Albanian Journal of Trauma and Emergency Surgery (2021) 5/1: 791-796
DOI: 10.32391/ajtes.v5i1.178

REVIEW ARTICLES

Efficacy and Safety of AZD1222, BNT162b2 and mRNA-1273 vaccines against SARS-CoV-2

Ilir Alimehmeti*

Received: 28 December 2020 / *Accepted:* 11 January 2021 / *Published online:* 20 January 2021

Abstract

SARS-CoV-2, the beta coronavirus causing COVID-19, was isolated and categorizes as a novel one on January 7th, 2020 in China.[1] To date, official reports depict that SARS-CoV-2 has already infected 88.828.387 persons and caused 1.926.625 deaths worldwide.[2] On January 12th, 2020, China officials made public its genetic sequence, thus paving the way towards the research and development of diagnostic tests and vaccines.

With regard to vaccination, e large number of clinical trials were designed and are currently undergoing, of which 189 are listed in ClinicalTrials.gov. [3] However, up to date, only three vaccines have published their respective phase III clinical trial results in peer-reviewed medical journals. [4-6]

Vaccines are needed to reduce the morbidity and mortality associated with Covid-19, and multiple vaccine platforms as AZD1222 (AstraZeneca) [4], BNT162b2 (Pfizer/BioNTech) [5] and mRNA-1273 (Moderna) have been involved in the rapid development of vaccine candidates.

Methodology: In this review, PubMed, Embase, Web of Science, Scopus, medRxiv, and bioRxiv were systematically scrutinized for peer-reviewed and preprint articles on phase III clinical trials of vaccines against SARS-CoV-2. In total, only three peer-reviewed papers fulfilling the search criteria were identified.

Conclusions: All vaccine candidates should publish in peer-reviewed journals their efficacy and safety well before requesting approval to the national or international authorities…

Keywords: COVID-19, SARS-CoV-2, vaccination, review, clinical trials

Introduction:

SARS-CoV-2, the beta coronavirus causing COVID-19, was isolated and categorizes as a novel one on January 7th, 2020 in China.[1]

To date, official reports depict that SARS-CoV-2 has already infected 88.828.387 persons and caused 1.926.625 deaths worldwide.[2]

On January 12th, 2020, China officials made public its genetic sequence, thus paving the way towards the research and development of diagnostic tests and vaccines.

With regard to vaccination, e large number of clinical trials were designed and are currently undergoing, of which 189 are listed in ClinicalTrials.gov. [3] However, up to date only three vaccines have published their respective phase III clinical trials results in peer-reviewed medical journals. [4-6]

The above-mentioned vaccines AZD1222 (Astra-Zeneca) [4], BNT162b2 (Pfizer/BioNTech) [5] and mRNA-1273 Moderna [6] have already been approved from the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA) and national boards in different countries. [7-11] Recently a minimal vaccination wave has begun in Albania too, but such a vaccination program has been covered only by media sources, while to date it is short of an official report from the national health authorities. [12]

Nevertheless, the vaccines' development effort itself was characterized by a mediatic coverage that had the upper on scientific peer-reviewed publications worldwide, thus bypassing critical review of the published data, which is inherent of mediatic sources where not all the vital data are published, in contrast to the the scientific medical journals routine.

Original article, no submission or publication in advance or in parallel

* ***Corresponding author:***
Ilir ALIMEHMETI, MD, MSc, PhD
✉ *iliralimehmeti@gmail.com*

Clinical Epidemiologist - Endocrinologist
Faculty of Medicine, University of Medicine, Tirana, ALBANIAe

Therefore, the aim of this paper is to critically assess efficacy and safety of the anti-SARS-CoV-2 vaccines published phase III clinical trials data.

Methodology:

In this review, PubMed, Embase, Web of Science, Scopus, medRxiv and bioRxiv were systematically scrutinized for peer-reviewed and preprint articles on phase III clinical trials of vaccines against SARS-CoV2.

In total, only three peer-reviewed papers fulfilling the search criteria were identified. Chronologically, by publication order, these articles presented results from phase III trials of the following vaccines: AZD1222 (AstraZeneca) [4], BNT162b2 (Pfizer/BioNTech) [5] and mRNA- 1273 (Moderna) [6], which were all published closely to each-other, respectively on December 08th, 2020, December 10th, 2020 and December 30th, 2020. [4-6]

In this order, each publication was rigorously qualitatively reviewed to gather insights on: sample selection, inclusion and exclusion criteria, clinical trial methodology, reported safety and efficacy, and, last but not the least, external validity of the findings.

Results:

AZD1222 vaccine (AstraZeneca) [4]

The AZD1222 vaccine has been developed at the Oxford University and is compounded by a chimpanzee-derived replication-deficient adenoviral vector (ChAdOx1), which contains the gene for the SARS-CoV-2 structural surface glycoprotein antigen, also known as the spike protein. The clinical trial consists of a randomized controlled trial divided in three different arms that took place in the United Kingdom, Brazil and South Africa, which present major and unexplainable methodological differences.

Blinding:

The British and Brazilian groups underwent a single blind trial, while the South African trial was double blinded. Thus, in the first two arms, researchers had clear knowledge of who was being vaccinated and who was not, foretelling the hypothetical opportunity of subtle differential alterations of both registering and reporting processes, while the South African arm follows a rigorous and superior double-blind study design.

Control group:

Again, both the British and Brazilian arms do not inject placebo (saline solution) but have interestingly chosen to inject meningococcal vaccine in the control group. Yet aging the South African arm follows the robust design of employing placebo in the control group. It is worth mentioning that using another vaccine in the control group confounds the side effects findings of the at-study vaccine candidate, as most of these side effects would be similar to the side effects exerted by any vaccine employed as a control. Such shadowing would not be possible if placebo were employed.

Most interestingly, in the final publication, authors have reported only data from the British and Brazilian arms, dodging data from the South African arm, condoning their choice because of the lack of enough cases accrual during the study period.

Inclusion and exclusion criteria:

In the inclusion criteria is directly observable by how far the studied population differs from the general population, especially from the population at high risk for severe COVID-19.

Age:

The study population comprises no one aged beneath 18 years old, while 88% are 18-55 years old, 8% are 56-70 years old and only 4% are aged over 70 years old. Hence, from design this study lacks the statistical power to detect efficacy and safety in the underrepresented old age groups. Moreover, excluding old age groups is an old trick of vaccine clinical trials, as, physiologically, old aged persons gradually lose the ability to create or retain the vaccine-induced immunity memory, and such an exclusion would result in an expectable overestimation of the immune response to the vaccine.

Body mass index:

The study population presents an almost ideal body mass index averaging around 25 kg/m^2, whilst obesity is a known risk for severe COVID-19.

Chronic diseases:

Given the relatively young and healthy study population, also chronic diseases present a low prevalence, respectively: respiratory diseases 12%, cardiovascular diseases 11%, and diabetes only 2%. These low figures may undermine the external validity and generalizability of the efficacy and safety findings in the particularly at-risk individuals with several chronic diseases.

Special populations:

It is not clearly reported if persons with autoimmune diseases and pregnant or breastfeeding women have been included or excluded from the clinical trial.

Total study population:

In total, 11.636 have been studied, characterizing such a trial as a relatively small one, which is able to spot common and most uncommon side effects, but is not powered enough to identify rare side effects at an order lower than 1 out of 10.000 cases.

Follow-up:

The mean follow-up time was 2.4 months from the day of receiving the second vaccine dose. Again, such a period

might be sufficient for identifying common and rapid side effects, por cannot inform on rarer side effects or longer than three months appearing ones.

Primary outcome:

The main primary outcome was a positive RT-PCR result after complaining at least one symptom of COVID-19. Such an outcome is a soft and problematic one, more so if considered the relatively young and health study population, as such a population is not categorized as vulnerable. Hard outcomes worth considering would have been severe COVID-19, hospitalization, and mortality.

Efficacy:

In the follow-up period, symptomatic COVID-19 was diagnosed in 0.5% of the vaccinated persons and in 1.7% of the nonvaccinated controls. Such figures can be computed as a highly significant absolute risk reduction of 70%. Nevertheless, such a reduction is generalizable only to young and healthy population. In older age groups it can only be speculated that the effect would be expected to be lower.

Importantly, no vaccinated individual was hospitalized, while there were 10 hospitalizations in the control arm. In long term such a number would be expected to surge in favour of the vaccine arm. The hospitalization outcome is far more impressive than the absolute risk reduction of positive RT- PCRs in such a young and healthy population and, although it lacks statistical significance, is a powerful positive signal of efficacy.

Safety:

Serious events were observed in 0.7% of the vaccinated persons and 0.8% of the control persons. But, taking into account that the control arm has been injected with the meningococcal vaccine and not placebo, it is deductible that AZD1222 causes no more serious events than the meningococcal vaccine does. Not the less, the real AZD1222 absolute risk of side effects cannot be assessed unless tested against placebo.

A total of 79 different serious events developed after vaccination, with the vast majority not being connected to the vaccine itself. The only alarming event was the identification of two cases of transverse myelitis that developed a few weeks after receiving both doses of the vaccine. As transverse myelitis is a rare disease with an incidence of 1 to 8 cases per million,[16] the incidence of 2 cases in only 6.000 vaccinated persons raised legitimate concern. One of the cases had multiple sclerosis, a known risk factor for transverse myelitis, but the other case had no risk factor at all. As the trial is underpowered to detect for rare side effects, pharmacovigilance data are vital to early detect incident cases during and after the vaccination campaigns.

Summary:

AZD1222 vaccine present an efficacy of around 70% generalizable to relatively young and healthy populations, but the trial also provides important harm signals that warrant further and larger studies. Such a vaccine might be recommendable to high-risk population, where benefit outweighs risks, but this is not the case for low-risk populations. Moreover, until further clarity is made on inclusion criteria, persons with autoimmune diseases, allergies, pregnant and breastfeeding women may be advised to stand by.

BNT162b2 (Pfizer/BioNTech) [5]

BNT162b2 is a lipidic nanoparticle with a nucleoside-level modified RNA, coding the whole sequence of the spike antigen of SARS-CoV-2, modified by two proline mutations blocking it into prefusion conformation. [13-15]

Blinding and control:

The phase III clinical trial employed a randomized, double-blind, placebo-controlled study design, a far more robust study design compared to the above-mentioned AZD1222.

Inclusion and exclusion criteria:

Inclusion age was 16 years old and older. However, less than 5% were aged over 75 years old. Chronic diseases were included only when they were deemed as stable. All persons under immunosuppressive therapy, with former allergy to vaccines, with autoimmune diseases, and pregnant or breastfeeding women were excluded. As a result, findings are not generalizable to these populations.

Again, as volunteers are fundamentally healthy and relatively young, the efficacy and safety results might be overestimated and not generalizable to elderly with chronic diseases, which is of particular interest given the fact that the mean number of chronic diseases in fatal cases of COVID-19 is 3.6. [17]

A positive figure is that prevalence of obesity was 35%, thus conferring external validity to the findings for the obese population, as it is a known risk factor for severe COVID-19.

Total study population:

In total, 43.548 persons were enrolled in the clinical trial ensuring high statistical power to find rare side effects with an estimated incidence of 1 out of 10.000 persons, but not lower.

Primary outcome:

Once more, the primary outcome was a positive RT-PCR finding after the possible manifestation of COVID-19 symptoms, a soft outcome compared to the most interesting hard outcome as severe COVID-19, hospitalizations, and mortality.

Efficacy:

COVID-19 was diagnosed in 0.05% of the vaccinated

persons and 0.9% of the placebo-controlled persons, thus an absolute risk reduction of nearly 95% can be calculated, a figure that is both an impressive and highly significant one.

An additional positive figure is that such efficacy seems to hold also in the over 75 years old age group, where five cases developed in the control arm, but none developed in the vaccinated group. Albeit no statistical significance could be computed due to the small sample, the signal remains positive.

Regarding severe COVID-19, only one vaccinated person and nine nonvaccinated persons developed it during the follow-up period. Absolute risk reduction is nearly 89% but, again due to the small study sample, the statistical significance cannot be achieved.

Safety:

A total of 240 severe events were registered in the vaccination arm, while 139 happened in the control arm, resulting in a 73% increase. However, researchers did not report a detailed list of severe events encountered, adopting instead an *en bloc* report. Following vaccination in the United Kingdom, at least two persons had an anaphylactic shock after receiving the vaccine, [18] thus highlighting the necessity to report every single type of severe events clearly.

Serious events were reported in 0.6% of the vaccinated and 0.5 of the control persons, with no significant difference but, again, with no clear listing of the event type.

Summary:

BNT162b2 vaccine showed a 95% absolute risk reduction of symptomatic COVID-19 in a relatively young and healthy sample and an 89% nonsignificant absolute risk reduction of severe COVID-19. Taking into account that 98.8% of the did not suffer any severe event, such a vaccine could be considered also in older adults and in high-risk persons, in whom the benefit/harm ratio is in favour of the vaccine employment. However, continuous observations are warranted to assess, care and report cases of anaphylaxis, if any. Up to date children aged under 16 years old, persons with allergies, autoimmune diseases, immune suppression, and pregnant or breastfeeding women should not use this vaccine until it is thoroughly tested.

mRNA-1273 (Moderna): [6]

mRNA-1273 vaccine shares the same technology as BNT162b2 does, but presents a small difference given that the second dose is distanced 28 days from the first one, compared to BNT162b2 that needs only a 21-day long period. Given the similarity in technology and action mechanisms, it follows that similar results were expectable.

Blinding and Control:

This phase III clinical trial employer a robust randomized, double-blind, place-controlled study design.

Inclusion and exclusion criteria:

Ages over 18 years old were included in the study, yet again only 5% were aged over 75 years old. Participants had to be healthy or in a stable chronic condition. Exclusion criteria were presence of allergies, immune suppression, and pregnancy or breastfeeding. The main body mass index was 29 kg/m^2, which resembles the source population.

Chronic diseases presented a low-to-medium prevalence: 5% had chronic pulmonary diseases, 5% had cardiovascular diseases, 7% were obese and 10 had diabetes.

Total study population:

In total, 30.420 participants were enrolled, an intermediate sample size with comparison made to the above-mentioned clinical trials.

Primary outcome:

Once more the primary outcome was a positive RT-PCR after developing at least two symptoms similar to COVID-19. Similarly, to the other trials, the primary outcome was a soft one and not severe COVID-19, hospitalization or mortality.

Efficacy:

Symptomatic COVID-19 was diagnosed in 0.07% of the vaccinated and 1.3% of the nonvaccinated persons, eliciting a highly significant absolute risk reduction of 94%. In the age group over 65 years old, an absolute risk reduction of 86% was observed, thus deducting that such a vaccine has a high efficacy also in this age groups, admitting that there are no data for ages over 80 years old.

Most interesting, severe COVID-19 developed in 30 persons of the control arm and in not a single one from the vaccinated arm.

Safety:

In both vaccinated and nonvaccinated arms 1.0% of the participants presented serious events. Though the difference is not significant, a ratio of 1 out 100 is not ideal. Nevertheless, dissimilarly from the BNT162b2 study group, the mRNA-1273 researchers reported a thorough list of all severe and serious events. After scrutinizing the list, no serious event could be considered as a vaccine liability, diversely from the cases of transverse myelitis in the AZD1222 clinical trial. Moreover, none of such serious events present any significant difference between the vaccine arm and the control arm.

Summary:

Taken together, data from the mRNA-1273 clinical trial provide solid basis of efficacy and safety. Nonetheless, there are no data on specific groups, including children and adolescents under 18 years old, elderly over 80 years old, people with a suppressed immune system, allergies, and pregnant or breastfeeding women. Whilst the high risk for severe COVID-19 in age groups over 80 years old may warrant their vaccination, such a notion does not hold in the other above-mentioned categories.

Discussion:

In summary of this systematic qualitative literature review of the efficacy and safety of the vaccines against SARS-CoV-2, published data could be found only on the following three vaccines: AZD1222, [4] BNT162b2 [5] and mRNA-1273[6].

After scrutinizing the methodology of each clinical trial, followed by the critical review of the results reported on their efficacy and safety, the highest safety profile appears to be provided by the mRNA-1273 (Moderna) vaccine, closely followed by the BNT162b2 (Pfizer/BioNTech) vaccine, whereas in the clinical trial of AZD1222 (AstraZeneca) important signals of alarming side effects could be found. However, all studies are powered enough to find side effects ranging from common to uncommon but are unsuited to identify rare side effects. Such a fact should be carefully considered given the very high absolute number of people that have to be vaccinated in each country in order to achieve herd immunity. Pharmacovigilance and transparent reporting of serious events in each country are highly warranted.

Regarding efficacy, mRNA-1273 (Moderna) and BNT162b2 (Pfizer/BioNTech) exhibit almost identical efficacities but that can be generalizable only to relatively younger and healthier populations. While BNT162b2 (Pfizer/BioNTech) has supporting nonsignificant data up to 70 years old, mRNA-1273 (Moderna) extends such a claim also to age groups up to 80 years old. Nevertheless, given the high risk for severe COVID-19, also older age groups can be eligible to vaccination with the above-mentioned vaccines, but further studies are needed to exactly assess efficacy and safety in these age groups. On the other hand, AZD1222 (AstraZeneca) present a lower efficacy profile, only 70%, and at the same time presents the same issues of external validity, thus being inferior to both other RNA-based vaccines.

Additionally, the AZD1222 (AstraZeneca) clinical trial presents different very important biases in its methodology, including a single blind design and employment of a meningococcal vaccine instead of placebo in the control arm.

Collectively, all three studies not including a representative number of elders present an overestimation of the efficacy and safety of their products that presents no external validity and, most probably, including older ages would have slightly diluted their quite optimistic findings. ***In conclusion;*** larger studies are warranted including not only older ages but also paediatric ones.

In lack of these data, vaccination should be avoided in children and adolescents under the age of the respective trial inclusion criteria, whilst efficacy and safety of the vaccination of persons over 70 years old must be actively assessed during the national vaccination campaigns. Last but not least, further vaccine candidates should publish in peer-reviewed journals their efficacy and safety well before requesting approval to the national or international authorities.

COI Statement: This paper has not been submitted in parallel. It has not been presented fully or partially at a meeting or podium or congress. It has not been published nor submitted for consideration beforehand.

This research received no specific grant from any funding agency in the public, commercial, or non- profit sectors. There are no relevant or minor financial relationships from authors, their relatives or next of kin with external companies.

Disclosure: The authors declared no conflict of interest. No funding was received for this study.

Reference:

1. World Health Organization. Novel Coronavirus (2019-nCoV) Situation Report – 1. 21 January 2020. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200121-sitrep-1-2019- ncov.pdf
2. World Health Organization. Weekly Operational Update on COVID-19. 11 January 2020. https://www.who.int/publications/m/item/weekly-operational-update-on-covid-19---11-january-2021
3. https://clinicaltrials.gov/ct2/results?cond=%28covid-19+OR+Sars-Cov-2%29+AND+vaccine&term. Last accessed on January 12th, 2021.
4. Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. The Lancet 2021; 397; 10269: 99-111, December 08, 2020 https://doi.org/10.1016/S0140-6736(20)32661-1
5. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med 2020; 383:2603-2615, December 10, 2020 doi: 10.1056/NEJMoa2034577
6. Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. December 30, 2020 doi: 10.1056/NEJMoa2035389
7. https://www.ema.europa.eu/en/news/ema-recommends-first-covid-19-vaccine-authorisation-eu. Last accessed on January 12th, 2021.
8. https://www.ema.europa.eu/en/news/ema-recommends-covid-19-vaccine-moderna-authorisation-eu. Last accessed on January 12th, 2021.
9. https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid- 19/pfizer-biontech-covid-19-vaccine. Last accessed on January 12th, 2021.

10. https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid- 19/moderna-covid-19-vaccine. Last accessed on January 12th, 2021.
11. https://www.astrazeneca.com/media-centre/press-releases/2020/astrazenecas-covid-19-vaccine-authorised-in-uk.html. Last accessed on January 12th, 2021.
12. https://www.evropaelire.org/a/shqiperi-vaksinimi-covid-19-/31041855.html. Last accessed on January 12th, 2021.
13. Pardi N, Tuyishime S, Muramatsu H, et al. Expression kinetics of nucleosidemodified mRNA delivered in lipid nanoparticles to mice by various routes. J Control Release 2015; 217: 345-51.
14. Karikó K, Muramatsu H, Welsh FA, et al. Incorporation of pseudouridine into mRNA yields superior nonimmunogenic vector with increased translational capacity and biological stability. Mol Ther 2008; 16:1833-40.
15. Wrapp D, Wang N, Corbett KS, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 2020; 367: 1260-3.
16. Rare Diseases Database. https://rarediseases.org/rare-diseases/transverse-myelitis/ Last accessed on January 12th, 2021.
17. Istituto Superiore della Sanità Gruppo della Sorveglianza SARS-CoV-2, Palmieri L, Agazio E, Andrianou X, et al. Caratteristiche dei pazienti deceduti positivi all'infezione da SARS-CoV-2 in Italia. Rapporto December 16th 2020.
18. https://www.pharmacist.com/article/two-uk-suffer-allergic-reaction-pfizers-covid-19-vaccine. Last accessed on January 12th, 2021.