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SYSTEMATIC REVIEW OF EFFICACY, IMMUNOGENICITY DOSING SCHEDULE, TECHNOLOGICAL PLATFORM AND SAFETY OF COVID-19 VACCINE

Mandana zafari* Health reproductive research center, Sari Branch, Islamic Azad University, Sari, Iran*corresponding author

Fateme Mohseni Bachelor Student of Midwifery, Sari Branch, Islamic Azad University, Sari, Iran

Amirreza Hashemi Student, Andishmand High School, Sari, Iran

Fateme Badele ungraduated student of medical laboratory science, Islamic Azad university, Sari, Mazandaran, Iran

mehrangiz ghabimi PHD student in nursing, Faculty of nursing and midwifery, Birjand university of medical science, Birjand, Iran

Atousa Kialashaki Health reproductive research center, Sari Branch, Islamic Azad University, Sari, Iran

ABSTRACT

Introduction: SARS-CoV-2 was first identified in Wuhan, China in early December 2019, it is responsible COVID-19 pandemic. Currently different platforms of vaccines such as; inactivated whole virus, live-attenuated virus and protein subunit of the virus, next-generation technique including m RNA, viral vector-based technology are used. The aim of this study is the systematic review of COVID 19 vaccines s efficacy and side effects. **Methods:** We reviewed the literature from various databases from February to May 2021. We have used these key words for search in databases: Corona virus, SARS-CoV-2, COVID-19 pandemic, vaccine, efficacy, side effect. No limitations on public status, study design were imposed. We had just language limitations , also, the PICO framework was applied in literature review. All papers on efficacy of COVID vaccines were selected and entered in this review study. Two reviewers independently extracted the data, any disagreement in opinion was resolved by consensus in agreement with a third reviewer. Data were extracted from published papers. Data were checked for study characteristics duration, pharmaceutical company, and type of COVID vaccine, immunization schedule, dosage, and route of administration, number, age of participants. **Results:** the efficacy of COVID vaccine was 50.4% to 95% , and the most common side effect of vaccine was: pain, redness, swelling, fever, fatigue, headaches, muscle pain, nausea, vomiting, itching, and rarely complications such as; thrombosis, thrombocytopenia, anaphylactic shock. **Conclusion:** In conclusion, immunization is helping to control the pandemic by reducing viral spread and severity of symptoms.

KEY WORDS : Corona virus, SARS-CoV-2, COVID-19 pandemic, vaccine, efficacy, side effect.

Introduction:

SARS-CoV-2 was first identified in Wuhan, China in early December 2019 and has been named as the Coronavirus Disease -2019 (COVID-19)(1).

SARS-CoV-2, that is responsible COVID-19 pandemic, is an RNA virus, and it generally has a high rare mutation. Despite the large amount of studies carried out at the beginning of its pandemic, there is still much unknown information regarding this virus. (2)SARS-CoV-2 virus is a part of betacorona virus family and it includes the SARS-CoV-1 and MERS-CoV. SARS (2003) and MERS (2014) caused short – lived epidemic with a high mortality. (3)

The severe respiratory syndrome corona virus 2 (SARS-CoV-2) disease has caused global pandemic that has not been resolved yet and it is highly contagious and has caused disruption of the word's health and economy. The prevalence and mortality rate of this disease are changing daily. World health organization has reported, the pandemic of covid -19 involved 216 countries and 80,161,578,00 peoples have been affected with a mortality rate of 2.19%. Also people are facing major health care challenging, anxiety and no specific treatment or prevention. Covid-19 induced sociological, psychological, and economic challenges. Also, it increased risk of mental health problems, and decreased positive emotions and life satisfaction among the general population as well as elderly population. Regarding rapid spread of this infection, vaccination would be a significant tool in this pandemic. creating successful, safe and efficacious vaccines requires an enormous effort (4, 5)

Covid 19 has 4 major structural protein: spike (s), membrane (M), envelope (E), (all of these proteins are in viral surface envelope) and nucleocapsid (N) protein is in ribonucleoprotein core. S protein (as a main protein), recognize the host cellular receptor to initiate virus entry, M protein shapes the virion envelope , E protein is crucial for its infectivity and N protein makes up the helix form of nucleocapsid and adhere among the viral RNA genome. Three covid 19 vaccines based on adenovirus (Ad5, chAdox1, Ad26) induced n Ab production and balanced TH 1 and TH2 immune response in NHPS. M and E proteins are poorly immunogenic for humoral immunity. Since M & E proteins didn't protect mice against covid 19 , so these proteins have never been explored as vaccine targets. But if these induced in covid 19 vaccine may help to broaden the cell response & improve cross protection. Inactivated and live-attenuated virus vaccines have all structural proteins (S,N, M, E proteins) . It means it can induce broader antibody and T cell responses. Picovacc elicited S protein and N-specific antibodies, but it and another inactivated vaccine did not induce T cell responses, on the other hand they protected NHPs against covid 19 infection. Some studies declare that these vaccines did not induce neither TH1 nor TH2 association cytokines in it. (6)

Eleven months after the definition of SARS-CoV-2 genome, over 150 official vaccine projects have been started (2)In June 2020 we had a global race for an approved vaccine targeting SARA-CoV-2. There are more than 200 vaccines at different stage of process especially against SARA-CoV-2. (7)the main protective effect of vaccines is to reduce antibodies against spike protein or its receptor-binding domain (2). Vaccines provide active immunity and are introduced in the body via injection, nasal, mouth against foreign specific disease (8)

***Corresponding Author Mandana zafari**

Health reproductive research center, Sari Branch, Islamic Azad University, Sari, Iran.

The development process of vaccines is stepwise or pyramid and selective (fig 1). If the start of study (in cell or animal) is successful, human vaccine will enter the phase I stage. In this stage the safety, dosage immunogenicity of vaccine will assess in small number of healthy people. Also a small proportion of vaccine candidates progress to phase II trials, which assesses to identify optimal for mutation , number of doses and dosing interval finally phase III vaccine trial will evaluate the efficacy and safety of vaccine. (3)

Fig 1 The development process of vaccines

Currently, 63 candidate vaccines on several different platforms such as; inactivated whole virus, live-attenuated virus and protein subunit of the virus, next-generation technique including m RNA, viral vector-based technology are at clinical stage of development. 22 of them are in phase III development, 18 of vaccines are being tested in phase III trials, and also, four candidates are in phase II trial. (9) (5)

Now, thirteen COVID-19 vaccines are being evaluated in phase 3 study. Pfizer/BioNTech vaccine is the first confirmed vaccine with the efficacy of 95%, it was authorized for Emergency Use Authorization (EUA) by the Food and Drug Administration (FDA) and it approved for emergency use in early December in UK, Canada and US. Another COVID -19 mRNA vaccines is Moderna with the efficacy of 94.5%, it approved by FDA on December 15, 2020. Four Adenovirus vaccines are AZD1222 from AstraZenca/Oxford, Ad26.COV.S from Johnson & Jonson/Janssen, Ad5-nCoV from CanSino Biological and Gam-COVID-Vac Gamalya Reseach Institue. Astrazenca/ Oxford reduces 70% COVID-19 infection and plan to apply for EUA and Ad5-nCoV received Military Specially – needed Drug approval use in the Chinese military on 25 June 2020. Inactivated vaccines are BBIBP-CorV (From Beijing Institute of Biological products), Sinopharm, Corona Vac (from the Wuhan Institute of Biological products) and BBV 152(from Baharat Biotech of India). BBIBP-CorV and Corona Vac submitted for a marketing application to the FDA at the end of December 2020. Two proteins subunit vaccines from Novax and Anhui Zhifei longcom Biopharmaceutical are in phase 3 of study. (1) (7)

Regarding the history of weakened microbe traditional technology vaccine, all of them are effective and stimulate the immune system and inducing a strong and persistent immune memory. Also, rare but significant side effects could be expected. These vaccines have short duration of immune memory which needs demands inculcation of a higher amount of the vaccine or the association of the weakened microorganism with an adjuvant. Also, this immune response is against spike protein and may other SARS-CoV-2 antigen. The spike protein or its fragments are the target of vaccines to activate a robust immune response, these vaccines exploit adjutants. The m RNA vaccines and their variants coding the spike protein or its variants and fragments. The DNA coding for the spike protein can be ended into the cells by viral vector. In this vaccine the DNA gets inserted in a virus and it is able to infect and deliver the m RNA into human cells, but it loses its ability of replication and the target antigen coded by the DNA, if not by the spike protein or its variants or its fragments. The nasal viral vector vaccine is effective by induction a mucosal immunity capable. (2)

Regarding clinical trial data of these vaccines, the phase III for mRNA vaccines that are built on the same platform, which identical antigen-producing mRNA sequencing and their blend of LNP encapsulation. The most common side effects of these vaccines are pain at the injected area, headache, and fever. Although these adverse events appear after boosting dose specially 7 days post injection. The results of trial show the novel technology of mRNA vaccines which has never received approval for any vaccine previously. After EUA approval of these vaccines, severe allergic reaction cases have risen, although this reaction is rare (1 in a million) and the cause of its reaction refers to polyethylene glycol (PEG) that is found in its formulation. The main mechanism of this reaction is unknown, there is some hypothesis include IgE antibodies to PEG, non – Ig E complement activation-related pseudo-allergy (CARPA), nanoparticle aggregation and a negative charged linkage of lipid to PEG. Also, there is a significant difference between Pfizer and Moderna in the rate of allergic reaction, 11.1 vs 2.5 per million injections, respectively. (7)BNT1 is nanoparticle-formulated nucleoside-modified RNA encoding the spike protein. Moderna m RNA -1273 encodes the S-2P antigen consisting SARS-CoV-2 glycoprotein with a transmembrane anchor and an intact S1-S2 cleavage site. In phase I , study of this vaccine was able to induce immunity response, also in phase III, with 94.1% efficacy. (5)

Viral vector vaccines are Astra Zeneca AZD1222, Can Sino, Gamalya Gam- COVID-Vac and J&J (Jansen). AZ/OX was published peer-review phase III trial on the 8th of December 2020. Overall its efficacy is 70.4%. (7) ChAdOx1 nCoV-19 (Astra Zeneca AZD1222) was produced at Oxford University; it consists of a replication-deficient chimpanzee adenoviral vector and contain the SARS-CoV-2 spike protein gene. First dose of this vaccine can introduce specific antibody and the response the T cell. The result of phase I/II showed that after two dose of vaccines the level of anti-spike protein neutralizing antibody accelerate with an acceptable safety profile. The result of phase II/III showed it is highly tolerable and can generate immunogenicity in most trial participants. Ad26.COVID2.5 produced by Janssen, consisted replication –incompetent adenovirus serotype 26 vectors encoding a full –length SARS-COV-2 spike protein. (5)This vaccine induced high immunity with efficacy of 66%. J&J vaccine has 66% efficacy rate, acceptable safety, tolerability, and immunogenicity. (7)

Can Sino vaccine has been used in china with efficacy 65.7%. The Gamaleya Sputnic V has 91.6% efficacy rate and adequate safety profile and the induction of virus-specific antibody response. (7)

16-18% of subjects had fever after first dose of these vaccines and it is similar in frequently to the second dose of mRNA vaccines (7).

The platform of protein-based vaccine includes Novavax and Medicago has excellent immunogenicity. Novax (NVX-CoV2373) has 89.3% efficacy. Both of them are safe and have common adverse effects such as; pain of injection site, headache. (7)

At the first time we believe that inactivated vaccine have lower efficacy compared to the m RNA platform vaccines, but now WHO announced that sinopharm (Beijing), sinopharm (Wohan) and sinivac s corno Vac have efficacy 79.3-86% , 72.5% and 50.4% (Brazil) respectively. Covaxin has been approved in India with efficacy higher than 50%. This group of vaccines have low incidence of adverse events such as; pain, fever and headache compare to m RNA or viral vector vaccines (7).

Currently, there isn't effective drug to treat covid-19. This pandemic has imposed a powerful financial and social damage. One of the best approaches for terminating this pandemic is the development of vaccine. (10)

It is important to compare the intensity and duration of protective responses, other factors such as; cost, side effects following these vaccines. This study reviews and discuses published papers about efficacy and safety of approved vaccines.

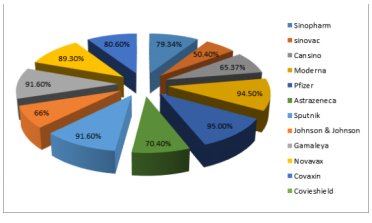

Figure2, the pie chart show the efficacy of approved vaccines.

Material and methods:

Search strategy and study eligibility:

The required data were collected from relevant database. We reviewed the literature from various databases such as; Web of science, pubmed, Medline, Embase, world health organization (WHO), US food and Drug Administration (FDA) , Center for Disease Control (CDC) regional ministries, health institute and scholar Google from February to May 2021. We have used these key words for search in databases: Corona virus, SARS-CoV-2, COVID-19 pandemic, vaccine, efficacy, side effect. No limitations on public status, study design was imposed. We had just language limitation, it means only English and Persian publications were enrolled in our study. In this review the PICO framework was applied in literature review, we considered P; patiet problem (prevention of COVID-19), I; intervention (COVID-19 vaccines), C; comparison (vaccines vs. negative control), O; outcome (efficacy of vaccines).

Study selection:

All papers on efficacy of VONID vaccines were selected and entered in this review study. Two reviewers independently extracted the data, any disagreement in opinion was resolved by consensus in agreement with a third reviewer.

Figure 3, show the relative flow diagram. this study considered all items that recommended by the PRISMA-P checklist.
Fig 3.

Data extraction:

Data were extracted from published papers. Data were checked for study characteristics duration, pharmaceutical company, and type of COVID vaccine, immunization schedule, dosage, and route of administration, number, age of participants.

End point:

The endpoint of this study was to identifying the clinically effects and side effects of routine COVID vaccines.

Data synthesis and analysis:
Ethical approval was not required.

Results:

Data obtained from papers that entered in this systematic review.

Table 1. review of efficacy, side effects and participants s characters of this study.

	Vaccine	Author (year)	Efficacy	Number of participants	Age of participants	Side Effects
1	Sinopharm (11)	Gregory	79.34% (18 years old above)	----------	18 and above	milder side effects like headache, fever, and pain on injection site, etc.
2	SinoVa	Shivaji Kashte (2021)	50.4%	9/000	------	milder side effects like headache, fever and pain on injection sites.
3	CanSino Biologics(12)	Shivaji Kashte (2021)	65.37%	40/000	18 to 60 years old	pain, redness, and swelling at the injection site, fever, headache, fatigue, and muscle or joint pain.
4	Moderna (4)	S.A Meo (2021)	94.5%	30/000	Over 18 years old	pain, redness or swelling at the site of vaccine shot, fever, fatigue, headache, muscle pain, nausea, vomiting, itching, chills, and joint pain, and can also rarely cause anaphylactic shock.
5	Pfizer/BioNtech (4)	S.A Meo (2021)	95%	44/000	18 to 55 years old	Pain, swelling, redness, fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, joint pain, lymphadenopathy, shoulder injury, right axillary lymphadenopathy, paroxysmal ventricular arrhythmia, syncope, and right leg paresthesia.
6	AstraZeneca (5)	Hang Fai Kwok (2021)	70.4%	11/636	18-55	-----
7	Sputnik(13)	Comment (Jan Johns) (2021)	91.6%	20/000	18 years old and older	------
8	Johnson & Johnson (14)	Abdolmajid Eslahtalab (2021)	66%	40/000	----------	The most common side effects are pain at the injection site, headache, tiredness, muscle pain and nausea, affecting more than 1 in 10 people. Coughing, joint pain, fever, chills, redness, and swelling at the injection site occurred in less than 1 in 10 people.
9	Gamaleya(15)	Colin D (2021)	91.6%	------	------	Pain, fever, headach
10	Novavax (14)	Abdolmajid Eslahtalab (2021)	89.3 %	--------	-------	Fatigue,headache, muscle pain
11	Covaxin' (16)	Khan Sharun (2021)	80.6%	-----	------	-----

12	Covieshield	Dear Editor (2021)	-----	------	------	After four hours (First vaccination) : myalgia, nausea, tenderness at the injection site, feverish feeling. After 12 hours (First vaccination) : fever and chills. Second Vaccination : myalgia and tenderness at the injection site
13	Pfizer /BioNtech	CDC COVID-19 Response Team; Food and Drug Administration	--- --	1,893,360	25-60 years	Most (86%) anaphylaxis cases had symptom onset within 30 minutes of vaccination
14	Pfizer /BioNtech (4)	S.A. MEO (2021)	95%	44/000	Over 16 years old	pain, redness or swelling at the site of vaccine shot, fever, fatigue, headache, muscle pain, nausea, vomiting, itching, chills, and joint pain, and can also rarely cause anaphylactic shock.
15	Moderna (4)	S.A.MEO (2021)	94/5 %	30/000	Over 18 years old	pain, redness or swelling at the site of vaccine shot, fever, fatigue, headache, muscle pain, nausea, vomiting, itching, chills, and joint pain, and can also rarely cause anaphylactic shock.
16	Pfizer /BioNtech	Amadea Britton, MD (2021)	In the phase 3 clinical trial, efficacy during the interval between first and second doses was estimated at 52%	463 person	<60 - ≥85 years	------
17	ChAdOx 1 nCoV-19 (AstraZeneca)	Marie Scully, M.D. (2021)	------	23 patients	the median age was 46 years (range, 21 to 77)	thrombosis and thrombocytopenia 6 to 24 days after receiving the first dose
18	ChAdOx 1 nCoV-19 (AstraZeneca)	Maheshi N Ramasamy (2020)	- -----	560 participants were enrolled	an age-escalation manner, into 18–55 years, 56–69 years, and 70 years and older immunogenicity subgroups.	Fatigue, headache, feverishness, and myalgia
19	ChAdOx 1 nCoV-19 (AstraZeneca)	Nina H 2021	-- ----	five patients	32 to 54 years of age	thrombosis in unusual sites and severe thrombocytopenia.
20	ChAdOx 1 nCoV-19 (AstraZeneca)	Andreas Greinacher, M.D. (2021)	- ------	11 patients	median age of 36 years (range, 22 to 49).	thrombosis or thrombocytopenia
21	ChAdOx 1 nCoV-19 (AstraZeneca)	S.A. Madhi (2021)	10.4%	3022 patient	(median age, 30 years); Adults 18 to less than 65 years of age	---- ---
22	ChAdOx 1 nCoV-19 (AstraZeneca)	Merryn Voysey (2021)	70·4%	23848 participants	18–≥70	---- ----

Discussion:

In this systematic review study, we assess the efficacy and side effects of approved vaccines.

We believe that all vaccines has acceptance efficacy also have rare side effects. Pfizer & Moderna have been recommended to people 16 years of age and older, does 30 µg and 50 µg , cost 19.50 $ and 32-37 $, efficacy of 95% and 94.5% respectively. Both vaccines can cause serious adverse in some cases and is rare, had reported severe allergic reaction, including anaphylaxis (4).

In general adult population the effectiveness of Pfizer during days 14-20 and 21- 27 was 46%, 60% respectively against PCR- confirmed infection. (amadea britton) after first does a relatively weak immune response was appeared a few weeks , but strong reaction will appear after second does injection. (Edward H livingston)

CDC had conducted descriptive analyses the safety of Pfizer & moderna at the first month of vaccination. Among 13.794.904 injections, 6994 cases had adverse events such as; 90.8% non serious (headache (22.4%), fatigue (16.5%) and dizziness (16.5%)) and 9.2% has serious events such as anaphylaxic (rare) death (113) cases with any casual relation with vaccine. They believed that vaccine reaction were more frequent after first does rather than second does of Pfizer – Biontech. (julianne Gee)

In the clinical trial of Pfizer vaccine multiple side effects have been reported. For example; the pain injection site, myalgia, fever, fatigue, anaphylactic shock. But in februray 2, 2021, Guillain – Barre Syndrom (GBS) accrue in an 82 year old female. GBS is associated with many viral infections. In 30 % of patients it can end to respiratory failure. (sadia waheed) the US drug company Moderna has suggested that, the immunity of this vaccine may wane against south African variants. This company is starting a clinical program of two booster does of this vaccine to reinforce protection to the new variants. (Janice hopkins)

Anaphylaxis shock occurred in 21 cases after first does of Pfizer. Although, this allergic reaction occurs rarely within minutes to hours after vaccination. In this study median interval from vaccine injection to onset of symptoms was 13 minutes, 19% were hospitalized, and the most common symptoms were urticarial, angioedema, rash, and sense of throat closure. (tom shimabukuro)(JAMA 23, feb, 2021-325-8)(MMWR 15, 2021, vol, 70, no 2)

One study compared biological, pharmacological characteristics and advers effects of Pfizer/BioNTech and Moderna vaccine, they believed that, Pfizer/BioNTech vaccine has been recommended to people older than 16 years old and it protects against SARS-C0V-2 infection at least 119 days after first vaccination with 95% efficacy. Moderna vaccine has been suggested to peoples 18 years old and older with efficacy of 94.5% for at least 119 days after first vaccination. The occurrence of adverse effects following Pfizer vaccine is lower than Moderna vaccine but the transportation and storage of Moderna is easier than Pfizer (4).

16-18% of subjects had fever after first dose of viral vector based vaccines and it is similar in frequency to the second dose of mRNA vaccines. Also the appearance of fever reduced after second dose. (colin D.funk). one study described a case of cardiac involvement in a 56 year old man who had previous covid 19 infection on the third day after second does of BNT162b2. (enrico ammirati) The increase reactogenicity of vaccine in children was seen, so, Pfizer has considered and used low does vaccine for children (12).

In study of phase 1 clinical randomized study of BBV152 375 candidates were vaccinated (100 candidates with 3 µg with algel-IMDG, 100 candidates with Algel-IMDG and 100 candidates 6 µg with Algel also 75 in control group). All adverse events were mild or moderate (inhection site pain, fever, nausea & vomiting), and resolved within , 24 hours of onset , also these were more frequent after the first fatalities than second does. IgG titers to all epitopes such as spike protein, receptor – binding domain & nucleocapsid protein increased rapidly after two doses. Sero conversion rate (based on MNT50, after second does) were 87.9%, 91.9% and 82.8% in 3 µg with Algel –IMDG group, 6 µg with Algel-IMDG group and 6 µg with Algel group respectively. it induced binding & neutralizing antibody responses similar to other inactivated SARS-COV vaccines . (raches ella)

The COVE trial provides a short term efficacy of mRNA -1237 vaccine to prevent symptomatic and severe covid-19 disease , complication and death , also the side effects of it was transient. (L.R. Baden)

An important and relevant question regarding vaccines is " how much efficacy is needed for a vaccine to be considered immunogenic?" researcher believe that " efficacy > 70% is able to eradicate the infection and an efficacy < 70% may add to obliterating the virus also it may decrease the length of infection . For prevention the pandemic situation, the vaccine efficacy should be at least 60% with vaccination coverage. The major administration of vaccine is intramuscularly, it induces a strong Ig G response and can protect the lower respiratory tract, but it doesn't initiate the secretory Ig A response to protect the upper part of respiratory tract (12).

Both protein –based vaccines induces high level immune responses after second dose, also Medicago inceases antiviral antibody titr and spike protein specific (INF- CD4+) after the second dose .After the second dose of Medicago the probablity of fever accelerates as simmlar as m RNA vaccines. At the time of writing this paper, there is not enough evidence for Novax vaccine (colin D.funk). These vaccines appear to elicite the strongest immunity among all vaccines. (Guido Forni)

Figure 2.page 12 (colin D.funk).this figure show the ranking of vaccines according to closeness to target product profile criteria. This figure show the race between vaccines according; safety, efficacy, logistics and COGS (cost of goods sold). We conducted that inactivated vaccines have high scores also viral vector vaccines have lower point for about safety. The higher and lower efficacy was for mRNA and inactivated vaccines. For about COGS inactivated vaccines are easy to produce also are cheap, but the price of Chinese vaccines are very high. On the other hand the viral vector vaccines are the cheapest to prepare. Regarding vaccine stability and storage, there are significant differences in vaccine stability at usual refrigerator temperature between m RNA and other vaccines. In this area the inactivated and viral vector vaccines have the highest scores. (colin D.funk).

In a person who has been affected by SARS-COV-2, the level of antibody lasts several months, we don't know if they need booster dose? Also, we don't have enough evidence of immunological correlate of protein against SARA-C0V-2 that produce after vaccination. Pfizer and Moderna showed efficacy after 11 days after the first dose. New variants of corona are emerging all around the world, for example; UK (B.1.1.7), south Africa (B.1.351 also known s 501 Y2) and Brazil (P.1). Now m RNA vaccines are still effective against B.1.1.7. Another mutation such as B.1.351 causes the reduction efficacy of J& J and Novavax vaccination in the South Africa. (colin D.funk).

Certainly AZD1222, BNT162b2, m RNA-123 and Sputnic V showed a high clinical effect in protection against corona. Also, they believed that the type of vaccine, age and gender of recipients were not modifying factors that modulate the efficacy of vaccines. (Luigino calzetta)

Astrazeneca induce homoral and IFNy T cell response after the first does, and its immunity increases after the second does. These authors believe that this humoral immunity is like the people who observed in convalescent plasma from patients who have recovered after covid-19 infection. Phase 1 of this trial was briefly which was linked to multiple sclerosis . also the phase 3 was paused because of transverse myelitis. Regarding moderna the humoral responses were similar in the affected people also, cellular responses mainly biased toward CD4 + th1 cell and CD8+ Tcell responses were marginal. P fizer the cellular & humoral immune response were detected 2 weeks after the second dose of Pfizer and Biontech. Also, BNT162b2 produced a higher Tcell response with safty profile. The strong neutralizing vaccine of J&J CD4+ and CD8, the cell immune response were seen 28 days after Gamalya vaccine (11)

A randomized controlled trial study was done in Brazil, south Africa and UK for safety and efficacy of AZD1222 against SARS-cov-2. The ages of participants were 18-55, 56-69, and ≥ 70 years. Participants who received two standard doses of vaccine vs. who received low does followed by standard does , the efficacy was 62.1% and 90% respectively. The overall vaccine efficacy was 70.4%. Serious adverse events occurred in 168 cases , such as; hemolytic anemia, transverse myelitis, fever higher than 40 c and multiple sclerosis. (merry voysey 1)

Another study was done as a pooled analysis of four randomized trials of AZD1222 (phase ½ in UK, phase 2/3 in UK, phase 3 in Brazil and one double blind phase ½ in South Africa). 17178 cases (8597

participants received chAdox 1 and 8581 participants in control group). The most efficacy of vaccine in two groups (two standard does and low does plus standard does) was in prime- boost interval ≥12 weeks. The efficacy of the vaccine regarding symptomatic covid-19 cases appeared more than 14 days after second does was higher in low does plus standard does with prime –boost interval ≥ 12 weeks. Also, efficacy of vaccine against any NAAT-positive (nucleic acide amplification test) covid 19 cases more than 14 days after second does in two standard does was higher with prim-boost interval 9-11 weeks and in low does plus standard does was with prime-boost interval ≥12 weeks. A single standard does of vaccine provide immunity against primary symptomatic infection in the first 3 months with the efficacy of 76%. Efficacy of a single standard does against any NAAT-positive was 63.9% from 22 days to 90 days after injection.(Merry voysey 2)

A single – blind, multicentric randomized study was done in UK, regarding safety & efficacy of AZD1222. In 69% of the cases occurred primary symptomatic covid 19 causes by B.1.1.7 variant, occurred in vaccinated patients (standard does or low does). The efficacy of the vaccines in this group was 70.4% and for other variants was 81.5%. Also, the efficacy of vaccine against a symptomatic or unknown infection against B.1.1.7 variants was 28.9% and other variants was 69.7%. The efficacy of vaccine regarding the report of any NAAT positive infection for B.1.1.7 variants was 61.7% and for other variants was 77.3 %.(Katherine rw emary)

A study was done in south African (phase 1-II) regarding safety and efficacy of AZD1222. Among 1010 vaccine candidates with the ages of 18-65 years, The only serious adverse events were fever higher than 40 C. humoral responses to vaccine included strong neutralizing antibodies 28 days after first does and rose further after second does. These researchers reported that the results of this study was similar to the study which was done in the UK and Brazil. In this study, authors compared the efficacy of the 2 doses of the vaccine (75%), but it had no efficacy against non-hospitalized mild to moderate in infection in B1.351 variants. (shabir madhi)

Regarding the efficacy of AZD1222 , researchers reported for two of the four ongoing trials (UK, Brazil) , in 11363 participants with the ages of 18-55 years , the efficacy of standard does and low does were 62.1% and 67.4-97% respectively. they reported some serious adverse events ; transvers myelitis, haemolytic anemia and fever higher than 40 C. (maria deloriknoll)(merrn voysey)

Phases 1-2 study of ChAdox1 vaccine were done in 5 centers in UK. 1077 participants had enrolled (543 candidates received ChAdox 1and 543 candidates received AnAcwy). They didn't report serious adverse events related to ChAdox1. In the candidates who received ChAdox1, spike- protein T cell responses speaked on 14th and anti-spike Ig G responses rose 28th after secondary does. Neutralizing antibody responses were detected 91% and 100% after single does, (were measured in MNA80 and PRNT50 respectively). All candidates had acceptable hormonal & cellular immune responses. (pedro m folgatti)

One study showed that the two doses of ChAdox1 don't protect against mild to moderate covid infection due to the B.1.351 variants. Humoral responses induced strong neutralizing antibodies 28 days after the first does and rose further after the second does. (S.A madhi, v) a study showed that the ChAdox1 covid -19 vaccine is safe and it will tolerate well with a lower reactogenicity profile in adult also, the standard does of vaccine has higher reactogenic than the lower does. (Elisabeth mahase) J&J , as a single does vaccine had an overall efficacy 60% against symptomatic disease , 85% against severe symptomatic . regarding against mild disease , this vaccine has 72% efficacy in united states, 66% in latin America and 57% in south Africa, with no one who required hospitalization or death. Grey and other researchers believe that mRNA vaccine might not do much better than J&J. (Jon cohen) Novax vaccine , that produced by the US biotechnologhy company with 95.6% efficacy against SARS-cov-2. (Elisabeth mahase) also, Novax is 85% and less than 50% effective against UK variants and South African variant respectively. (Even callaway & smriti mallapaty) . NVX – cov 2337 as a recombinant nanoparticle vaccine , that induces multifunctional CD4 + Tcell responses of IFN-Y, IL2 and TNf-αbiased towards a Th1 phenotype and produce antigen-specific germinal center B cell in the spleen. (mimi Guebre - xabier)

The efficacy and safety of vaccines may differ in different populations. The result of phase III study of vaccines show that, the immune response of elderly population that triggered by vaccines were different from younger people due to the decline of their immune system, comorbidities and pharmacological treatments. For example, phase III study of ChAdOx1 show that 88% of participants (between ages 18-55 years old) had primary efficacy. Also, the efficacy of BNT162b2 were 95.6%, 93.7%, 94.7% and 100% in age subgroup 16-55, above 55, above 65 and above 75 years old respectively. In the mRNA -1273 the efficacy of vaccine in the ages of 18-65 and the ages higher than 65 years old were 95.6% and 86.4% respectively (5).

A study was done on 560 participants in 20 centers of UK. 160 participants aged 18-55 years and 160 aged 56-69 years and 240 aged ≥70 years. 300 patients received low does and 260 participants received standard does. Ig G against RBD and trimeric spike protein were detected in this study. Participants who received prime does vaccine of standard does had similar anti spike antibody titrs as those who received a low does. Also, the level of anti-spike protein Ig G responses at the day 28 decreased with increasing age at both dies level. 13 serious adverse events were reported in this study. They believe that T cell responses are important in controlling covid 19, and the peak of spike – specific T cell responses occurred at 14 days after prime does. (maheshin ramasamy)

28 days after Cansino vaccination neutralizing antibody titers increased. Also, neutralizing antibody increased 14 days after second does. The immunity in this vaccine was age dependent. It means neutralizing antibody responses were significantly higher in the ages 18- 39 years old compare than adult age 40-59 years. Also, the strong response were noted in the people given does on 28 days than 14 days. (George A Poland)

Corona vac is an inactivated SARS-COV-2 vaccine developed by sinovac life science (Beiding , china) , included acceptable hormonal responses in adults with the ages of 60 years and older also was well tolerated (phase 1-2 study). 72 candidates in phase 1 and 350 candidates in phase 2 with age ≥60 years old enrolled in RCT. They received 3 µg and 6 µg in phase 1 and 1.5, 3, 6 µg in phase 2. 71% in phase 1 and 97% in phase 2 had eligible immunity at day 28 after second dies. Also, the neutralizing antibody titrs induced by 3 µg were similar to 6 µg but higher than 1.5 µg.(zhiwei wu)

Regarding the efficacy of vaccine against asymptomatic infection, phase III of studies show that, ChAdO1 nCoV-19 was very low, mRNA-1273 100% effective against severe form of infection. (Hang Faiwok)

Regarding to the side effects of AstraZeneca, widespread blood clots, low platelet and bleeding (especially in women under 65 years old) have been reported from seven countries. Some of the countries have stopped administration of this vaccine, and billions of doses of it distribute in low-and middle– income countries. (Daniel clery).

Covishield (a weakened version of adenovirus) is a version of the oxford university. Astrazeneca vaccine with the efficacy of 70.4% , that is producing by the serum Institue of India. Both of them require two doses to activate the immune system with covid- spike protein. (kamala thiagarajan)(Dr. A.Indira, nandini jaganaragan)

The oral and intranasal route of inactivated virus vaccine could induce a mucosal immunity based on secretory IgA and Ig M. (Guido Forni)

The limitation of quantitative comparison of vaccines' efficacy, there is no international standard for titrating IgG antispike serum antibodies or T cell responses. (Guido Forni)

We conducted that inactivated vaccines are weaker than induced by attenuated vaccine and it is more easily handed, less expensive and safer.(Guido Forni)

BBV152 induced higher neutralizing antibody responses 3 months after the second does, with higher hormonal and cell-mediated immune responses. The results of phase 2 of BBV152 vaccine showed that high immunity, and induced antibody binding to spike protein. This neutralizing antibody responses were similar to those induced by inactivated vaccines. And no severe or life threatening adverse events. Also, it indices T-cell memory responses which was shown by an increased frequency of antigen-specific T-cells expressing the memory pherotype marker CD45Rot. (raches ella) Covaxin (BBV152) is the first vaccne that produce in india. This inactivated vaccine is produced by Baharat Biotech , can effectively neutralize UK variants. (khan sharun)

Russia vaccine (sputnik v) was the first country in the world to approve a vaccine against SARS- cov-2 , on Agust 11, 2020 . this vaccine is based on two adenovirus vectors is quite effective and induce strong immunity. (Tolha khan Burki)

Sputnk V is adenovirus –based vaccine has a good safety profile, also induced strong hormonal and cellular immune response. (vijay shankar balakrishnan)adenoviral vector vaccine (sputnik V) induces cellular and humoral immunity after the first does, so we can propose this vaccine as an emergency prophylaxis tool in pandemic. Injecting of the second dose induces long-lasting immune response. This combined vector vaccine consists of rAd type 26 (rAd26) and rAd type 5 (rAd5), both of them carry the gene for SARS-CoV-2 full – length glycoproteins. rAd 26-s and rAd5-s are administrated separately with 21 days interval. This vaccine tolerate well and has high immunogenic in healthy population. (Denis Y logunov)(jan dones , polly ray)

Two of 12 vaccines (can sino, J&J janssen) use single dose. (colin D.funk).

Corona virus is like infulanza vaccine and mutates and requires an annual booster. There are some challenges regarding developing the COVID-19 vaccines, for example; getting infected after vaccination , new mutant variants, tht recessive against vaccines. We suspect that, a successful vaccine must have cross-reactive antibodies for protection against all variants of this virus.(zameer shervani)

It seems that the current vaccines work against the new variants. Vaccines are designed to create many different antibodies to different parts of COVID-19 virus. If one part of virus mutates, the antibodies will recognize another part of virus. Of course, it is possible that a new mutant variants reduced the efficacy of vaccines. (Edward H)

In fact, there is a strong correlation between serum antibody levels and protection for infectious disease, but this protective level has nt yet been determine for SARS-CoV-2.(rita rubin)

One of the most important goals, that we want to do in this pandemic is to keep people away from severe form and hospitalization. (rita rubin)

Because of the changes in the virus, the vaccines had to be updated.

On the other hand mutations in the spike protein will spur vaccine efficacy concerns. Trials studies were done for Novax, J& J and Asterazeneca in South Africa against B.1.351 variant has a lower vaccine efficacy compared same trials in other countries. In phase I of Moderna vaccine, the efficacy of it against Wuhan-Hu-1 spike protein was higher than B.1.351 variants. (rita rubin)

It is difficult and we can't predict what kind of immune response and vaccine is the most effective, also, we don't have" the best covid -19 vaccine. Each vaccine has its unique technological platforms so could induce different forms of immunity. Some vaccines are more appropriate in different population, locations or geographic context. (Guido Forni)

Conclusion: ten of 12 vaccines in this review have received authorization to use in different countries in 2021. In conclusion, immunization is helping to control the pandemic by reducing viral spread and severity of symptoms.

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Limitation: Un approved vaccines didn't enrolled in this study.

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