



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Short Communication

Vaccines for COVID-19: learning from ten phase II trials to inform clinical and public health vaccination programmes

Sunil S. Bhopal ^{a, *}, Bayanne Olabi ^b, Raj Bhopal ^c^a Population Health Sciences Institute, Newcastle University, Newcastle Upon Tyne, UK^b Biosciences Institute, Newcastle University, Newcastle Upon Tyne, UK^c Usher Institute, University of Edinburgh, Edinburgh, UK

ARTICLE INFO

Article history:

Received 18 January 2021

Accepted 21 January 2021

Available online 29 January 2021

Keywords:

Public health

Vaccine

Vaccination

COVID-19

SARS-CoV-2

ABSTRACT

Public health professionals and clinicians, in many countries, are immersed in the ongoing and upcoming vaccination programmes for COVID-19. Published information from vaccine trials is complex. There are important and helpful insights about the nature of the available and forthcoming vaccines, immune responses and side-effects from phase II trials. We have systematically summarised information from 10 such trials on the nature of the vaccines, exclusions from the trials, immunological effects and side-effects. Some important information within these trial reports is not available in the phase III trial articles, so a complete picture requires examination of phase II and phase III trials for each vaccine. We recommend our systematic approach for the examination of other upcoming COVID-19 vaccine phase II and III trials.

© 2021 The Royal Society for Public Health. Published by Elsevier Ltd. All rights reserved.

Introduction

The COVID-19 pandemic is having a serious impact on physical and mental health, the social order and economic development worldwide, with the long-term primary solution being population (herd) immunity through vaccination, with a contribution from natural infection particularly in children and young people, for whom vaccines will not be available in the foreseeable future.¹

Governments, public health agencies, scientists and the media concur that a global return to normality will require swift production and administration of safe and effective vaccines to willing and cooperative populations.^{2,3} There are reasons for optimism, not least the speed with which scientific advance is occurring,⁴ including the number and variety of clinical trials of vaccines which are in progress at all of phases I, II and III.⁵ There are more than 200 individual trials registered to date.⁶ Three vaccines, commonly known as the BioNTech–Pfizer, Moderna and AstraZeneca (Oxford) vaccines, have gained emergency approvals based on phase III trials. Other vaccines gained approval before phase III trial information was publicly available (e.g the Indian Bharat Biotech vaccine).⁷ The extremely promising results of phase III trials are

becoming available to health professionals or the public either in academic journals or regulatory agencies' websites.⁸ Phase III trials are extremely complex and outside the scope of this article, but results for the Moderna phase III,⁹ Oxford¹⁰ and Pfizer–BioNTech¹¹ trials have recently been published.

We have synthesised the published results of phase II COVID-19 vaccine trials, including the nature of the vaccines, the design of the trial, exclusions, benefits relating to immunity and adverse events. In this article, we provide an overview in an easily accessible way to inform the public, healthcare workers, scientists and policymakers. In the [Supplementary file](#), we provide simplified versions of the detailed tables in our preprint.¹²

Phase II trials, vaccines and immunological outcomes

The phase II trials were based in the United Kingdom,¹³ Russia,¹⁴ China,^{15–18} the United States^{19,20}, Australia,²¹ Germany²² and Belgium²⁰ and involved 3929 participants, none of whom were younger than 18 years, with very few in the oldest age groups. The trial characteristics and immunological outcomes are summarised in online [Supplementary Table 1](#). [Box 1](#) indicates the nature of the vaccines, and [Box 2](#) provides some details on the participants. All vaccines were given by intramuscular injection. Excepting the two mRNA vaccines from Pfizer, the vaccines underwent standard development methods ([Box 1](#)). The AstraZeneca trial was an

* Corresponding author.

E-mail address: sunil.bhopal@newcastle.ac.uk (S.S. Bhopal).

Box 1

Biological nature of the vaccine candidates.

- 1) Inactivated SARS-CoV-2 vaccines^{15–17}
- 2) Viral vector vaccines^{13,14,18,20} (genetically engineered virus to produce coronavirus proteins to generate an immune response)
- 3) RNA vaccines^{19,22} (genetically engineered RNA used to generate a protein to prompt an immune response)
- 4) Protein-based vaccines²¹ (fragments of protein mimic the COVID-19 virus)

Box 2

Characteristics of the participants in the trials.

The number of participants ranged from 20 to 1077 (Supplementary Table 1), the largest number vaccinated being 634.²⁰

There were 1918 men and 2055 women.

Most trials recruited participants aged between 18 and 60 years (none younger than 18 years).

The mean or median age of participants ranged from 26.4 years¹⁴ to 43.5 years,¹⁵ with few in older ages.

exception in using another vaccine (meningococcal) as a control. All vaccines produced detectable neutralising antibodies, and T-cell responses were found where measured.

There were a multiplicity of reasons for exclusion from trials, which are summarised in online Box 3. Details on each trial are available online.¹²

Adverse effects of the vaccines in ten phase II trials

Side-effects were common but were highly variable across vaccines, with few side-effects reported for the Sinopharm and Sinovac vaccines (online Supplementary Table 2 and online Box 4). Publications rarely reported the duration of side-effects, but they were presumed to be mostly transient.

There were five reported serious adverse events, one of which was deemed to be vaccine related; this participant was hospitalised with fever because of suspicion of COVID-19 infection (Supplementary Table 2). Some serious adverse events have been reported in ongoing phase III trials, as discussed in the following section.

Insights and implications for public health professionals and clinicians delivering or preparing for vaccination programmes

Given the importance of COVID-19 vaccination for exiting pandemic restrictions, public health and clinical professionals across the world need to plan in advance of publication of phase III trials, not least because some vaccines are being implemented on the basis of phase II trials. However, only phase III and IV trials can provide important information on whether vaccination protects recipients from acquiring disease, or reduces the severity of acquired disease (especially death), and whether it prevents or reduces transmission. Definitive information is mainly on efficacy in reducing severity.^{9–11} Phase II trials provide important additional insights. They indicate that an immune response is produced with

all 10 vaccines considered, which provides optimism in relation to the numerous vaccines under development.

Vaccine recipients need to know the range of side-effects and judge that these are commensurate with the benefits in preventing the disease and its adverse effects. The public and patients justifiably have questions about side-effects. Fortunately, high-quality evidence on common, short-term side-effects is available in phase II trials. Side-effects are common with most of the vaccines and mimic COVID-19 symptoms. The variability of side-effects across vaccines, and notably their low prevalence in the Sinopharm and Sinovac vaccines (Supplementary Table 2), needs exploration. Such side-effects are likely to be acceptable to those in the most vulnerable age and comorbidity groups, but possibly less so in previously healthy children and young people, especially as no trial has recruited people younger than 18 years, AND BECAUSE the disease is usually asymptomatic, mild and self-limiting in young people (aged 18–25), although serious morbidity and even death does occasionally occur.^{23–26} The common side-effects mimic COVID-19, with one report of hospitalisation with possible COVID-19 after vaccination (Johnson and Johnson vaccine),²⁰ raising questions about differentiating cases of the disease from vaccine symptoms shortly after vaccination. The implications of transient neutropenia and lymphopenia need monitoring.

Serious adverse effects seem to be rare. Even current phase III studies are not likely to quantify accurately rare serious events, and ongoing large pharmacovigilance studies will be required, particularly because even phase III trials were not conducted with the population that is being vaccinated first (older people and those with comorbidities).²⁷ In light of these facts, doctors in Norway have been advised by the Norwegian Medicines Agency to more thoroughly consider risks and benefits of COVID-19 vaccines for frail, elderly people because of 23 deaths in the frail elderly possibly related to vaccination.²⁸ Investigations to understand this further are ongoing.

In some vaccination strategies, including those for influenza, children are vaccinated to increase herd (population) immunity, offering indirect protection for everyone. Presently, given these vaccines are not being tested in children younger than 18 years, it is unlikely to be recommended in this age group until appropriate child-specific research has been carried out.²⁹ Current plans in the United Kingdom are not to vaccinate the whole population, but to focus on those older than 50 years and those providing health care, social care and front-line services.

There are concerns that a COVID-19 vaccine could cause antibody-dependent enhancement on exposure to challenge or community exposure to the virus.³⁰ Previous trials have indicated that Ad-5 vector vaccines might increase the risk of HIV infection in men in particular,³¹ and this will need close monitoring.

Notwithstanding the finding of about 90% or more effectiveness of the BioNTech-Pfizer¹¹ and Moderna vaccines,⁹ the finding of about 70% effectiveness of the Oxford vaccine¹⁰ and reports of similar results of the Sputnik vaccine (no published results available at the time of writing), governments are emphasising the need to observe control measures, especially through the 2020 winter period.

Our synthesis of phase II trials highlights some of the clinical and communication challenges that need to be surmounted to allow widespread vaccination in 2021. These observations may help inform researchers, public health specialists, policymakers and the public in relation to preparing for the forthcoming vaccination programmes. Finally, vaccine trials are being led from Europe, the United States, Australia and China, so further trials will be needed in other contexts including Africa, given the different age structure and impact of disease.³²

Key messages

Public health professionals and clinicians need information about the nature of the vaccines, exclusions from trials, the common side-effects and the impact on immunity to help inform the public, patients and vaccination strategies and plans.

A multiplicity of vaccines will become available in 2021, but currently, information from phase III trials has only been published for three vaccines and is complex.

Ten phase II publications provide insights into public health and clinical purposes that are complementary to phase III trials, e.g., on the nature of these vaccines, exclusions from trials, their effects on immunity and side-effects. Phase II trials enrolled no one younger than 18 years and very few people older than 80 years, and there were many reasons for exclusion.

Vaccines of several types, some using novel methodologies, produce immune responses, indicating that there will be many other successful vaccines in the near future.

Side-effects were mild or moderate but common, mimicking the symptoms of COVID-19, i.e., muscle ache, fatigue, fever and headache, posing challenges for clinicians in differentiating these adverse effects from COVID-19 illness and managing patients after vaccination.

Our approach to systematically tabulate information should now be applied to all trials. This is a task for an international agency such as the World Health Organization.

Author statements

Ethical approval

None sought.

Funding

No additional or external funding underpinned the production of this manuscript.

Competing interests

All authors have completed the ICMJE uniform disclosure form and declare no support from any organisation for the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years and no other relationships or activities that could appear to have influenced the submitted work.

Contributors and sources

R.B. proposed this synthesis to systematise observations. S.S.B. and B.O. identified and synthesised the data. The sources of information and methods are described in our SSRN preprint,¹². In summary, Medline, MedRxiv and the ClinicalTrials.gov trial register up to November 2, 2020, were searched to identify peer-reviewed publications and preprint articles reporting results from ten phase II COVID-19 vaccination trials (details in preprint). Essentially, the authors used database search techniques for academic papers and preprints to find phase II trials. Using the published preprint, the authors simplified the material for this commentary and updated the text taking into account events up to January 15, 2021.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.puhe.2021.01.011>.

References

- Bhopal RS. COVID-19 zugzwang: potential public health moves towards population (herd) immunity. *Publ Health Pract* 2020;1:100031. <https://doi.org/10.1016/j.puhip.2020.100031>.
- Bingham K. The UK Government's Vaccine Taskforce: strategy for protecting the UK and the world. *Lancet* 2021 Jan 2;397(10268):68–70.
- The_Guardian. When will a coronavirus vaccine be ready?. 2020 [cited 2020 08 Nov]. Available from: <https://www.theguardian.com/world/2020/apr/06/when-will-coronavirus-vaccine-be-ready>. [Accessed 8 November 2020].
- Lurie N, Saville M, Hatchett R, Halton J. Developing Covid-19 vaccines at pandemic speed. *N Engl J Med* 2020;382(21):1969–73.
- Krammer F. SARS-CoV-2 vaccines in development. *Nature* 2020:1–16.
- NIH. *ClinicalTrials.gov*. 2020 [cited 2020 01 Nov]. Available from: <https://www.clinicaltrials.gov/ct2/home>. [Accessed 1 November 2020].
- Biotech B. Bharat biotech's 'COVAXIN™' emergency use authorization approval by DCGI-CDSCO, MoH&FW, a significant landmark in India's scientific discovery, and scientists capability. 2021.
- Martin-Moreno JM, Middleton J, Sheek-Hussein M, Green M. Covid-19 vaccines: where are the data?. 2020 [Available from: https://blogs.bmj.com/bmj/2020/11/27/covid-19-vaccines-where-are-the-data/?=&utm_source=adestra&utm_medium=email&utm_campaign=usage&utm_content=daily&utm_term=text].
- Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med* 2020. <https://doi.org/10.1056/NEJMoa2035389> [published Online First: 2020/12/31].
- Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, 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. *Lancet* 2021;397(10269):99–111. [https://doi.org/10.1016/S0140-6736\(20\)32661-1](https://doi.org/10.1016/S0140-6736(20)32661-1).
- Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine. *N Engl J Med* 2020;383(27):2603–15. <https://doi.org/10.1056/NEJMoa2034577>.
- Bhopal S, Olabi B, Bhopal R. Nature Of, Immune Reaction to and Side Effects of Ten COVID-19 Vaccines: Synthesis of Information Including Exclusions from Ten Phase II Trials for Planning Vaccination Programmes (November 18, 2020). Available at SSRN: <http://doi.org/10.2139/ssrn.3732847>.
- Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, Bellij-Rammerstorfer S, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. *Lancet* 2020;396(10249):467–78.
- Logunov DY, Dolzhikova IV, Zubkova OV, Tukhvatullin AI, Shcheblyakov DV, Dzharullaeva AS, et al. Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia. *Lancet* 2020;396(10255):887–97.
- Xia S, Duan K, Zhang Y, Zhao D, Zhang H, Xie Z, et al. Effect of an inactivated vaccine against SARS-CoV-2 on safety and immunogenicity outcomes: interim analysis of 2 randomized clinical trials. *Jama* 2020;324(10):951–60.
- Zhang Y-J, Zeng G, Pan H-X, Li CG, Kan B, Hu YL, et al. Immunogenicity and safety of a SARS-CoV-2 inactivated vaccine in healthy adults aged 18–59 years: report of the randomized, double-blind, and placebo-controlled phase 2 clinical trial. *MedRxiv* 2020 Jan 1.
- Xia S, Zhang Y, Wang Y, Wang H, Yang Y, Gao GF, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial. *Lancet Infect Dis* 2021 Jan 1;21(1):39–51.
- Zhu F-C, Guan X-H, Li Y-H, Huang JY, Jiang T, Hou LH, et al. Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet* 2020;396(10249):479–88. [https://doi.org/10.1016/S0140-6736\(20\)31605-6](https://doi.org/10.1016/S0140-6736(20)31605-6).
- Mulligan MJ, Lyke KE, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults. *Nature* 2020:1–5.
- Sadoff J, Le Gars M, Shukarev G, Heerwegh D, Truyers C, de Groot AM, et al. Safety and immunogenicity of the Ad26. COV2. S COVID-19 vaccine candidate: interim results of a phase 1/2a, double-blind, randomized, placebo-controlled trial. *MedRxiv* 2020 Sep 25. <https://doi.org/10.1101/2020.09.23.20199604>.
- Keech C, Albert G, Cho I, Robertson A, Reed P, Neal S, et al. Phase 1–2 trial of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine. *N Engl J Med* 2020 Dec 10;383(24):2320–32.
- Sahin U, Muik A, Derhovanessian E, Vogler I, Kranz LM, Vormehr M, et al. COVID-19 vaccine BNT162b1 elicits human antibody and TH1 T-cell responses. *Nature* 2020:1–9.
- Bhopal S, Bagaria J, Bhopal R. Children's mortality from COVID-19 compared with all-deaths and other relevant causes of death: epidemiological information for decision-making by parents, teachers, clinicians and policymakers. *Publ Health* 2020 Aug;185:19.

24. Bhopal S, Bagaria J, Olabi B, Bhopal R. Children and young people remain at low risk from COVID-19 mortality: updated time trends from USA, United Kingdom, Italy, Germany, Spain, France and South Korea. *OSF Preprints* 13 January 2021. Available: <https://doi.org/10.31219/osf.io/ezdf2>.
25. Bhopal SS, Bagaria J, Olabi B, Bhopal R. COVID-19 deaths in children: comparison with all-and other causes and trends in incidence of mortality. *Publ Health* 2020 Nov;**188**:32–4. <https://doi.org/10.1016/j.puhe.2020.08.022>.
26. Olabi B, Bagaria J, Bhopal S, Bhopal R. *Population perspective comparing COVID-19 to all and common causes of death in seven European countries*. 2020.
27. Hodgson SH, Mansatta K, Mallett G, Harris V, Emary KR, Pollard AJ. What defines an efficacious COVID-19 vaccine? A review of the challenges assessing the clinical efficacy of vaccines against SARS-CoV-2. *Lancet Infect Dis* February 2021;**21**(2):e26–35.
28. Torjesen I. Covid-19: Norway investigates 23 deaths in frail elderly patients after vaccination. *BMJ* 2021;**372**:n149. <https://doi.org/10.1136/bmj.n149>.
29. Velavan TP, Pollard AJ, Kreamsner PG. Herd immunity and vaccination of children for COVID-19. *Int J Infect Dis* 2020;**98**:14–5.
30. Cardozo T, Veazey R. Informed consent disclosure to vaccine trial subjects of risk of COVID-19 vaccines worsening clinical disease. *Int J Clin Pract* 2020: e13795.
31. Buchbinder SP, McElrath MJ, Dieffenbach C, Corey L. Use of adenovirus type-5 vectored vaccines: a cautionary tale. *Lancet* Oct 31 2020;**396**(10260):e68–9.
32. Church J, Bhopal R. *COVID-19 global mortality: comparing actual and modelled patterns in space and time using an infection fatality rate (IFR) model*. Preprint: SSRN; 2020.