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

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PUBLIC HEALTH: SUBMISSION AS A COMMENTARY

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

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Summary

Public health professionals and clinicians are immersed in the ongoing and, in many countries, coming 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 papers, 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.

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 the 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] and the number and variety of trials in progress, with currently numerous vaccines being tested in phase I/II and a few phase III clinical trials.[5] There are over 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 have gained approval prior to phase III trials being published, with information not publicly available (e.g. The Indian Bharat Biontec 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 paper, but results for the Moderna phase III,[9] Oxford[10] and Pfizer-BioNTech[11] 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 paper 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].

The phase II trials, vaccines and immunological outcomes

The phase II trials were based in the United Kingdom[13], Russia[14], China[15-18], United States[19 20], Australia[21], Germany[22] and Belgium[20] and involved 3,929 participants, none of whom were under the age of 18, 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 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 exception in using another vaccine (meningococcal) as a control. All vaccines produced detectable neutralising antibodies, and T-cell responses were found where measured.

Box 1: The 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 vaccines[21] (fragments of protein mimic the COVID-19 virus)

Box 2: The characteristics of the participants in the trials

Participant numbers ranged from 20 to 1,077 (Supplementary Table 1), the largest number vaccinated being 634[20]

There were 1,918 men and 2,055 women

Most trials recruited between participants aged between 18-60 years (none under 18 years)

The mean or median age of participants ranged from 26.4 years[14] to 43.5 years[15], with few

in older ages

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].

Online Box 3: Reasons for exclusion from one or more of the phase II trials	
Vaccination	Recent or planned Coronavirus or other vaccination
Immune system	Recent immunoglobulin use
	Immune suppressed or deficient
	Autoimmune condition
	Allergy, angioedema or anaphylaxis
Pregnancy/breastfeeding	Pregnant or lactating women
Co-morbidity	Cancer
	Chronic respiratory diseases, including mild asthma
	Chronic disease including cardiovascular disease, hypertension, gastrointestinal disease, liver disease, renal disease, endocrine disorder (including diabetes) and neurological illness (excluding migraine)
	Congenital, developmental disorder
	Other serious chronic illness or Doctor/Investigator judged contraindication
Other comorbidity	Abnormal laboratory finding
	Psychiatric disorder
	Bleeding disorder
	Recent transfusion
	Low or high blood pressure / heart rate
COVID-19	Known previous COVID-19 disease (PCR or antibodies)
	Current COVID-19 PCR positive
	Symptoms of COVID-19 since Feb 2020
	High risk of exposure to COVID-19 including healthcare workers, contact with Wuhan
Social, lifestyle and other factors	Smoking
	Over- or under-weight
	Alcohol use in excess
	Drug / narcotic use suspected or known

	Lives with vulnerable person

Adverse effects of the vaccines in ten phase II trials

Side effects were common but 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.

Online Box 4: Adverse effects

The common symptoms in most vaccines included fatigue, muscle ache and fever and were more common in COVID-19 vaccine participants than controls, for example, as follows:

In the largest, AstraZeneca, study[13],

70% of participants reported post-vaccination fatigue (48% in meningococcal vaccine controls)

68% had headache (38% in controls)

60% had muscle ache (25% in controls)

18% had fever (<1% in controls)

Laboratory abnormalities were reported as mostly mild.

Transient neutropenia was reported in 46% of a subgroup of 54 participants in the AstraZeneca trial[13]

Transient lymphopenia was also reported in two further trials

100% had laboratory adverse events (mostly changes in a variety of white cells) in the Gamaleya (Logunov et al.) trial[14]

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 below.

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

Given the importance of a 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 to prepare. 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), need 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 under 18 years, and in younger people (18-25 years), in whom the disease is usually asymptomatic, mild and self-limiting 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 following 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 who are being vaccinated first (older people, and those with co-morbidities).[27] In this light, 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 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 under 18 years of age, it is unlikely to be recommended in this age group until appropriate child-specific research has been done[29]. Current plans in the United Kingdom are not to vaccinate the whole population, but to focus on those over 50-years of age and those providing healthcare, social care and frontline 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-Pfizer[11] and Moderna vaccines[9], and 70% in the Oxford vaccine[10], and reports of similar results in the Sputnik vaccine (no published results available at 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 will need to be surmounted to allow widespread vaccination in 2021. These observations 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 for 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 under 18 years and very few people over 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 post-vaccination.

Our approach to systematically tabulating information should now be applied to all trials. This is a task for an international agency like WHO.

Company (Trial registration number) Country	Study design	Vaccine	Control	Dose range (route)	Number of participants (intervention group)	Sex (M:F)	Age (years)		Neutralising antibody response (n +/- % participants)		T cell response
							Range of recruitment eligibility	Age of recruited participants	After prime	After boost	
AstraZeneca (Oxford)[13] (NCT04324606) United Kingdom	Single-blind RCT	ChAdOx1 nCoV-19 (AZD1222) (non-replicating chimpanzee AdV expressing spike protein)	Meningococcal conjugate vaccine (MenACWY)	5 x 10^{10} viral particles (1x or 2x IM)	1,077 (543)	541:536	18-55	Median 35, IQR 28-44	32 of 35 (91%)	35 of 35 (100%)	Yes
Gamaleva Research Institute[14] (NCT04436471, NCT04437875) Russia	Open label, non-randomised single-arm trial	Sputnik-V (rAd26-S/rAd5-S (frozen))	None	1x 10^{11} viral particles (2x IM)	20	14:6	18-60	Mean 26.4, SD 4.4	61.1%	100%	Yes: 100%
		Sputnik-V (rAd26-S/rAd5-S (lyophilised))			20	14:6	18-60	Mean 26.7, SD 5.8		100%	Yes: 100%
Sinopharm[15] (ChiCTR2000031809) China	Double-blind RCT	Inactivated whole-virus covid-19	Aluminium hydroxide injection	5µg (2x IM)	224 (168)	82:142	18-59	Mean 43.5, SD 9.1	-	41 of 42 (97.6%)	ND
Sinovac[16] (NCT04352608) China	Double-blind RCT	CoronaVac (inactivated SARS-CoV-2 + aluminium hydroxide)	Aluminium hydroxide injection	3µg or 6µg (2x IM)	600 (480)	283:317	18-59	Mean per group 40.6-44.3 (SD 7.6-10.2)	-	100% in 6µg 0,28-day group	ND
CanSino[18] (NCT04341389) China	Double-blind RCT	Ad5-vectored covid-19 vaccine	Vaccine excipients only	1 × 10^{11} or 5 × 10^{1}□ viral particles	508 (382)	254:254	18+	Mean 39.7, SD 12.5	148 of 253 (59%)	-	Yes: 90%
BioNTech-Pfizer (Mulligan)[19] (NCT04368728) United States	Placebo-controlled, randomised, observer-blind dose escalation study	BNT162b1 mRNA vaccine	0.9% saline injection	10 µg, 30 µg, or 100 µg (1 or 2x IM)	45 (36)	46:44	18-55	Mean 35.4 (range 19-54)	-	Yes	ND
Novavax[21] (NCT04368988) Australia	Double-blind RCT	NVX-CoV2373 (recombinant nanoparticle vaccine)	0.9% saline injection	5µg or 25µg (+/- adjuvant) (1x or 2x IM)	131 (108)	66:65	18-59	30.8±10.2	-	Yes	Yes in all 16 randomly selected – strong Th1 bias

Johnson & Johnson[20] (NCT04436276) United States / Belgium	Double-blind RCT	Ad26.COV2.S (non-replicating vector-based vaccine)	0.9% saline injection	$5x10^{10}$ or $1x10^{11}$ viral particles (1x or 2x IM)	796 (634) (394 in ≥65-year cohort)	385:410 *	18-55	Median 34 (range 18-55)	-	98% (97 of 99) in 18-55 years cohort; 100% (6 of 6) in ≥65-year cohort	Yes: Th1 skewed
							≥65	Median 69 (range 65-88)			
BioNTech-Pfizer (Sahin)[22] (NCT04380701) Germany	Non-randomised, observe-blind, dose escalation study	BNT162b1 mRNA vaccine	N/A	1µg, 10µg, 30µg, 50µg or 60µg (1 or 2x IM)	60 (60)	30:30	18-55	Mean 37.5 (SD 10.9)	-	Modest increase in dose-dependent manner	Yes, almost all participants – Th1 polarisation
Sinopharm[17] (ChiCTR2000032459) China	Double-blind RCT	BBIBP-CorV (inactivated SARS-CoV-2)	Saline + aluminium hydroxide adjuvant	4µg or 8µg (1 or 2x IM)	448 (336)	203:245	18-59	Mean 41.7 (SD 9.9)	-	Yes in 100%	ND

*Supplementary table 1: Summary of phase II covid-19 vaccine trial results. Abbreviations: M = male, F = female, RCT = randomised controlled trial, IM = intramuscular, IQR = interquartile range, SD = standard deviation, ND = not determined, N/A = not applicable. *1 participant undifferentiated*

Trial	Fatigue / asthenia		Headache		Localised Pain		Muscle aches / joint pain		Fever / hyperthermia		Feeling feverish / chills		Laboratory AEs		Grade 3 (severe) AEs		Grade 4 AE	Unsolicited serious AEs	
	Vaccine	Control	Vaccine	Control	Vaccine	Control	Vaccine	Control	Vaccine	Control	Vaccine	Control	Vaccine	Control	Vaccine	Control		Vaccine	Control
AstraZeneca[13]	340 (70%)	227 (48%)	331 (68%)	195 (41%)	328 (67%)	180 (38%)	294 (60%)	118 (25%)	87 (18%)	2 (<1%)	250 (51%)	38 (8%)	In subgroup of 54: 25 (46%) had neutropenia	In subgroup of 44: 3 (7%) had neutropenia	Pain 4 (1%); Redness 1 (0%); Swelling 1 (0%); Induration 1 (0%); Tenderness 4 (1%); Feverish 40 (8%); Fever>38 8 (2%); Chills 39 (8%); Joint pain 6 (1%); Muscle-ache 19 (4%); Fatigue 30 (6%); Headache 27 (6%); Malaise 36 (7%); Nausea 10 (2%)	Pain 1 (0%); Tenderness 1 (0%); Joint pain 1 (0%); Fatigue 1 (0%); Headache 3 (1%); Malaise 1 (0%);	None	None	1 - new haemolytic anaemia nine days after vaccination
Gamaleya Research Institute[14] (Frozen / lyophilised)	11 (55%)	n/a	9 (45%)	n/a	8 (40%)	n/a	4 (20%)	n/a	19 (95%)	n/a	NR	n/a	20 (100%)	n/a	None	-	None	None	n/a
	4 (20%)		5 (25%)		12 (60%)		4 (20%)		6 (30%)		NR		18 (90%)	n/a	None	-	None	None	n/a
Sinopharm[15]	0 (0%)	0 (0%)	0 (0%)	1 (3.6%)	12 (14.3%)	4 (14.3%)	NR	NR	2 (2.4%)	1 (3.6%)	NR	NR	NR	NR	1 (1.2%) - Fever 39°C day 11 post 2nd injection	-	None	None	None
Sinovac[16]	3 (2.5%)	2 (3.3%)	1 (0.8%)	0 (0.0%)	13 (10.8%)	6 (10.0%)	4 (3.3%)	3 (5.0%)	4 (3.3%)	1 (1.7%)	NR	NR	NR	NR	None	-	None	3; no details provided. Not deemed to be vaccine related	NR
CanSino[18]	106 (42%)	21 (17%)	73 (29%)	17 (13%)	145 (57%)	11 (9%)	39 (15%)	3 (2%)	82 (32%)	12 (10%)	NR	NR	NR	NR	Induration 2 (1%); Swelling 1 (<1%); Fever 20 (8%); Headache 2 (1%); Fatigue 1 (<1%); Muscle-pain 1 (<1%); Joint-pain 1 (<1%); Dyspnoea 1 (<1%)	None	None	None	None
BioNTech-Pfizer (Mulligan)[19]	10 (83.3%)	1 (16.7%)	12 (100%)	0 (0.0%)	12 (100%)	2 (33.3%)	7 (58.3%)	0 (0.0%)	9 (75%)	0 (0.0%)	8 (66.7%)	0 (0.0%)	5 of 11 had lymphopenia (1 grade 3), 1 grade-2 neutropenia,	NR	Pyrexia two days after vaccination 1; Chills 1	None	None	None	None
Novavax[21]	12 (46.2%)	3 (14.30%)	12 (46.2%)	6 (28.60 %)	15(57.7 %)	2 (9.5%)	12 (46.2%)	3 (14.3%)	0 (0.0%)	0 (0.0%)	NR	NR	13 participants (10%) had grade 2 or higher changes: reduced haemoglobin or raised liver enzymes	1 had elevated liver enzymes	Muscle pain 1 (3.8%); Fatigue 1 (3.8%);– Joint pain/arthralgia 1 (3.8%)	Fatigue 1 (4.8%)	None	None	None
Johnson & Johnson[20]	NR	NR	NR	NR	NR	NR	NR	NR	76 (19%)	NR	NR	NR	-	-	Fever 22 (5%) in all cohorts 18-55 year cohort: 41 (10.9%); 8 unsolicited WBC rise, malaise, back pain x2,	-	None	One participants, hospitalized overnight with fever and suspicion of Covid-19, recovered 12 hrs later	None

													hypotensive crisis, insomnia, fever, lightheadedness) ≥65-year cohort: 4 unsolicited (dizziness, vomiting, hypertension x2)					
BioNTech-Pfizer (Sahin)[22]	9 (75%)	N/A	8 (66%)	N/A	10 (83%)	N/A	6 (50%)	N/A	6 (50%)	N/A	8 (66%)	N/A	Transient lymphopenia and raised CRP	N/A	Pain 2 (16.7%); Fatigue 3 (25.0%); Chills 4 (33.3%); Headache 4 (33.3%); Fever 2 (16.7%)	N/A	None	None	N/A
Sinopharm[17]	1 (1.1%)	3 (11.0%)	1 (1.1%)	2 (7%)	10 (12%)	1 (4%)	0 (0%)	0 (0%)	3 (4%)	1 (4%)	NR	NR	ND	ND	None	Fever 1 (4%)	None	None	None

Supplementary table 2: Adverse effects reported in ten phase II covid-19 vaccine trials. Abbreviations: AE = adverse event, N/A = not applicable, NR = not reported

Note: Adverse effects reported here reflect the dose/regimen giving highest neutralising titre (Astrazeneca: participants without paracetamol; Sinopharm: 0 & 21 day; Sinovac: 3 micrograms, 0 & 28 days; Cansino: $1x10^{11}$ cohort; BioNTech-Pfizer (Mulligan): 30 microgram dose; Novavax: Group C; Sahin: 50microgram dose – day with most effects following boost reported; Sinopharm 4microgram day 0 & 21

STATEMENTS

Conflict of Interest

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, no other relationships or activities that could appear to have influenced the submitted work.

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RB proposed this synthesis to systematise observations. SB and BO identified and synthesised the data. The sources of information and methods are described in our SSRN preprint[12] and briefly were searching Medline, MedRxiv and the ClinicalTrials.gov trial register up to 2 November 2020 to identify peer-reviewed publications and pre-print articles reporting results from ten phase II COVID19 vaccination trials (details in preprint). Essentially, we used database search techniques for academic papers and preprints to find phase II trials. Using the published preprint we simplified the material for this commentary and updated the text taking into account events up to 15 January 2021.

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Highlights

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 for 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 under 18 years and very few people over 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 post-vaccination.

Our approach to systematically tabulating information should now be applied to all trials. This is a task for an international agency like WHO.