

## Literature screening report

# Covid-19 vaccines: early post-vaccination data about efficacy and safety

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## Preamble

A large number of scientific publications become available on a daily basis, reflecting the rapid development of knowledge and progress of science on COVID-19 related issues. Leading authorities should base decisions or policies on this knowledge; hence they need to master the actual state of this knowledge. Due to the large number of publications shared daily, decision makers heavily depend on accurate summaries of these publications, in the different public health domains. Therefore, the authors of this report were mandated by the Swiss School of Public Health plus (SSPH+), upon request of the Federal Office of Public Health (FOPH), to inform the FOPH on recent findings from the literature.

## Background

Covid-19 vaccines have already been administered to millions of people worldwide following an Emergency Use Authorisation (EUA) by local and international health authorities<sup>1</sup>. Although efficacy and safety of those vaccines have been reported in phase III clinical trials [1-6], the design, interim results, and short follow-up of included participants, among other factors, invite us to not only be cautious but also to be motivated to seek validation of those results in real-world settings.

<sup>1</sup> <https://ourworldindata.org/grapher/share-people-vaccinated-covid?tab=chart&stackMode=absolute&time=earliest..latest&country=BHR~BGD~BRA~CHL~DNK~FRA~DEU~IDN~ISR~ITA~NOR~POL~RUS~SRB~SVK~ESP~TUR~GBR~USA~ARE~CHE&region=World> (accessed on 05.03.2021).

Moreover, Covid-19 clinical trials have left many unanswered questions that requires data about, but not limited to:

- Booster dose timing and efficacy of a single dose.
- Virus transmissibility and shedding in the vaccinee population.
- Efficacy of emergency-authorized vaccines on current virus mutations/variants.
- Efficacy of vaccines in real world settings, includes previously infected persons and other subpopulations.
- Rare but serious adverse events at short or longer term
- Longevity of protection
- Cost-effectiveness of currently available vaccines (e.g., head-to-head comparison)

Fortunately, several important studies, press releases, and newly vaccine candidates -granted an EUA - have been published since our literature review of February 09, 2021. More specifically, there exist some data resulted from mass vaccination of millions of people and more and more data come from Covid-19 literature at regular basis.

## Questions addressed

- What are the newly emergency-authorized vaccines, by WHO, the FDA or Swissmedic, for example?
- Which is the efficacy of a single dose of emergency-authorized vaccines?
- What data exist about transmission and infectiousness of SARS-CoV2 after vaccination?
- What is the efficacy of emergency-authorized vaccines new variants or strains?
- What is the efficacy of emergency-authorized vaccines in real-world settings (e.g., observational studies)?

## Methodology

As previously reported, we conducted a rapid systematic review [7] of the published Covid-19 literature and adhered to PRISMA guidelines while any derogations (if occurs) are reported in the discussion or limitation section of the full report.

### Literature and information search

We designed a search strategy composed of text words (e.g., coronavirus disease), MeSH or Emtree terms (e.g., covid-19 vaccine or 'sars-cov-2 vaccine'/exp), boolean terms (e.g., AND, OR) and truncations (e.g., immune\*) to electronically identify studies related to candidate SARS-CoV-2 vaccines efficacy and/or safety. **By March 08, 2021**, we interrogated the following databases: Medline, Embase, Cochrane Library, MedRxiv & BioRxiv, clinical trials.gov, WHO international registry of clinical trials, airfinity, as well as google search for potentially relevant contents. In addition, we screened the references of included studies and hand-searched potentially relevant articles.

### Eligibility of studies

Eligible studies were those reporting any data about efficacy (e.g., prevention of SARS-CoV-2 infection) and safety (e.g., adverse events) of candidate Covid-19 vaccines whether they have been marketed, under assessment or still under development. No language restriction was used but the studies were limited by publication date (for this report: January 28, 2021 – March 08, 2021).

### Risk of bias (quality) assessment

At this stage, the risk of bias and quality of included studies are not evaluated. It is expected, however, to do so in the next versions once we get a fuller picture of included studies.

### Data abstraction and analysis

We extracted data from included studies that include, but not limited to, vaccine name, manufacturer (country), platform, effect estimates of phase III clinical trials, safety (adverse events), health authorities' approval, and relevant ongoing studies.

## Synthesis of information

We analysed the data based on the specific questions cited in the introduction and tried to answer them as part of this report.

## Results and Findings

What are the newly emergency-authorized vaccines, by the FDA, WHO or Swissmedic, for example?

### Summary:

Among those under clinical development, 4 vaccines [Pfizer-BioNTech COVID-19 vaccine (BNT162b2/COMIRNATY®), Moderna COVID-19 vaccine/ mRNA-1273, Janssen Covid-19 vaccine (Ad26.COV2.S), and AstraZeneca/Oxford vaccine (ChAdOx1 nCoV-19/AZD1222/Covishield)] have been authorized for an emergency use by the FDA (first 3), WHO (first and last) or Swissmedic (first and second). Many others are still under evaluation for an emergency use listing by the WHO such as (Novavax, Sputnik V, Sinopharm, or Sinovac). Swissmedic is undergoing an evaluation for AstraZeneca/Oxford vaccine.

### Results

After Pfizer-BioNTech COVID-19 vaccine (BNT162b2), the World Health Organization (WHO) has recently approved AstraZeneca/Oxford vaccine (ChAdOx1 nCoV-19/AZD1222/Covishield) around mid-February 2021 for an Emergency Use Listing (EUL)<sup>2</sup>.

The United states food and drug administration (FDA) has granted an Emergency Use Authorization (EUA) to Janssen Covid-19 vaccine (Ad26.COV2.S)<sup>3</sup>. As reported in the FDA review memorandum, Janssen vaccine has showed an overall efficacy of 66.9% (95% confidence interval (CI) 59.03 to 73.40) and 66.1% (95% (CI) 55.01 to 74.80) in preventing moderate to severe/critical COVID-19 occurring at least 14 days and 28 days after vaccination, respectively. Surprisingly, we did not find any peer-reviewed paper for phase III clinical trial for Janssen Covid-19 vaccine.

<sup>2</sup> <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines> (accessed on 05.03.2021).

<sup>3</sup> <https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/janssen-covid-19-vaccine> (accessed on 05.03.2021).

Of note, the FDA has stated that a Covid-19 vaccine should be at least 50% effective to get its EUA approval<sup>4</sup>.

Swissmedic has already approved two vaccines [namely, Pfizer-BioNTech COVID-19 vaccine (BNT162b2/COMIRNATY®) and Moderna COVID-19 vaccine/ mRNA-1273 (Moderna, USA) and other vaccines are pending<sup>5</sup> such as AstraZeneca/Oxford vaccine (ChAdOx1 nCoV-19/AZD1222/Covishield). Preliminary results for Novavax (NVX-CoV2373) vaccine at phase II clinical trial in South Africa showed an overall efficacy of 49.4 (95% CI (6.1 to 72.8) and an efficacy of 60.1 (95% CI (19.9 to 80.1) among HIV-negative participants [8]. As part of a national vaccination program, Swissmedic<sup>6</sup> has so far evaluated 364 reports of suspected adverse events to Covid-19 vaccines in Switzerland. Of those, 95 (26%) were serious cases that needed treatment or considered medically important. Those adverse events were shingles (n=8), fever (n=8), headache (n=7), Covid-19 infections (n=9) and allergic reactions, including four cases of anaphylactic reactions. Sixteen deaths (mean age 86 years old) were reported but were judged to be unrelated to vaccines. Interestingly, injection site erythema and delayed skin reactions were reported more frequently in the Moderna Covid-19 vaccine compared with Pfizer-BioNTech COVID-19 Vaccine.

<sup>4</sup> <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-vaccines-prevent-covid-19> (accessed on 05.03.2021).

<sup>5</sup> <https://www.bag.admin.ch/bag/en/home/krankheiten/ausbrueche-epidemien-pandemien/aktuelle-ausbrueche-epidemien/novel-cov/impfen.html#1210867030> (accessed on 05.03.2021).

<sup>6</sup> <https://www.swissmedic.ch/swissmedic/en/home/news/coronavirus-covid-19/nebenwirkungen-covid-19-impfungen-ch-update.html> (accessed on 05.03.2021).

Which is the efficacy of a single dose of emergency-authorized vaccines?

**Summary:**

Doses schedules have been tested in phase III clinical trials and manufactures of those vaccines recommend a two-dose regimen. However, the efficacy of a single dose has been evaluated in many studies for any better outcomes. While the benefits of such ‘out of label’ use of vaccines are potentially important, caution is reasonable, and more studies are warranted. In terms of supply and administration restrictions, potential use of a single-dose vaccine is promising. Interestingly, there exists an FDA-authorized one (namely Janssen Covid-19 vaccine).

**Results:**

Phase III clinical trials [1-6] was primarily designed to evaluate Covid-19 vaccines efficacy after a two-dose regimen, except Janssen Covid-19 vaccine (Ad26.COVS.S) which was authorized by the FDA as a single dose for an emergency use. It is common practice that the dosing regimen and schedule is established at phase I or II studies, not apparently the case in the current speedy process in Covid-19 vaccines. However, interim or secondary analysis of efficacy after first dose was estimated as 52% (95% CI 29.5 to 68.4) for Pfizer-BioNTech COVID-19 Vaccine (BNT162b2) [4] , 80.2% (95% CI 55.2%, 92.5%) for Moderna COVID-19 Vaccine (mRNA-1273)<sup>7</sup>, 64.1% (95% CI 50.5 to 73.9) or 76.0% (59.3 to 85.9) for AstraZeneca/Oxford vaccine (ChAdOx1 nCoV-19/AZD1222/Covishield) [5, 6], and 66% for Janssen vaccine (Ad26.COVS.S)<sup>8</sup>. No publicly available data for inactivated (InCoV) (Sinopharm/Beijing Bio-Institute of Biological Products Co-Ltd, China and inactivated virus base vaccine manufactured by SINOVAC, China) or Gam-COVID-Vac/Sputnik V about the efficacy of a single shot. The latter, though, is undergoing a clinical trial<sup>9</sup> to evaluate a single dose of the vaccine (Sputnik light). Of note, the single-dose efficacy results were reported in phase III clinical trials that bear quite

<sup>7</sup> <https://www.fda.gov/media/144434/download> (accessed on 04.03.2021).

<sup>8</sup> <https://www.deutsche-apotheker-zeitung.de/news/artikel/2021/03/01/fda-erteilt-covid-19-impfstoff-von-johnson-johnson-notfallzulassung/chapter:2> (accessed on 04.03.2021).

<sup>9</sup> <https://clinicaltrials.gov/ct2/show/NCT04713488> (accessed on 04.03.2021).



similar concerns or limitations to two-dose regimen such as short follow-up of trial participants. Although those analyses were usually part of secondary outcomes per protocol, we ignore for how long this protection lasts. The modelling analysis [6] for AstraZeneca/Oxford vaccine showed a single-dose protection with mild waning of antibody levels by day 90 (3-month follow-up). Both Pfizer-BioNTech and Moderna COVID-19 vaccines have not compared participants with single doses versus two-dose regimen or placebo more than 21 or 28 days, respectively. A single dose of AstraZeneca/Oxford vaccine (Covishield by Serum Institute, Pune, India) showed a higher antibody response among previously infected compared to seronegative healthcare workers [9].

In fact, booster doses (i.e., 2<sup>nd</sup> or 3<sup>rd</sup> doses after a first dose) are scientifically established in other licensed vaccines as polio, hepatitis B, or tetanus. Unlike those diseases, the timing of a booster dose is still to be optimized for Covid-19 vaccines. There are some studies that advocate for delaying or cancelling the booster dose (i.e., second dose) of Covid-19 vaccines to maximize efficacy [6], for less infections, hospitalizations or mortality reductions [10-13], for being 'unnecessary' or having poor antigen-specific antibody-secreting cell responses in previously infected persons [14-16] or for an absence of incremental benefits after the second dose in a re-analysis of data from Pfizer-BioNTech vaccine clinical trial [17].

What data exist about transmission and infectiousness of SARS-CoV-2 after vaccination?

**Summary:**

Phase III clinical trials used SARS-CoV-2 infection as a primary endpoint that would indirectly reduce community transmission. However, the potentially infected persons who remain asymptomatic may still transmit the virus as they usually will not be tested. Although preliminary studies suggested vaccine provide direct and indirect transmission reduction, the existing risk of viral transmissibility encourage us to continue physical interventions (e.g., masks and social distancing) to achieve herd immunity.

**Results:**

Phase III clinical trials [1-6] used SARS-CoV-2 infection incidence as a primary endpoint to measure vaccine efficacy. However, the trials provided little to no data about prevention of infection in asymptomatic patients and about virus transmission or viral shedding. Testing for SARS-CoV-2 infection was mainly triggered by symptoms and that relatives and contacts of trial participants were not followed up as well. In practice, the presence of the SARS-CoV-2 infection in the nasal olfactory epithelium would remain a potential threat to transmit and shed the virus in asymptomatic vaccinees [18]. A modeling approach - under certain assumptions - estimated an efficacy of 61% to prevent transmission after a single dose of Moderna Covid-19 vaccine [19]. AstraZeneca/Oxford vaccine showed a statistically insignificant efficacy of 22.2% [95% CI (-9.9 to 45.0)] to prevent asymptomatic infections in a cohort of participants in the United Kingdom [6]. More studies are needed to establish whether current emergency-authorized vaccines would directly reduce virus transmissibility among individuals while being asymptomatic.

What is the efficacy of emergency-authorized vaccines on new variants or strains?

**Summary:**

New variants represent a potential threat to efficacy of vaccines used in current mass vaccinations. The good news is that several studies have still shown a certain level of efficacy, but we still lack a specific correlate of protection in a way that we are reassured that such protection level is always still sufficient. Importantly, South Africa stopped the rollout of AstraZeneca/Oxford vaccine upon preliminary results of a randomized clinical trial. Pfizer-BioNTech has recently announced the study of a booster dose (3<sup>rd</sup> dose) to evaluate its efficacy on new variants.

**Results:**

As with other viruses, mutations of SARS-CoV-2 have been reported in many countries [20-22]. Compared to the wild-type, SARS-CoV-2 variants (due to a single or multiple mutations) may minimize immune responses triggered by vaccines. Practically speaking, clinical trials conducted in countries with variant dominance have shown variable efficacy as low as 52% in South Africa to as high as 74.4 in the United States (for Janssen Covid-19 vaccine at least 14 days after vaccination)<sup>10</sup>. Several studies [23-29] have shown a partial loss of virus-neutralizing activity caused by such variants after vaccination. AstraZeneca/Oxford vaccine was deemed ineffective [21.9% (95% CI (-49.9 to 59.8))] to prevent mild and moderate Covid-19 infections in patients with the B.1.351 variant in South Africa [3], causing a halt to an ongoing rollout<sup>11</sup>. It is noteworthy that subgroup analyses of phase III clinical trial in South Africa reported an efficacy of approximately 75% after a single dose but that was before the dominance of the variant in the country<sup>12</sup>. One study [26] showed a moderate yet significant resistance of N501Y/K417N/E484K mutants to

<sup>10</sup> <https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/janssen-covid-19-vaccine> (04.03.2021)

<sup>11</sup> <https://www.cidrap.umn.edu/news-perspective/2021/02/south-africa-share-covid-vaccine-europe-weighs-jj-vaccine> (accessed on 04.03.2021).

<sup>12</sup> <https://www.theguardian.com/world/2021/feb/08/oxford-covid-vaccine-10-effective-south-african-variant-study> (accessed on 04.03.2021).

convalescent or post-vaccine sera. This may translate to lower vaccine efficacy to prevent infection but not necessarily the severity of the disease. A comparison among emergency-authorized vaccines would be interesting but an 'upgrade' of currently available vaccines would be expectedly necessary in the coming months/years. The recent announcement<sup>13</sup> of Pfizer-BioNTech to follow-up trial participants to study the efficacy of a booster dose (3<sup>rd</sup> dose) on new variants or strains is one way forward in this direction.

<sup>13</sup> <https://abc7.com/pfizer-third-vaccine-dose-covid-vaccines-3rd-shot-pfizers-efficacy/10369726/> (accessed on 08.03.2021).

What is the efficacy of emergency-authorized vaccines in real-world settings (e.g., observational studies)?

**Summary:**

Due to limited sample size of phase III clinical trials, mass vaccinations may help confirm the effectiveness and safety (e.g., rare adverse events) of vaccines. Such data may also inform any potential contraindications or add relevant information. Many studies showed that vaccines (namely, Pfizer-BioNTech COVID-19 vaccine) were effective to prevent SARS-CoV-2 infections in Israel. Some of those studies support the efficacy of a single dose with varied estimations. Unlike Pfizer-BioNTech COVID-19 vaccine phase III clinical trial, diarrhea and vomiting have been reported 'more frequently' in vaccine recipients and added to the systemic adverse events list. Although evidence is still preliminary, immune thrombocytopenia was reported as rare but serious adverse event. Vaccination may probably be discouraged to known susceptible persons such as those with hereditary thrombocytopenia or documented abnormal platelet counts after benefits/risk evaluation.

**Results:**

Many nations are rushing to massively vaccinate their populations<sup>14</sup> that would unintentionally create an opportunity to evaluate the effectiveness and safety (e.g., rare adverse events) of currently marketed vaccines in real-world settings. Preliminary studies [26, 30-37] have shown that Pfizer-BioNTech COVID-19 vaccine (BNT162b2) was effective in Israeli population. Of those, two studies reported a reduction of the viral load in infected individuals that would have probably curbed the virus transmission. Interestingly, one study [30] showed no efficacy (before 3 weeks) of a single dose of BNT162b2 in disagreement to another study [31] that showed an efficacy of 51% (13-24 days follow-up). Re-analysis and modeling of the same Israeli

<sup>14</sup> <https://ourworldindata.org/grapher/share-people-vaccinated-covid?tab=chart&stackMode=absolute&time=earliest..latest&country=BHR~BGD~BRA~CHL~DNK~FRA~DEU~IDN~ISR~ITA~NOR~POL~RUS~SRB~SVK~ESP~TUR~GBR~USA~ARE~CHE&region=World> (accessed on 05.03.2021).

data resulted in 90% efficacy at day 21 [33]. In addition, two-doses regimen showed up to 97% efficacy on 14 days from 2<sup>nd</sup> dose [30]. Those differences in (under-) estimations were potentially related to other factors, mainly the lockdown in early January and the reported increase in incidence of cases by roughly 35% in the general population<sup>15</sup> or probably due to the ease of protective measures (e.g., social distancing) by the vaccinee population. Another study [37] reported initial trend of benefits of vaccination by comparing the timing and outcomes in vaccinated versus unvaccinated cities in Israel. One more study in the United States reported that vaccinations were effective in preventing infection and reducing 14-day hospital admission rate [38]. In the United Kingdom, early vaccination benefits (decrease in symptomatic SARS-CoV-2 infection, lower risk of emergency hospitalization, and Covid-19 related mortality prevention) have been reported [39] where Pfizer-BioNTech Covid-19 vaccine has been used besides initial use of AstraZenca/Oxford vaccine. Notably, all previous studies are preprints and have not yet been published in peer-reviewed journals. Given the rollout of several millions of doses, more data on safety of Covid-19 vaccines would be of interest. Originally reported in the Pfizer-BioNTech COVID-19 vaccine as equal among vaccine or placebo recipients<sup>16</sup>, diarrhea and vomiting have now been added to the systemic adverse events list<sup>17</sup>. De novo or secondary immune thrombocytopenia [40] has been reported mainly after the 2<sup>nd</sup> dose of Pfizer-BioNTech COVID-19 vaccine (BNT162b2/COMIRNATY®) or Moderna COVID-19 vaccine/ mRNA-1273]. Pharmacovigilance and surveillance programs (or even population surveys [41]) are necessary to provide more safety data while maintaining vaccination campaigns.

<sup>15</sup> <https://data.gov.il/dataset/covid-19> (accessed on 04.03.2021).

<sup>16</sup> <https://www.cdc.gov/vaccines/covid-19/info-by-product/pfizer/reactogenicity.html> (accessed on 08.03.2021).

<sup>17</sup> <https://www.precisionvaccinations.com/vaccines/pfizer-biontech-covid-19-vaccine> (accessed on 08.03.2021).

## Ongoing studies

Since January 2021, several clinical trials, including phase IV, and longer follow-up of trial participants (listed here: <https://bit.ly/3cc52Vo>) are still ongoing on many domains. For example, clinical studies aims to evaluate breast milk effects<sup>18</sup> (though there exist some observational studies [42-45]), efficacy on immunocompromised patients<sup>19</sup>, efficacy of 'Vero cell' vaccine<sup>20</sup>, SINOVAC<sup>21</sup> vaccine, combination of two vaccines (AstraZeneca/Oxford and Sputnik V)<sup>22</sup> or a third dose (booster) of Pfizer-BioNTech vaccine<sup>23</sup>.

NB: Table 1 – in literature review 1- will be updated once we have peer-reviewed results for any phase III clinical trial Covid-19 vaccine.

<sup>18</sup> [https://www.clinicaltrials.gov/ct2/show/NCT04751734?cond=Covid-19&intr=Vaccine&strd\\_s=01%2F01%2F2021&draw=2&rank=10](https://www.clinicaltrials.gov/ct2/show/NCT04751734?cond=Covid-19&intr=Vaccine&strd_s=01%2F01%2F2021&draw=2&rank=10)

<sup>19</sup> [https://www.clinicaltrials.gov/ct2/show/NCT04780659?cond=Covid-19&intr=Vaccine&strd\\_s=01%2F01%2F2021&draw=2&rank=4](https://www.clinicaltrials.gov/ct2/show/NCT04780659?cond=Covid-19&intr=Vaccine&strd_s=01%2F01%2F2021&draw=2&rank=4)

<sup>20</sup> [https://www.clinicaltrials.gov/ct2/show/NCT04659239?cond=Covid-19&intr=Vaccine&strd\\_s=01%2F01%2F2021&draw=3](https://www.clinicaltrials.gov/ct2/show/NCT04659239?cond=Covid-19&intr=Vaccine&strd_s=01%2F01%2F2021&draw=3)

<sup>21</sup> [https://www.clinicaltrials.gov/ct2/show/NCT04747821?cond=Covid-19&intr=Vaccine&strd\\_s=01%2F01%2F2021&draw=2](https://www.clinicaltrials.gov/ct2/show/NCT04747821?cond=Covid-19&intr=Vaccine&strd_s=01%2F01%2F2021&draw=2)

<sup>22</sup> [https://www.clinicaltrials.gov/ct2/show/NCT04684446?cond=Covid-19&intr=Vaccine&strd\\_s=01%2F01%2F2021&draw=5](https://www.clinicaltrials.gov/ct2/show/NCT04684446?cond=Covid-19&intr=Vaccine&strd_s=01%2F01%2F2021&draw=5)

<sup>23</sup> <https://abc7.com/pfizer-third-vaccine-dose-covid-vaccines-3rd-shot-pfizers-efficacy/10369726/> (accessed on 08.03.2021).

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