Literature screening report

COVID-19 vaccines: efficacy and safety

(Literature Review 1)

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Content

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+), on request of the Federal Office of Public Health (FOPH), to inform the FOPH on recent findings from the literature.

Background

Historically, vaccines have been a vital element in infectious diseases prevention and public health interventions. Development of vaccines involve many stages: animal models, preclinical, and clinical (phase I-III) studies as well as post-vaccine rollout studies [1]. To get a market authorization approval, vaccines need to be proved safe, efficacious, and effective against the targeted disease. Vaccine efficacy is defined as the percentage by which the rate of disease incidence is reduced in vaccinated groups as compared to placebo [2]. Since the outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (Covid-19), 238 candidate vaccines have been registered in the World health organization (WHO) landscape and tracker[1]. Of those, 15 candidate vaccines are undergoing assessment for WHO Emergency Use Listing (EUL) and prequalification (PQ). As of February 02, 2021, 22 candidate vaccines have reached phase III clinical trials or have already obtained a market authorization from local and/or international health authorities[2].

Beforehand, health authorities need to check safety and efficacy before giving a green light to a vaccine candidate, but political pressure is not excluded in a devastating situation and socioeconomical unrest caused by Covid-19 [3]. For instance, it has been argued that a Human Adenovirus Vector-base vaccine, developed by Russia, has been approved by Russian health authorities but also by Hungary[3] before phase III clinical trials or despite spotting apparently duplicate data [4]. Another vaccine, an inactivated virus developed by China, was approved by some Arab nations (namely, the United Arab Emirates and Bahrain) without publicly available data [5]. A thorough systematic investigation of such allegations may be helpful and aid in informed decision making for national vaccination strategies.

Current SARS-CoV-2 vaccine development employed a variety of platforms and strategies (e.g., inactivated virus, live attenuated virus, RNA- or DNA-based vaccine, recombinant protein, protein subunit, or replicating viral vector) [6] and hence the quality of the immune response [7], the efficacy and safety of the corresponding vaccines may be variable as such diversified biotechnologies target the same contagious disease.

Current market-authorized Covid-19 vaccines, where some were developed in unprecedented pace of 11 months or less, has raised many controversial debates and public trust challenges [8, 9]. People preferences and choices about vaccine acceptability and uptake may vary from one nation to another [10] but safety and efficacy remain the most valuable attributes when it comes to an individual's health. Furthermore, subpopulations such as pregnant women and children were excluded from published clinical trials and, therefore, relevant data are warranted [11]. We aimed to review the current evidence in the literature about safety and efficacy data for approved SARS-CoV-2 vaccines or those seeking market authorization at local or international level and highlight new candidate vaccines and ongoing clinical trials.

[1] https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines (accessed on February 03, 2021).
[2] https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines (accessed on February 03, 2021).
[3] https://www.bbc.com/news/world-europe-55747623 (accessed on February 03, 2021).

Methodology

We conducted a rapid systematic review [12] of the published literature and adhered to PRISMA guidelines while any derogations are reported in the limitation section.

Literature and information search

We designed a search strategy composed of text words (e.g., coronavirus disease), MeSH terms (e.g., covid-19 vaccine), 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 January 28, 2021, we interrogated the following databases: Medline, Embase, Cochrane Library, MedRxiv (limited to December 2020 onwards), 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 by February 5th, 2021.

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 (December 2019 and upwards).

Risk of bias (quality) assessment

At this stage of the review, the risk of bias and quality of included studies are not evaluated. It is expected, however, to do so in the next versions.

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 status of candidate vaccines as of February 5th, 2021. The status of vaccines is categorized into three stages: market-approved vaccines, pre-market authorization vaccines (those at phase III clinical trials), and new candidate vaccines (at any early stage). We reported the efficacy estimates and adverse events as stated in the clinical trials.

Findings and results

Summary

Comments and conclusions

In an unprecedented pace of drug development, several vaccines have already obtained a market authorization approval from national regulatory authorities. We reviewed the current evidence on safety and efficacy of those candidate vaccines and shed a light on other vaccines at early stage of development. Our findings revealed that at least 4 candidate vaccines [14, 21, 24, 27] have published safety and efficacy data from randomised clinical trials (phase III). While the efficacy and safety of those vaccines are deemed promising, the design, short follow-up and preliminary analyses of uncompleted trials should be seen with caution. There exist other important concerns such as the logistical challenges (e.g., cold chain requirements for mRNA-based vaccines) that may pose an obstacle or even make the vaccination program infeasible in settings, such as low-income countries[4]. Much data is still needed for all candidate vaccines. Rare events were hardly detectable in clinical trials due to the relatively small sample size, compared to licensed vaccines [33, 34]. According to Pfizer[5], serious allergic reactions have been reported during mass vaccination campaigns. Transparency and data sharing should be a criterion to maintain public trust, and communication of data (especially adverse effects) at individual level should be established before vaccination, besides national surveillance system. The current literature review bears its own limitations. First, we may have missed relevant studies despite systematic search strategy due to the growing number of publications and the time-lag between indexing in databases and publication of the respective studies. An update of the current report is, therefore, necessary (starting from January 28, 2021 and onwards). Second, we did not evaluate the quality of the studies nor assessed the risk of bias.

Results

Literature search

The electronic and hand search yielded 3,391 references that were screened, after duplicate removal, at title/abstract level and full-text level for any relevant contents. We finally retrieved 20 studies [13-32] of which 4 were included and related to phase III clinical trials. The study selection process is illustrated in **Figure 1**.

Study selection and characteristics

Most included studies were of phase I or phase II clinical studies [13, 15-20, 22, 23, 25, 26, 29-32]. **Table 1** is limited to candidate vaccines with phase III clinical trials [14, 21, 24, 27]. The efficacy ranged from as low as 70.4% for ChAdOx1 nCoV-19/AZD1222/Covishield (AstraZeneca/Oxford, UK,

[4] https://www.msf.org/taking-fridge-out-equation (accessed on February. 08, 2021).
[5] https://www.pfizer.com/news/press-release/press-release-detail/vitro-study-shows-pfizer-biontech-covid-19-vaccine-elicits (accessed on February. 08, 2021).

and Serum institute of India, India) to as high as 95% for BNT162b2/COMIRNATY® (Pfizer-BioNTech SE, USA). The design of the studies, settings and recruitment varied (to be explored later in quality appraisal and risk of bias assessment). Safety and other aspects are summarized in **Table 1**.

Market-authorized vaccines

As of February 03, 2020, at least 7 candidate vaccines have been granted an Emergency Use Authorization (EUA) by local and international regulatory agencies. The United states food and drug administration (FDA) has granted an EUA to two American vaccines [namely, Pfizer-BioNTech COVID-19 Vaccine (BNT162b2/COMIRNATY®) and Moderna COVID-19 Vaccine/ mRNA-1273 (Moderna, USA)[6]. An EUA means that the FDA may only determine if a product is efficacious and that benefits are likely to outweigh risks, not necessarily safety and effectiveness [3]. Pfizer-BioNTech COVID-19 Vaccine has also been approved by the European medicines agency (EMA), World health organization (WHO) Emergency Use Listing (EUL) and a list of countries including Switzerland. While both FDA and EMA approved the Moderna COVID-19 Vaccine, it is still under assessment by the WHO (decision is expected at the end of February 2021). Both vaccines were respectively authorized for use in adults ≥ 16 years old and ≥ 18 years old, excluding children and apparently pregnant women. The EMA and Medicines and Healthcare products Regulatory Agency (MHRA, UK) have approved a third vaccine [namely, ChAdOx1 nCoV-19/AZD1222/Covishield (AstraZeneca/Oxford, UK, and Serum institute of India, India)] but it is still under assessment by the WHO (decision is expected by mid-end February 2021). Three additional vaccines [Gam-COVID-Vac/SPUTNIK V (Gamaleya Research Institute, Russia), inactivated (lnCoV) (Sinopharm/Beijing Bio-Institute of Biological Products Co-Ltd, China and inactivated virus base vaccine manufactured by SINOVAC, China) have obtained an EUA by local and international authorities[7].

In general, market authorisation approval requires that the vaccine candidate should have available data on efficacy and safety. In practice, it is difficult to get robust data before phase III clinical trials, thanks to the sufficient power and the large number of participants that allow better detection of rare adverse events.

In phase III clinical trial [24], the efficacy of BNT162b2/COMIRNATY® (Pfizer-BioNTech) vaccine showed an efficacy of 94.6% (95% CI, 89.9 to 97.3) in population with or without prior infection. In no prior or existing infection, vaccine efficacy was 95.0% (95% CI, 90.3 to 97.6). Four related serious adverse events were reported among vaccine recipients (shoulder injury related to vaccine

[6] https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization (accessed on February 04, 2021).
[7] https://www.ft.com/content/ac5e5ef8-bccb-482b-9f8d-0dab5cac6f9a (accessed on February 08, 2021).

administration, right axillary lymphadenopathy, paroxysmal ventricular arrhythmia, and right leg paresthesia).

Common adverse reactions in participants 16 years of age and older included pain at the injection site (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), fever (14.2%), injection site swelling (10.5%), injection site redness (9.5%), nausea (1.1%), malaise (0.5%), and lymphadenopathy (0.3%)[8]. In phase III clinical trial [14], the efficacy of Moderna COVID-19 Vaccine (mRNA-1273) was estimated as 94.1% (95% CI, 89.3 to 96.8%; P<0.001) for the prevention of symptomatic SARS-CoV-2 infection as compared with placebo. The study of 30,420 volunteers reported an incidence of 79.7 Covid-19 cases per 1000 person-years (95% confidence interval [CI], 70.5 to 89.9) among participants in the placebo group with no evidence of previous SARS-CoV-2 infection. In a primary analysis of 63 days median follow-up, 96 cases of Covid-19 were diagnosed: 11 cases in the vaccine group (3.3 per 1000 person-years; 95% CI, 1.7 to 6.0) and 185 cases in the placebo group (56.5 per 1000 person-years; 95% CI, 48.7 to 65.3). The study reported more adverse events in the vaccine group compared with placebo. Common adverse events included, but not limited to, headache, fatigue, myalgia, arthralgia, and pain at injection site (**Table 1**).

Interim results from phase III clinical trials [27] revealed that the efficacy of ChAdOx1 nCoV-19/AZD1222/Covishield (AstraZeneca/Oxford, UK, and Serum institute of India, India) vaccine was 70·4% (95% CI 54·8 to 80·6), starting from 14 days after 2nd dose. For any nucleic acid amplification test-positive swab: efficacy was 55·7% (95% CI 41·1 to 66·7). Subgroup two standard doses: efficacy was 62·1% (95% CI 41·0 to 75·7) while those with first low dose and standard 2nd dose the efficacy was 90·0% (95% CI 67·4 to 97·0).

Serious adverse events occurred in 168 participants, 79 of whom received the vaccine and 89 of whom received MenACWY (meningococcal group A, C, W, and Y conjugate vaccine) or saline control. There were 175 serious adverse events (84 in the vaccine group and 91 in the control group), three of which were possibly related to the intervention: transverse myelitis occurring 14 days after a vaccine booster dose, haemolytic anaemia in a control recipient, and fever higher than 40°C in a participant still masked to group allocation.

Interim results from phase III clinical trials [21] showed that the efficacy of Gam-COVID-Vac/SPUTNIK V (Gamaleya Research Institute, Russia) was 91.6% ((95% CI 85·6–95·2) with a median follow-up of 48 days.

Most common adverse events were flu-like illness, injection site reactions, headache, and asthenia. Most of the reported adverse events (7485 [94·0%] of 7966) were grade 1; 451 were grade 2 (5·66%)

[8] https://www.pfizer.com/news/press-release/press-release-detail/vitro-study-shows-pfizer-biontech-covid-19-vaccine-elicits (accessed on Februray 08, 2021).

and 30 were grade 3 (0·38%) [see terms in https://www.meddra.org/user-groups]. One hundred twenty-two rare adverse events were reported in the study (91 in the vaccine group and 31 in the placebo group).

We did not find any phase III clinical trials for the Sinopharm/Beijing Bio-Institute of Biological Products Co-Ltd or SINOVAC candidate vaccines. However, Sinopharm claims an efficacy of 79% or 86%, based on unpublished data from a clinical trial in the United Arab Emirates[9] [5].

Future clinical trials/observational studies would tell us about the viral shedding after infection and the incidence of asymptomatic SARS-CoV-2 infections in immunized persons [14]. In fact, any vaccine that is effective on preventing the disease and the transmission of the virus will be more valuable as studies proved that a good proportion of asymptomatic or pre-symptomatic people spread the virus in the community.

Pre-market authorization vaccines

As of February 03, 2020, at least 22 candidate vaccines have reached phase III clinical trials, the 'final' stage before applying to health authorities for full market authorization[10]. Many of this list are expected to apply for WHO EUL and that the data derived from phase III clinical trials will be available/published. For example, Janssen-Cilag AG is running a phase III clinical trial in the USA[11].

New candidate vaccines

As of February 2nd, 2021, there exist 172 candidate vaccines which are under development or at pre-clinical stage[12]. Interestingly, development of two candidate vaccines had been suspended which were at phase I/II clinical trials. It is premature to predict the output of those candidate vaccines but given the speedy process, we expect that some will see the light in the near future.

Ongoing studies and pending research questions

A list of ongoing clinical trials can be sent upon request (as of January 28, 2021).

Here are some of the pending research questions:

What is the efficacy of candidate vaccines on the UK and South African strains of SARS-CoV-2?

What is the longevity of protection for each vaccine candidate?

[9] https://www.ft.com/content/ac5e5ef8-bccb-482b-9f8d-0dab5cac6f9a (accessed on February 08, 2021).
[10] https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines (accessed on February 08, 2021)
[11] https://local.nihr.ac.uk/documents/a-randomized-double-blind-controlled-phase-3-study-to-assess-the-efficacy-and-safety-of-ad26cov2s-for-the-prevention-of-sars-cov-2-mediated-covid-19-in-adults-aged-18-years-and-older/26403 (accessed on February 08, 2020).
[12] https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines (accessed on February 08, 2021)

To what extent the efficacy of the candidate vaccines on reducing transmission via asymptomatic persons?

Which vaccine is cost-effective?

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Figures and Tables

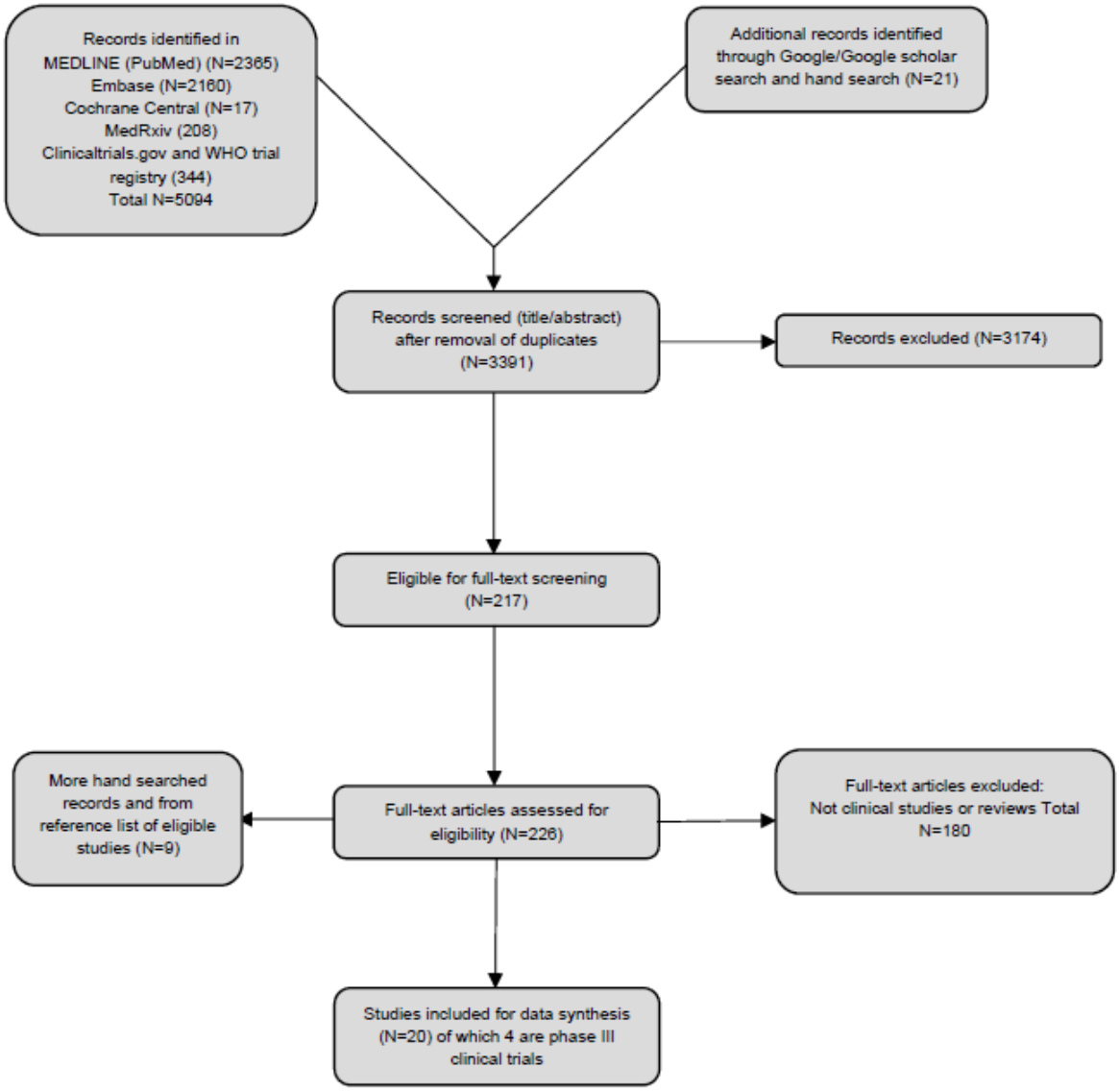

Figure 1: Flow chart of search results.

Table 1 : Main characteristics of market-approved SARS-Cov-2 vaccines

Vaccine name (Manufacturer, country)	Platform	Clinical trials (phase III)	Number of participants (vaccine/placebo)	Population	Total Covid-19 cases (vaccine/placebo)	Efficacy estimates	Safety (adverse events)	Health authorities' approval (Name of authority)	Comments /ongoing studies
BNT162b2/ COMIRNATY (Pfizer-BioNTech SE, USA)	Lipid nanoparticle–formulated, nucleoside-modified RNA vaccine	Polack 2020	≥18 years old, volunteers from the Unites States.	≥16 years old, volunteers from (United States, Argentina, Brazil, South Africa, Germany, and Turkey)	170(8/162)	Starting from 7 days after 2nd dose: 8 Covid-19 cases in the vaccine group and 162 cases in the placebo group Efficacy of **95.0%** (95% CI, 90.3 to 97.6) in population without prior SARS-CoV-2 infection. Efficacy of 94.6% (95% CI, 89.9 to 97.3) in population with or without prior infection.	Death (judged unrelated to the vaccine or placebo): 4 in the placebo and 2 in the vaccine group. Adverse events: 21% in the vaccine and 5% in the placebo. Four related serious adverse events were reported among vaccine recipients (shoulder injury related to vaccine administration, right axillary lymphadenopathy, paroxysmal ventricular arrhythmia, and right leg paresthesia). Other adverse events commonly reported in the vaccine group (pain at the injection site, fatigue, and headache)	FDA, EMA, WHO EUL, and list of countries (including Switzerland)	HIV patients were excluded from the current analysis
Moderna COVID-19 Vaccine/ mRNA-1273 (Moderna, USA)	Lipid nanoparticle–encapsulated mRNA-based vaccine	Baden 2021	30420 (15,210/15,210)	≥18 years old, volunteers from the Unites States.	196 (11/185)	After a median follow-up of less than 63 days: 11 Covid-19 cases in the vaccine group (3.3 per 1000 person-years; 95% CI, 1.7 to 6.0) and 185 cases in the placebo group (56.5 per 1000 person-years; 95% CI, 48.7 to 65.3). Efficacy of **94.1%** (95% CI, 89.3 to 96.8; P<0.001).	Death (judged unrelated to the vaccine or placebo): 2 in the vaccine group versus 3 in the placebo group. Bell's palsy (judged by chance): 3 in the vaccine group versus 1 in the placebo group. Common adverse events: pain at injection site, headache, fatigue, myalgia, arthralgia (all more often or clinically significant in the vaccine group compared to placebo)	FDA, EMA, WHO EUL (pending) list of countries	Evaluation of the incidence of asymptomatic or subclinical infection and viral shedding after infection are under way, to assess whether vaccination affects infectiousness. Calculation of efficacy were not based on the total number of confirmed Covid-19 cases (269 in both groups).

ChAdOx1 nCoV-19/AZD1222/Covishield (AstraZeneca/Oxford, UK, and Serum institute of India, India)	Chimpanzee Adenovirus-vectored vaccine	Voysey 2021	11636 (5807/5829)	≥18 years old, volunteers in Brazil and the UK.	131 (30/101)	In participants with two standard doses: efficacy was 62·1% (95% CI 41·0 to 75·7) while those with first low dose and standard 2nd dose the efficacy was 90·0% (95% CI 67·4 to 97·0). Pooled analysis efficacy was **70·4**% (95% CI 54·8 to 80·6). For any nucleic acid amplification test-positive swab: efficacy of 55·7% (95% CI 41·1 to 66·7).	Serious adverse events occurred in 168 participants, 79 of whom received the vaccine and 89 of whom received MenACWY or saline control. There were 175 serious adverse events (84 in the vaccine group and 91 in the control group), three of which were possibly related to the intervention: transverse myelitis occurring 14 days after a vaccine booster dose, hemolytic anemia in a control recipient, and fever higher than 40°C in a participant still masked to group allocation.	MHRA, EMA, DCGI	This was an interim analysis. Older adults >55 years were few [1418 (12·1%)]. More data is required. Some protection against asymptomatic or unknown symptoms with efficacy of (27·3% (−17·2 to 54·9).
Gam-COVID-VacSPUTNIK V (Gamaleya Research Institute, Russia)	Human Adenovirus Vector-based Covid-19 vaccine	Logunov 2021	12296 (14964/4902)	≥18 years old, volunteers in Russia	78 (16/62)	After a median follow-up of 48 days: Efficacy was 91·6% (95% CI 85·6–95·2)	Death (judged unrelated to the vaccine or placebo): 3 in the vaccine group versus 1 in the placebo group. The most common adverse events were flu-like illness, injection site reactions, headache, and asthenia. Most of the reported adverse events (7485 [94·0%] of 7966) were grade 1; 451 were grade 2 (5·66%) and 30 were grade 3 (0·38%). 122 rare adverse events were reported in the study (91	Russian health authorities; list of countries[1]	This was an interim analysis. The safety analyses were done with an attrition (bias) rate of approximately 38% from those received 2nd dose and 55% from initial randomization. Deviation to the initial protocol (modified on Nov. 5, 2020), as no target number of events (confirmed SARS-CoV-2 infection) was stipulated. Single dose trial is ongoing.

[1] www.sputnikvaccine.com

							in the vaccine group and 31 in the placebo group.		

FDA: the united states food and drug administration
EMA: European Medicines Agency
MenACWY: meningococcal group A, C, W, and Y conjugate vaccine
MHRA: Medicines and Healthcare products Regulatory Agency
DCGI: Drugs Controller General of India
WHO EUL : World Health Organization Emergency Use Listing