these results, Pfizer and BioNTech became the first company to submit a request for a vaccine against SARS-CoV-2 to the FDA.

One ingredient found in mRNA vaccines of particular concern for allergic reactions is a chemical called polyethylene glycol (PEG). In mRNA vaccines, PEG is used to coat mRNA molecules and support their entry into cells. Since PEG is generally not a component of previous vaccines, there is limited information on its allergic effects.

An article on the journal Pediatrics reported 7 cases of clinical myocarditis or myopericarditis that developed in 14- to 19-year-old males within 4 days of receiving the second dose of the Pfizer-BioNTech COVID-19 vaccine with no evidence of acute SARS-CoV-2 infection. (MARSHALL, FERGUSON, LEWIS 2021) These individuals developed chest pain within 4 days after the second shot of the vaccine, and developed fever before and after the onset. Further studies need to be conducted to determine causation.

6.2 Moderna COVID-19 Vaccine (mRNA-1273)

mRNA-1273 is a vaccine developed by the company Moderna that uses mRNA that is translated into the SARS-CoV-2 Spike protein to elicit an immune response.

On November 18th 2020, Moderna published their vaccine Phase 3 clinical study. 24,907 (82.1%) participants who were considered to be at occupational risk for acquiring the SARS-CoV-2 infection, of whom around 25% were healthcare workers. This preliminary analysis was performed 14 days after the second vaccination and included 95 confirmed COVID-19 cases among the participants, 90 of which belonged to the group receiving placebo and 5 cases belonged to the group receiving the vaccine, resulting in a calculated efficacy of the candidate vaccine of 94.5%. Furthermore, of the 11 cases that were considered severe, none were in the vaccinated group, which indicates that mRNA-1273 may also prevent severe COVID-19.

As for the safety of mRNA-1273, mainly mild to moderate events have been reported. The most frequent severe adverse effects were soreness at the injection site after the first dose (2.7%), and myalgia (8.9%), arthralgia (5.2%), fatigue (9.7%). Overall, these effects were described as short-lived. (Moderna 2020)

7 SUBUNIT VACCINES

7.1 ZF2001

ZF2001 is a protein subunit COVID-19 vaccine developed by Anhui Zhifei Longcom. It uses a traditional alum-based adjuvant with a long safety profile.

50 participants in phase 1 trial, 900 participants in phase 2 trial, randomly assigned to receive two doses of placebo, 25 μg vaccine, or 50 μg vaccine, or three doses of placebo, 25 μg vaccine, or 50 μg vaccine. (YANG, LI, DAI 2021)

In the three doses of 25 μg vaccine group, the most common local adverse reactions included pain at the injection site (12%), swelling (14%), induration (9%), redness (16%) and itching (19%). The most common systemic adverse reactions in this group included fever (8%), cough (1%), headache (2%) and fatigue (0%). In general, most volunteers had no adverse reactions or only minor adverse reactions. In terms of humoral immunity, the seroconversion rates of serum antibodies were 69% after the first injection, and reached 100% 30 days after the second injection. Notably, neutralizing antibodies were detected in 97% of the 25ug group. 14 days after the third injection, neutralizing antibody titers of the 25ug group exceeded those in the serum level of the recovered patients. In terms of cellular immunity (T cell response), the researchers performed an ELISpot test on the peripheral blood of volunteers and determined that both the 25μg group or the 50μg group could induce moderate Th1 (IFN-γ and IL-2) and Th2 (IL-4 and IL-5) responses after vaccination.

The data from Phase I/II suggest that ZF2001 offers a safe profile and strong immunogenicity. Therefore, it was finally decided to use a three-dose of 25ug (30 days between each injection) in the phase 3 clinical trial.

7.2 CIGB-66

CIGB-66 is a protein subunit COVID-19 vaccine developed by the Center for Genetic Engineering and Biotechnology in Cuba.

On June 22,2021, official Cuban government sources reported that the results of an initial study involving 48,290 participants administered vaccines in 3 doses, with a 2 weeks space. Result showed that CIGB-66 had a 92.28% efficacy rate at preventing symptomatic COVID-19. the analysis was based on 153 infection cases, including 11 in the vaccination group and 142 in the placebo group.

8 VACCINE INGREDIENTS WITH POTENTIAL ALLERGIC SIDE EFFECTS

In the vaccines described above, some ingredients have been known to cause allergic reactions. Below, we discuss the known side effects associated with each.

8.1 Beta-propiolactone

Beta-propiolactone (BPL) has been used for several decades in different vaccines, such as the ones for rabies. In 1987, a study by MC Anderson and colleagues saw an association between urticarial reactions and the rabies vaccine. (ANDERSON, BAER, FRAZIER 1987) By looking at IgE and IgG antibodies, researchers saw that besides developing IgG against the subvirion, immunized individuals also developed IgE and IgG to the BPL-Human serum albumin used as adjuvant in the vaccine, which seems to be the component that caused the strongest reaction. Immunized subjects without urticaria had no detectable IgE. The authors hypothesized that the allergic reactions are mostly due to IgE antibodies, since no fever, arthritis, lymphadenopathy or nephritis were part of the symptoms. For the double inactivated vaccine, beta-propiolactone, and human serum albumin, most subjects with a urticarial response to the booster had IgE. In contrast, undetectable IgE in immunized subjects without urticaria. A research article from 1987 also mentioned urticaria as a common reaction to a rabies vaccine, which also contained beta propiolactone. Studies have shown that these responses are not caused by the rabies virus antigens themselves, they are mostly caused by the PBL-HSA complex. Notably, this rabies vaccine response was very similar to that after penicillin, suggesting an association with IgE antibodies to penicillin metabolites that are haptens.

Apart from urticarial reactions, no adverse effects have been associated with the use of beta-propiolactone as an adjuvant, and therefore it seems to be a safe ingredient in vaccine formulations.

8.2 Hydroxypropyl-β-cyclodextrin

Hydroxypropyl-β-cyclodextrin (HP-β-CD) is a cyclic oligosaccharide of the cyclodextrin family that has been used safely as an excipient for pharmaceutical agents for decades. It is widely used to improve the solubility of different compounds and it has been as a excipient in pharmaceutical agents for several decades. HP-β-CD as a vaccine adjuvant has shown to induce IgG responses, but no IgE responses were detected. Subcutaneous injection of solutions containing HP-beta-CD is known to induce type I interferon release and responses in Th2 cells, leading to higher Ag-specific IgG titers, such as IgG1 and IgG2c. However, no systemic proinflammatory cytokine responses were detected. For this reason, and for its high adjuvant activity, HP-β-CD is still considered a safe adjuvant in vaccine formulations with the main adverse event being diarrhea and there have been no adverse events on kidney function. (GOULD, SCOTT 2005)

8.3 Alum-based

Potassium alum, commonly named simply alum, is an adjuvant with the formula $KAl(SO_4)_2$. Alum is well-tolerated in a vast majority of cases and does not usually induce clinically visible inflammatory reactions in vaccinated subjects. It is known, however, to cause nodules at the site of injection. These nodules contain a large quantity of fibrin, histone and host DNA and uric acid. It is hypothesized that this release of intracellular molecules may cause them to be recognized as damage-associated molecular patterns (DAMPs). (DESMET 2014) This release can trigger a noninfectious inflammatory response by binding to a pattern-recognition receptor. Aluminum-adjuvant-containing vaccines are typically given over relatively long intervals over a relatively short period of time. Aluminum adjuvants immunotherapy should take into consideration.

Aluminum salts are not currently used in immunotherapy in the United States; however, they are used in Europe as an immune stimulant. Some researchers state that aluminum salts are mostly irrelevant in immunotherapy. (TERHUNE, DETH 2014) Aluminum salts in allergy vaccines are known to contribute to increased allergen-specific IgE, at least in the 6 months following vaccine administration. (JUTEL AKDIS 2011) In a 1972

study, young healthy men experimentally immunized with ryegrass pollen allergens and alum allergens developed type I cutaneous hypersensitivity, specific histamine-releasing, and passively transferable of IgE antibodies. (MARSH, LICHTENSTEIN, NORMAN 1972)

8.4 Lipid Nanoparticles (LNPs)

The Pfizer-BioNTech vaccine includes 4 different LNPs: cholesterol, ALC-0159 (2-[(polyethylene glycol)2000]-N,N-ditetradecylacetamide),1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) and ALC-0315 [(4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2- hexyldecanoate)]. Cholesterol and DSPC are also ingredients of the Moderna vaccine and have been used in different pharmaceutical agents such as Doxil. ALC-0315 is an aminolipid that helps with mRNA compaction and is involved in its cellular delivery and cytoplasmic release, which is thought to happen by endosomal destabilization. The Moderna vaccine also contains an ionizable aminolipid, the formulation of which is not disclosed, but its thought to be heptadecan-9-yl8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate. ALC-0159 is present in the Pfizer-BioNTech vaccine at levels <2 mol % and it helps with nanoparticle stabilization by a steric mechanism through its (polyethylene glycol) PEG moiety. The Moderna vaccine has a similar compound named 1,2-dimyristoyl-rac-glycero-3-methoxyPEG2000, which is also a PEGylated lipid. These PEGylated lipids are thought to be the causative agents in the few cases, anaphylaxis was observed in individuals to whom the vaccines were administered. Complement activation was initially thought to be the cause of allergic reactions to pegylated nanodrugs. (MOGHIMI 2018) Although complement activation, was initially proposed as a possible reaction to vaccines, it does not seem to be the actual case, since anaphylaxis is very rare in both Pfizer-BioNTech and Moderna vaccines. (GANSON, POVSIC, SULLENGER 2016) In cases of anaphylactic reactions to the PEGylated nanomedicines, the mechanisms are still unknown. Although most people have high levels of anti-PEG IgG, adverse allergic reactions are not expected. This may be due to differences in the properties of anti-PEG antibodies, and individual differences in susceptibility to antibody-triggered responses cannot be ruled out. Still, the molecular basis of these responses in humans remains unknown.

In responding individuals, hypersensitivity reactions to LNP-based vaccines may be related to the pre-existing pre-existence of presumed anti-PEG IgE, in addition, the likely intradermal titers of anti-PEG IgG are expected to be extremely low to explain the hypersensitivity of vaccine recipients' reaction. (ZHOU, STONE, JAKUBOVIC 2021) Given the widespread presence of PEG in cosmetics and daily hygiene products, these products appear to be frequently used by people who have displayed allergic reactions to mRNA vaccines. It is reasonable since that other IgEs that cross-react with a heterogeneous set of allergenic determinants also recognize LNP and LNP aggregates, trace lipid/mRNA impurities. In addition, different epitopes on vesicles and PEG-lipid micelles that may coexist can also be recognized.

In summary, PEG 2000, which is used in the Pfizer-BioNTech and Moderna vaccines to stabilize lipid nanoparticles, is the only compound in these vaccines reported to cause anaphylaxis.

8.5 Polysorbate80

Polysorbate 80 is another compound similar to PEG 2000 that is present in many food and drugs, as well as the Oxford/AstraZeneca vaccine. Polysorbate 80 has is considered a potential trigger to anaphylactoid reacts and it is thought to cross-react with PEG. Polysorbate 80 is used as an excipient in many drugs and some vaccines. It can also use as a food additive. Polysorbate 80 is widely tolerated. However, it has been thought to potentiate anaphylactic reactions. (COORS, SEYBOLD, MERK 2005) The use of high molecular weight PEGs in a large variety of medications, cosmetic and cleaning products which may lead to sensitization in a more susceptible individuals.(STONE, LIU, RELLING 2019)

9 CONCLUSIONS

In this paper we reviewed the different types of vaccines, their ingredients and the reactions associated with them. With the fast spread of the COVID-19 pandemic and the appearance of different newly-developed vaccines against SARS-CoV-2, many concerns were raised regarding the efficacy and safety of these vaccines, particularly about the mRNA ones based on newer technologies.

Although the ingredients in the vaccines herein analyzed seem safe for most, care should still be taken, and possible alternatives be sought. Virus-inactivators such as beta-propiolactone seems to cause allergic reactions in only a few subjects. Although it has proved to be a very effective viral inactivator, perhaps some non-immunological

alternatives such as radiation, formalin, or heat inactivation could be considered to inactivate the virus during the vaccine development stage. Several vaccines inactivated using these methods have shown great success in prevention. However, if a virulent strain is used to produce the virus stock, inadequate inactivation with formaldehyde can lead to several issues. A number of children immunized with an inactivated poliovirus vaccine preparation containing inadequately inactivated Mahoney poliovirus developed paralytic poliomyelitis. Furthermore, in the 1960s, a formalin-inactivated RSV vaccine made children sicker when they were exposed to natural infections, resulting in several deaths. Likewise, an inactivated measles vaccine was connected with an unusual rash after exposure to the wild-type virus, a reaction known as "atypical" measles. This brings us back to the vaccines that do not use inactivated forms of the virus, such as mRNA vaccines, where such issues are not expected to occur. Despite very few adverse reactions to beta-propiolactone, different alternatives can be explored, mainly to reduce public fear of vaccines and thus increase the number of people getting vaccinated.

Concerning possible alternatives to alum, HP-beta-CD seems to be a strong candidate, as it doesn't appear to elicit any IgE response. (GOULD, SCOTT 2005)

Alternatives to PEG as the main agent to different allergic responses have also been proposed. While compounds with a similar formulation are expected to still cause allergic responses, neutral stabilizers such as polyvinylpyrrolidone and its derivatives are a possible alternative. It is often administered to large numbers of individuals as a plasma expander to many individuals with no reports of severe reactions (BURNETT 2017).

Another factor to consider in COVID-19 vaccines, are potential changes in gene expression arising from the Spike protein S, which is present in some whole-protein vaccines or is the final translational product of mRNA vaccines, which have been recently described. (Evans 2021) These data are, however, very preliminary.

Excluding pregnant women and adolescents, the safety and effectiveness of these groups are unknown. Other vaccines lack these two groups in the most important phase III clinical trials. Clinical trials can be supplemented in the future. It is mainly carried out among healthy young men in the Middle East, while the number of the elderly, women, and patients with chronic diseases is limited.

As for efficacy, current vaccines seem to offer protection against new variants, such as the high-spreading Delta, and as such, their formulations are most likely remaining unaltered for a while. (GOV.UK 2021) In the trial of Heterologous ChAdOx1 nCoV-19 and BNT162b2 prime-boost vaccination elicits potent neutralizing antibody responses and T cell reactivity, a total of 26 volunteers aged 25-46 years (median age 30.5 years) received a dose of Oxford vaccine and then a dose of Pfizer vaccine 8 weeks later. The variants selected here are B.1.1.7 (Alpha, first discovered in the UK), B.1.351 (Beta, first discovered in South Africa) and B.1.617 (Delta, first discovered in India). (GROSS, ZANONI, SEIDEL 2021) Studies have shown that these variants are effectively neutralized by the sera of all vaccinators.

It is important to note, that despite adverse effects that are rare, COVID-19 vaccines are still considered to be much safer than exposure to the virus, that even for healthy people, might cause death or a variety of lingering cardiac and neurologic symptoms (NIKHRA 2021).

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