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Review

Licenced doses of approved COVID-19 vaccines may not be optimal: A review of the early-phase, dose-finding trials

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ABSTRACT

Although over 13 billion COVID-19 vaccine doses have been administered globally, the issue of whether the optimal doses are being used has received little attention. To address this question we reviewed the reports of early-phase dose-finding trials of the nine COVID-19 vaccines approved by World Health Organization, extracting information on study design and findings on reactogenicity and early humoral immune response. The number of different doses evaluated for each vaccine varied widely (range 1–7), as did the number of subjects studied per dose (range 15–190). As expected, the frequency and severity of adverse reactions generally increased at higher doses, although most were clinically tolerable. Higher doses also tended to elicit better immune responses, but differences between the highest dose and the second-highest dose evaluated were small, typically less than 1.6-fold for both binding antibody concentration and neutralising antibody titre. All of the trials had at least one important design limitation – few doses evaluated, large gaps between adjacent doses, or an inadequate sample size – although this is not a criticism of the study investigators, who were working under intense time pressures at the start of the epidemic. It is therefore open to question whether the single dose taken into clinical efficacy trials, and subsequently authorised by regulatory agencies, was optimal. In particular, our analysis indicates that the recommended doses for some vaccines appear to be unnecessarily high. Although reduced dosing for booster injections is an active area of research, the priming dose also merits study. We conclude by suggesting improvements in the design of future vaccine trials, for both next-generation COVID-19 vaccines and for vaccines against other pathogens.

Contents

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1. Introduction

By May 2023, 13.4 billion COVID-19 vaccine doses had been administered globally, with 70 % of the world population having received at least one dose [1]. However, their distribution has been inequitable, with only 30 % of people living in low-income countries having been vaccinated [1,2]. There is considerable interest in exploring the use of reduced vaccine doses ("fractional dosing") to stretch the global COVID-19 vaccine supply, lower the cost, and reduce the incidence of adverse reactions [3,4]. Given that most persons in high-income countries have received the primary vaccine series, the interest in reduced doses has focussed on booster injections [5].

To date, regulatory authorisation has been granted on the basis of the results of large, phase-3 clinical efficacy trials using a COVID-19 endpoint. All of these trials have evaluated a single vaccine dose (compared with placebo) with this dose being informed by preceding early-phase dose-finding studies. Here we examine the design, results, and interpretation of the early-phase trials relating to the approved COVID-19 vaccines. An important caveat of our critique is that the investigators of these trials were working under severe time pressures at the start of the epidemic. From this we draw conclusions which could lead to improvements in the design of future trials of candidate COVID-19 vaccines and other vaccines more generally.

2. Materials and methods

We reviewed the publications describing the early-phase dose-finding trials of all of the COVID-19 vaccines granted emergency use listing (EUL) by the World Health Organization by May 2023 [6]. Eleven vaccines have been approved, although two are different formulations of the same vaccine. The vaccines are listed in Table 1: two mRNA vaccines (BNT162b2, mRNA-1273), three viral vector vaccines (ChAdOx1, Ad26.COV2.S, Convidecia), one recombinant protein vaccine (NVX-CoV2373), and three whole virus inactivated vaccines (CoronaVac, BBIBP-CorV, BBV152) [7–15]. We acknowledge this is not a comprehensive, systematic review of all early-phase trials; however, this would have meant scrutinising studies of over one hundred COVID-19 vaccines and precluding the in-depth analysis we aimed to achieve [6].

The inconsistent way in which safety data from the trials were recorded and/or reported precluded a systematic quantitative analysis. Instead, we have noted the frequency of serious adverse events or severe reactions, as well as paraphrasing the original authors' interpretation of whether an association between vaccine dose and reactogenicity was observed. As severe reactions were infrequent, this interpretation is based on the frequency of mild/moderate short-term reactions (local and systemic) to the vaccine. Statistical significance tests were generally not employed to test dose–response associations and interpretation is therefore

Table 1
Key design features of the trials.

Vaccine	Developer	Vaccine type	Reference	Dosing schedule (weeks)	Placebo group	Age range (years)	Doses evaluated[a]	No. subjects allocated per dose[b]
BNT162b2	BioNTech/Pfizer	mRNA	7	0/3	Yes	18–55, 65–85	10, 20, **30**, 100	12 per age group
mRNA-1273	Moderna	mRNA	8	0/4	No	18–55	25, **100**, 250	15
ChAdOx	Oxford/ AstraZeneca	Viral vector	9	0 or 0/4[c]	Yes	18–55	5×10^5	543
Ad26.COV2.S	Johnson & Johnson	Viral vector	10	0 or 0/8	Yes	18–55, 65+	5×10^{10}, 1×10^{11}	158–162 per age group
Convidecia	CanSino Biologics	Viral vector	11	0	Yes	18–83	5×10^{10}, 1×10^{11}	129–253
NVX-CoV2373	Novavax	Recombinant protein	12	0 or 0/3	Yes	18–59	**5**, 25	25–29
CoronaVac	Sinovac Life Sciences	Inactivated	13	0/2 or 0/4	Yes	18–59	**3**, 6	144
BBIBP-CorV	Sinopharm - Beijing	Inactivated	14	0/4	Yes	18–59, 60+	2, **4**, 8	32 per age group
BBV152	Bharat Biotech International	Inactivated	15	0/4	No	12–65	3, **6**	190

a. Units are number of viral particles for viral vector vaccines; μg for all other vaccines. Dose assessed in efficacy trial shown in bold.
b. Number with endpoint data may be lower.
Notes.
ChAdOx nCoV-19: 10 participants only received booster vaccination; placebo group received a meningococcal conjugate vaccine; dose (5×10^5 viral particles) selected based on results of previous study of ChAdOx1 MERS vaccine. [PMCID: PMC7172901].
Ad26.COV2.S: factorial design with randomisation to low or high dose and one or two doses.
Convidecia: 2:1 allocation ratio (high:low).
NVX-CoV2373: Four active groups: 5/5 μg with adjuvant, 25/25 μg with adjuvant, 25/25 μg without adjuvant, single dose 25 μg without adjuvant.
CoronaVac: Studied two different formulations. Our review focuses on CoronaVac "phase 2" formulation with the 0/4 week vaccination schedule. A smaller separate study in adults 60 + was also conducted [PMCID: PMC7906628].
BBIBP-CorV: Paper also reported a separate evaluation of different dose schedules.
BBV152: Placebo was studied in a smaller preceding trial [PMCID: PMC8584828].

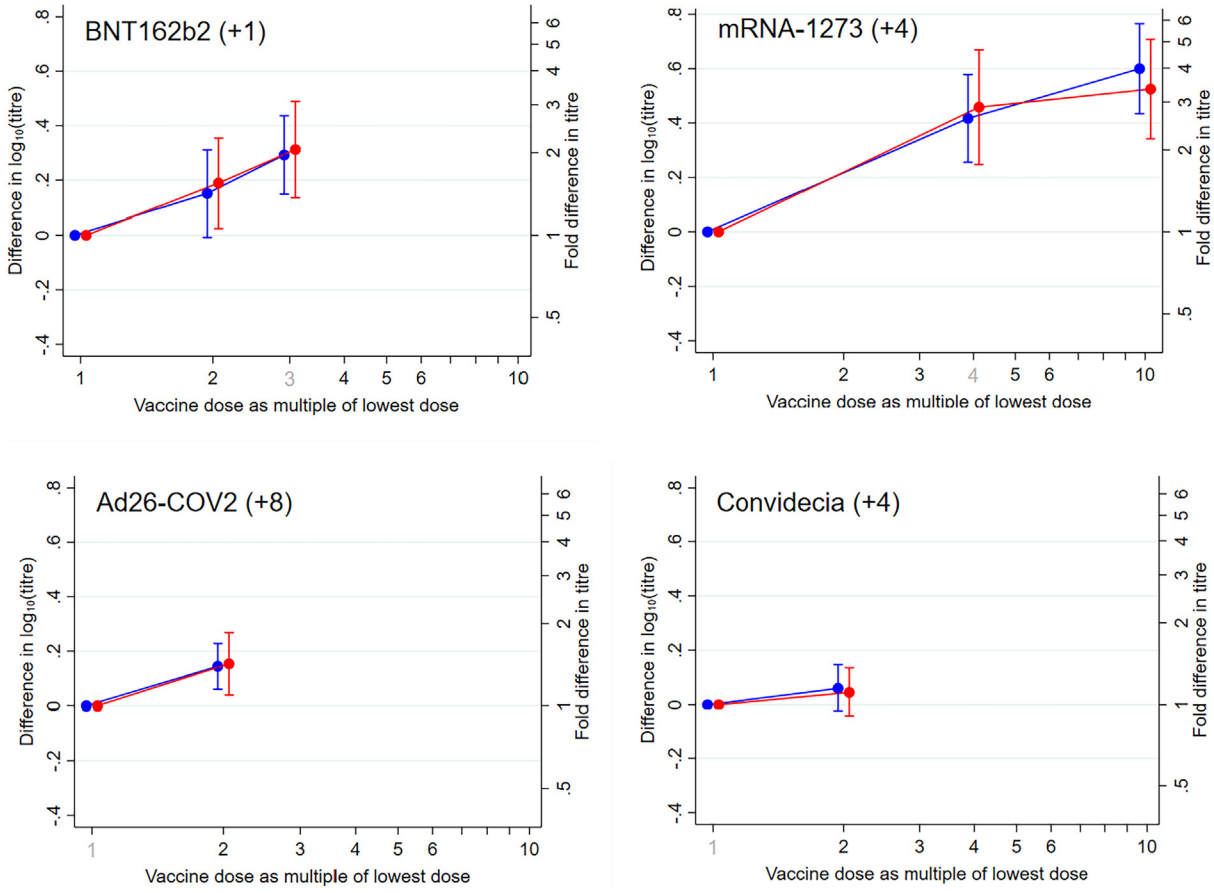

Fig. 1. Binding antibody and neutralising antibody response for individual vaccines, relative to the lowest dose. Footnote. Binding antibodies, blue line; neutralising antibodies, red line. Bars show 90 % confidence intervals. Where the confidence interval does not include zero, the difference between that dose and the lowest dose is statistically significant at 1-sided P < 0.05. Dose evaluated in phase-3 efficacy trial shown in grey. Value in brackets denotes number of weeks after final injection when immunology was assessed.

subjective. We have not presented any comparisons between active vaccine groups and placebo groups (see below). Other investigators have presented a more detailed overview of the safety profile of COVID-19 vaccines [16].

For immune response outcomes, the main focus of this article, we extracted data at the primary analysis timepoint, generally 2–4 weeks after the final injection. As different doses were evaluated for different vaccines, the average immune response *relative to the lowest dose* was calculated, to facilitate a comparison across vaccines. This was performed for both binding and neutralising antibodies on a $\log_{10}$ scale (effectively comparing geometric mean titres). 90 % confidence intervals, based on standard error estimates extracted from the individual papers, were also calculated and presented. Some studies measured binding and neutralising antibodies by two or more assays; the assay selected for presentation is specified in the footnote to Table 4. For studies that used age stratification, data were averaged (weighted average according to sample size) across the different strata.

3. Main design features

Table 1 shows the key design features of the reviewed trials. Most assessed a prime-boost strategy, although the Ad26.COV2.S trial employed a factorial design to evaluate the effects of both dose and a single versus two dose regimen. All trials, apart from mRNA-1273 and BBV152, included a placebo group. A recent systematic review found a high rate of reported adverse events in the placebo groups of COVID-19 vaccine trials, suggesting its importance as a baseline, comparator group [17]. Conversely, some vaccine reactogenicity is expected and the key issue is arguably whether the degree of reactogenicity is clinically tolerable. A placebo group is also of limited value in the immunogenicity analyses, apart from providing laboratory quality control data and information on the incidence of natural infection in the trial cohort.

Traditionally, to minimise potential harms to participants, early-phase trials are conducted in young, healthy volunteers. Accordingly, most trials had an upper age limit of between 55 and 59 years. However, this carries the significant disadvantage that no data (safety or immunogenicity) are generated on the elderly population, one of the first vulnerable groups to receive the vaccine when roll-out commences [18]. Thus several trials (BNT162b2, Ad26.COV2.S, BBIBP-CorV) used a stratified design to recruit a pre-determined number of both young and elderly participants. All first-in-human trials should now incorporate a dose escalation cohort, and this would usually be limited to younger adults [19].

The number of different doses evaluated varied widely between the trials. ChAdOx1 assessed a single dose only, partly because standardisation of dose is particularly challenging for viral vector vaccines [20]. Of interest, 24 % of subjects in the subsequent efficacy trial inadvertently received a first dose of vaccine that was approximately half that of the planned dose, and an interim analysis reported unexpectedly higher efficacy among these subjects than those who received two standard doses [21]. However, subsequent analyses found that this effect may have been due to a confounding effect of dosing interval rather than dose per se [22].

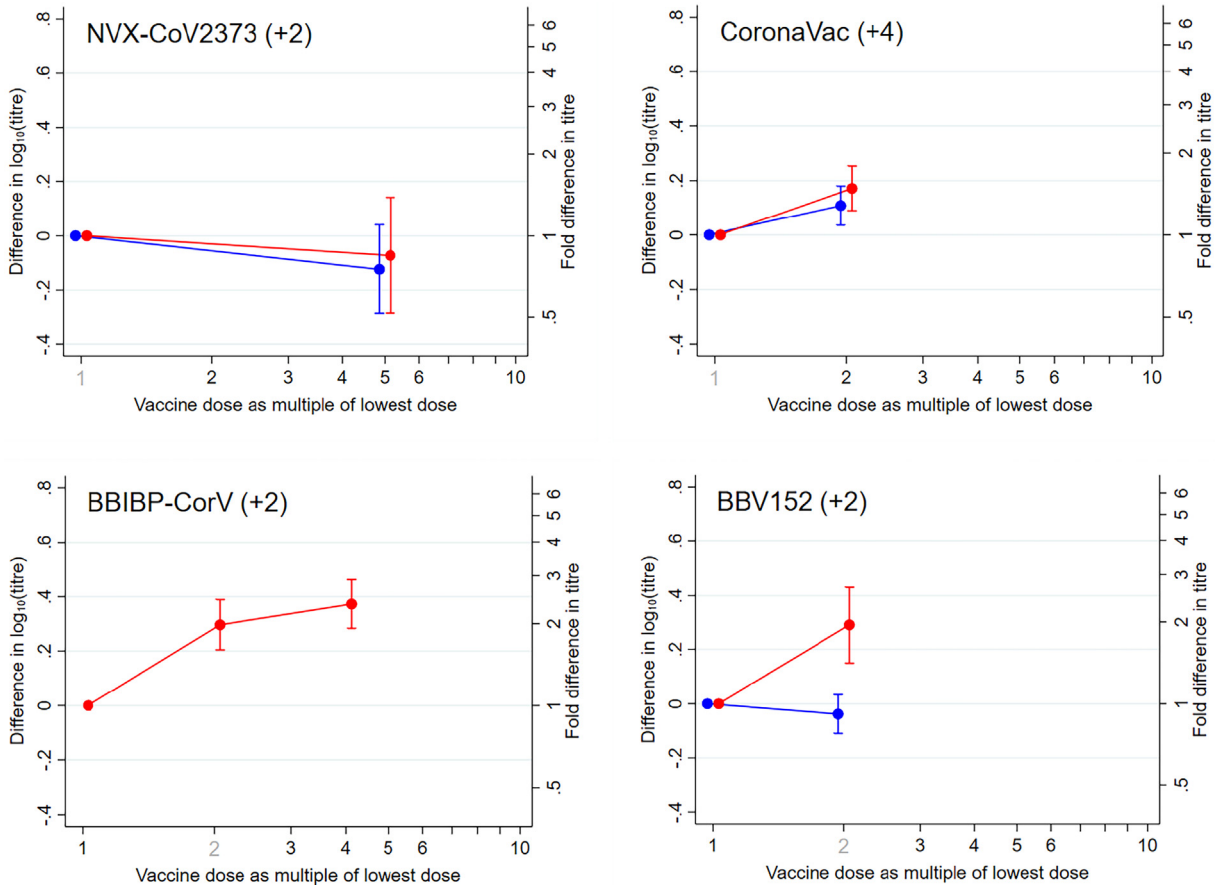

Fig. 1 (*continued*)

The trials of inactivated vaccines examined either two or three doses across a relatively narrow dosage range, with a 2-fold difference between adjacent doses. Developers of the more novel mRNA vaccines (BNT162b2, mRNA-1273) assessed a wider dosage range (10-fold) with large gaps between adjacent doses. The number of subjects also varied widely, ranging from 15 per dose (mRNA-1273) and 24 per dose (BNT162b2) to 190 subjects per dose (BBV152). The justification for the chosen sample size was usually vague, such as characterising immune response and/or safety, limited available vaccine, or following national guidelines. Only one trial (BBV152) used a formal statistical power calculation.

All studies reported local and systemic reactions after each vaccination (usually solicited for 7 days), as well as longer-term unsolicited adverse events, but the reporting of data was not standardised across studies. One study recorded whether the second vaccination had been withheld or delayed due to reactogenicity following the first vaccination, arguably the most clinically relevant outcome [12]. Serious adverse reactions, such as blood clots and myocarditis, are too rare to be reliably detected in small, early-phase trials.

The timing and details of the immunology assessments are shown in Table 2. Although methodologies were highly variable, our analyses of immune response are made within trials rather than between trials. Most trials quantified the level of binding antibodies against the spike protein, which all the vaccines aimed to induce. Neutralising antibodies only were measured in the trial of BBIBP-CorV, whereas CoronaVac and Convidecia quantified anti-RBD antibodies. All studies measured neutralising antibodies assessed against Wuhan strains of live or pseudo-virus (or both), although only a subset of participants were tested in the Ad26.COV2.S trial. Different levels of neutralisation were estimated, ranging from 50 % to 99 % (but frequently not specified). Few primary publications reported the results of T-cell assays, either because none had been performed or experiments had not been completed at the point of submission of the paper.

4. Trial findings

4.1. Safety

Notable safety findings and the authors' interpretation of whether a reactogenicity-dose association was observed are summarised in Table 3. Severe adverse reactions were not observed in any of the trials, and no dose was found to result in clinically unacceptable reactogenicity, except for the 100-μg dose of BNT162b2; this dose was abandoned after the first injection due to a high incidence of fever and one case of severe pain [23]. For the inactivated vaccines, reactogenicity was not observed to depend on dose, although only narrow dose ranges were studied. For the mRNA vaccines, the lowest dose elicited less reactogenicity but with no clear trend at higher doses. The higher dose of NVX-CoV2373, a recombinant protein vaccine, resulted in more systemic, but not local, side effects.

4.2. Immune response

Following the final injection, all of the vaccines achieved seroconversion rates (for both binding and neutralising antibodies) equal or close to 100 %. Humoral immune responses by dose are

Table 2
Key safety findings.

Vaccine	Reactogenicity-dose association	Notable clinical observations
BNT162b2	Participants in 100 μg group received one dose only due to unacceptable reactogenicity. Less reactogenicity with 10 μg than 20 μg or 30 μg. No clear difference between 20 μg and 30 μg.	100 μg dose abandoned due to high incidence of fever and one case of severe pain. No systemic events above grade 3 reported.
mRNA-1273	Less reactogenicity with 25 μg. No clear difference between 100 μg and 250 μg.	No SAEs reported. One participant withdrawn due to AE (transient urticaria,25 μg group), judged to be related to the first vaccination.
ChAdOx	Not applicable	No SAEs reported
Ad26.COV2.S	More reactogenicity at higher dose.	No discontinuations due to AEs reported
Convidecia	Higher rate of grade 3 solicited adverse reactions at higher dose.	No SAEs within 28 days reported
NVX-CoV2373	No difference in local reactogenicity by dose. More systemic reactogenicity with higher dose.	No SAEs or AEs of special interest reported. One participant did not receive a second vaccination due to an AE (cellulitis, 25 μg group). No second vaccinations withheld due to reactogenicity
CoronaVac	No association	No SARs within 28 days reported. One participant with acute hypersensitivity after first vaccination (6 μg group)
BBIBP-CorV	No association	No ARs above grade 2 (within 7 days) reported
BBV152	No association	One SAE (viral pneumonitis) reported (6 μg group), unrelated to vaccine.

AE, adverse event; SAE, serious adverse event; AR, adverse reaction (i.e. AE deemed related to vaccine).

Table 3
Details of the immunology assays.

Vaccine	Time of immunology assessments (weeks)*	Binding antibodies	Neutralisation antibodies	T cell assays
BNT162b2	0, 1, 3, 4, 5	Anti-S1 and anti-RBD IgG (Luminex immunoassay)	Pseudo virus. NT_{50}, NT_{90}.	Not reported, studies ongoing at time of publication
mRNA-1273	0, 2, 4, 5, 6, 8	Anti-S-2P and anti-RBD IgG (ELISA, performed at the NIAID Vaccine Research Center.	Live virus (plaque-reduction neutralization assay), Pseudo virus. NT_{50}. Live virus assessed at weeks 0 and 6 only.	Cytokine-staining assay. Data available on 25-μg and 100-μg groups only at time of report. No comparisons reported.
ChAdOx	0, 4	IgG against trimeric spike protein (in-house indirect ELISA). Anti-S and anti-RBD (Meso Scale Discovery multiplexed immunoassay	Live virus (plaque reduction neutralisation test), Pseudo virus. NT_{50}.	Ex-vivo interferon-γ enzyme-linked immunospot (ELISpot) assay
Ad26.COV2.S	0, 2, 4, 8, 10	Anti-S IgG (ELISA, developed and qualified at Nexelis, Laval, Canada.	Live virus (microneutralization assay). Random subset of participants (~50 per group). NT_{50}, NT_{80}.	S-specific T-cell responses measured by cytokine-staining assay at day 15.
Convidecia	0, 2, 4	RBD-specific IgG (in-house ELISA from Wantai BioPharm, Beijing, China)	Live virus and pseudo virus.). Percent neutralisation not specified.	Interferon-γ enzyme-linked immunospot (ELISpot) assay
NVX-CoV2373	0, 1, 3, 4, 5	Anti-S IgG (ELISA, performed at Novavax Clinical Immune Laboratory, Gaithersburg, MD).	Live virus (microneutralization assay). NT_{99}.	Cytokines measured in small subgroup of subjects. Numbers insufficient to allow comparison between doses.
CoronaVac	0, 4, 5, 6, 8	RBD-specific IgG (in-house ELISA from Sinovac)	Live virus (micro cytopathogenic effect assay). Percent neutralisation not specified.	Not assessed
BBIBP-CorV	0, 1, 2, 4, 6	Not assessed	Live virus. Percent neutralisation not specified.	Not assessed
BBV152	0, 4, 6, 8	Anti-S (s1), anti-RBD, anti-nucleocapsid IgG (in-house ELISA)	Live virus (microneutralisation and plaque reduction neutralisation assays). NT_{50}.	Subset of participants at weeks 6 and 8. Th1 and Th2 cytokines; T-cell memory response (CD4 + CD45RO + and CD4 + CD45RO + Cd27-).

* Weeks since first injection. As reported in primary publication; protocols may also have specified later assessments.

shown in Table 4 and Figure. 1 for each of the vaccines. The association between relative response and vaccine dose was very similar for binding and neutralising antibodies, apart from BBV152, where an association was observed for neutralising antibodies but not binding antibodies. An approximate linear relationship was observed across the dose range of BNT196b, compared with a more curve-linear relationship (plateau effect) for mRNA-1273 and BBIBP-CorV. There was a flat dose–response relationship for Ad26.COV2.S, Convidecia, and NVX-CoV2373, while CoronaVac showed a weak effect.

For the vaccines exhibiting a dose–response relationship it is important to consider the effects in a quantitative context. Specifically, the differences in immune response between the highest and the second-highest dose were small, typically less than 0.2 $\log_{10}$ (1.6-fold) for both binding antibody concentration and neutralising antibody titre. Whether this difference is clinically important is difficult to assess given uncertainty around the immunes correlates of protection [24]. Useful insights were provided by an analysis from the mRNA-1273 efficacy trial, which estimated the hazard ratios of the risk of COVID-19 according to anti-spike IgG

Table 4
Binding antibody and neutralising antibody responses.

Vaccine	Time of assessment (weeks)	Dose	Binding antibody concentration (U/ml, log_{10})					Neutralising antibody titre (log_{10})				
			n	Mean	SE	Relative value	90 % CI	n	Mean	SE	Relative value	90 % CI
BNT162b2	1	10 μg	11	3.6394	0.0595	REF		11	2.0532	0.0718	REF	
		20 μg	12	3.7904	0.0765	0.1510	−0.0084, 0.3104	12	2.2421	0.0701	0.1888	0.0238, 0.3539
		30 μg	12	3.9315	0.0641	0.2921	0.1482, 0.4360	12	2.3653	0.0803	0.3121	0.1349, 0.4893
mRNA-1273	4	25 μg	13	5.4768	0.0830	REF		13	1.9069	0.1016	REF	
		100 μg	14	5.8936	0.0519	0.4168	0.2558, 0.5779	14	2.3651	0.0778	0.4582	0.2478, 0.6687
		250 μg	13	6.0763	0.0570	0.5996	0.4339, 0.7652	14	2.4317	0.0454	0.5248	0.3417, 0.7079
Ad26-COV2	8	5×10^{10} vp	74	2.8493	0.0405	REF		25	2.4751	0.0442	REF	
		1×10^{11} vp	71	2.9934	0.0312	0.1442	0.0600, 0.2283	24	2.6283	0.0537	0.1533	0.0389, 0.2677
Convidecia	4	5×10^{10} vp	129	2.7566	0.0443	REF		129	1.7427	0.0442	REF	
		1×10^{11} vp	253	2.8169	0.0293	0.0603	−0.0270, 0.1476	253	1.7882	0.0324	0.0454	−0.0447, 0.1356
NVX-CoV2373	2	5 μg	29	4.8004	0.0649	REF		29	3.5917	0.0940	REF	
		25 μg	27	4.6769	0.0755	−0.1236	−0.2873, 0.0402	27	3.5192	0.0897	−0.0726	−0.2862, 0.1411
CoronaVac	4	3 μg	117	3.2514	0.0356	REF		117	1.6444	0.0375	REF	
		6 μg	117	3.3593	0.0256	0.1079	0.0358, 0.1799	118	1.8156	0.0329	0.1711	0.0890, 0.2532
BBIBP-CorV	2	2 μg	Not assessed					31	1.9252	0.0410	REF	
		4 μg						32	2.2218	0.0382	0.2966	0.2045, 0.3887
		8 μg						30	2.2980	0.0357	0.3728	0.2834, 0.4622
BBV152	2	3 μg	184	4.0176	0.0289	REF		184	2.0043	0.0682	REF	
		6 μg	177	3.9796	0.0323	−0.0380	−0.1093, 0.0333	177	2.2945	0.0518	0.2901	0.1492, 0.4311

Time of immunological assessment is number of weeks after final injection.
BNT162b2: Age groups combined; **mRNA-1273**: Pseudovirus neutralisation shown; **ChAdOx**: not shown as assessed single dose only; **Ad26.COV2.S**: Analysis based on Cohort 1a (18–55 years), where data are more mature. Week 8 timepoint analysed for both single dose and two dose schedules (day of second vaccination for latter group). NT_{50} values shown; **Convidecia**: anti-RBD binding antibody titres and pseudovirus neutralisation shown; **NVX-CoV2373**: Two dose group that included adjuvant shown; **CoronaVac**: "Phase 2" formulation with the 0/4 week vaccination schedule analysed. anti-RBD binding antibody titres shown; **BBIBP-CorV**: binding antibodies were not assessed; **BBV152**: Plaque-reduction neutralisation assay shown.

and pseudo-virus NT_{50} values measured four weeks after the second vaccination [25]. The authors found that a 0.2 log_{10} lower response in anti-spike IgG concentration predicts a 8.7 % (95 % CI: 2.6–14.9 %) increase in the risk of symptomatic COVID-19, and a 0.2 log_{10} lower response in NT_{50} predicts a 18.9 % (9.0–29.9 %) increase. These are modest clinical effects. However, the analysis should be interpreted cautiously as follow-up extended to only 16 weeks after the second vaccination and findings may not generalise to other vaccines.

The only vaccines for which substantive T-cell data were reported were Ad26.COV2.S, Convidecia, and BBV152. For Ad26.COV2.S and Convidecia, no association between dose and T-cell response was found; for BBV152, a more pronounced T-cell memory response was observed in the higher dose (6-μg) group.

5. Discussion

5.1. Dose selected for the phase-3 efficacy trial

Five trials assessed two different doses (Ad26.COV2.S, Convidecia, NVX-CoV2373, BBV152, CoronaVac). Three found a similar immunological effect of the lower dose and higher dose, and the lower dose was selected for the efficacy trial (Ad26.COV2.S, Convidecia, NVX-CoV2373). The higher dose of the BBV152 vaccine elicited a better neutralising antibody response (but a similar binding antibody response) and was taken forward. Finally, the higher dose of the CoronaVac vaccine elicited marginally better responses (differences of log_{10} 0.1–0.2). Pragmatically, the researchers took the lower dose forward on the grounds of production capacity. Three trials assessed three different doses (BNT162b2 [excluding the 100-μg dose], mRNA-1273, BBIBP-CorV). The pattern of results was similar for all three vaccines, with the lowest dose producing a weaker immune response but no clear difference between the highest and middle doses. The highest dose was evaluated in the efficacy trials of BNT162b2, while the efficacy trials of mRNA-1273 and BBIBP-CorV evaluated the middle dose.

5.2. Dose selection – general considerations

Although there is a large body of methodological literature on optimal designs for dose-finding studies, the innovations proposed have been rarely used in applied research [26,27]. Much of this work considers fixed designs (i.e. the doses evaluated and the number of subjects per dose are pre-specified) and how to optimise the design to find the most accurate estimate of a target dose. The target dose can be defined in various ways – the most relevant for COVID-19 vaccines is arguably the dose achieving a specified, acceptably high fraction of the maximum treatment (known as the ED_P) [26,27]. Fig. 2 illustrates this idea heuristically; this shows a plausible curve-linear relationship between vaccine efficacy and

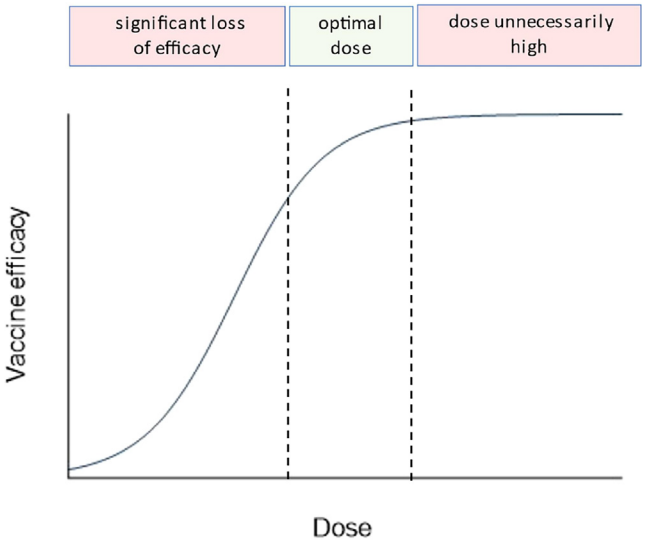

Fig. 2. Hypothetical relationship between vaccine efficacy and dose.

vaccine dose, with an acceptable target dose lying between the dotted lines [4]. As phase-3 efficacy trials generally examine a single dose only, this curve is hypothetical and cannot be validated. Instead, there is an implicit assumption that the shape of the curve between immune response (using the primary immunological marker) and dose closely mirrors that between clinical efficacy and dose.

It should be recognised that immune response may be influenced by other factors (e.g. sex, age, dosing interval) as well as vaccine dose [28,29]. However, the pertinent issue is whether these factors *modify* the relationship between clinical efficacy and dose i.e. does the optimal dose vary? Very extensive data are required to detect true variation in the optimal dose, and this is not a realistic objective for most early-phase studies [30].

5.3. Limitations in trial design

All of the trials in this review had at least one important design limitation: few doses evaluated, doses widely dispersed, or an inadequate sample size. First, if only two doses are assessed the best dose cannot possibly be identified – if the lower dose elicits a similar immune response to the higher dose then an even lower dose may be just as efficacious; if the higher dose elicits a better immune response than the lower dose then an even higher dose may be significantly more efficacious. Even with three doses, estimation of the dose–response curve may not be possible since several widely-used dose–response models include four or more parameters [27].

Second, identification of the optimal dose is compromised if adjacent doses are widely separated. For example, the 100-μg dose of mRNA-1273 out-performed the 25-μg dose but the possibility that an intermediate dose could have been as effective, or almost as effective, as 100-μg cannot be ruled out. Notably, the developers subsequently conducted another phase-2 study that compared 100-μg versus 50-μg and found no difference in reactogenicity or immunogenicity. However, the results of this study were too late to influence the dose used in the phase-3 efficacy trial of this vaccine [31].

Finally, the precision of the average response value calculated at each dose depends on the sample size. The sample was particularly small in the trials of mRNA-1273 (15 subjects per dose) and BNT162b2 (12 subjects per dose in each of two age groups), giving rise to wide confidence intervals when comparing different doses. This is acknowledged in the BNT162b2 paper: "With 10 to 12 valid results per assay from samples that could be evaluated for each group at each time point, pair-wise comparisons are subject to error and have no clear interpretation" [7]. This implicitly acknowledges that the trial was inadequately powered to identify the optimal dose. Although the developers of these two vaccines could not reasonably have predicted that their vaccines would have been so successful, there is a stark mismatch between these sample sizes and the billions of doses which have been supplied worldwide [32].

5.4. Improving the design of future trials

Our review should not be construed as a criticism of the scientists, working under intense time pressures, who designed and conducted these dose-finding studies. Also, the regulators had to make pragmatic decisions to ensure safe and effective vaccines were made available as quickly as possible. The key regulatory concern is safety, although dose-finding studies are too small to provide any useful data on serious, rare adverse events. However, some lessons can be learned which could improve the design of future studies. The regulatory landscape for COVID-19 vaccines has changed and licensure can now be granted on the basis of neutralising antibody responses compared with approved vaccines [33]. However, this does not obviate the problem of identifying the dose to be included in the licensure application.

A difficult issue in designing COVID-19 dose-finding trials was deciding the range of doses to study, particularly for mRNA vaccines. This is usually informed by prior dose-ranging studies in animal models but extrapolation to humans is problematic [24]. It is therefore prudent to study a wide range of doses, although this means that resources are spread thinly, with a small number of subjects studied per dose. Also, evidence may emerge quickly that some doses are demonstrably too low or too high. These problems are mitigated by the use of adaptive designs: here, rather than fixing the doses evaluated and the sample size per dose in advance, the dose received by a subject depends on outcomes observed on previous subjects [34]. Adaptive designs take longer to conduct, depending on how quickly the surrogate outcome can be measured and analysed. Time pressures clearly precluded their use for the first generation of COVID-19 vaccines but this is now less of a constraint, and such designs merit careful consideration.

Finally, efficacy trials in general rarely evaluate more than a single dose of the experimental vaccine or treatment, probably due to the additional complexity in the conduct and analysis of trials using multiple doses. However, such trials have a major advantage if these obstacles can be overcome. That is, the optimal dose can be selected on the basis of the clinical outcome of interest rather than a surrogate outcome, thereby avoiding the subtle assumptions and potential misleading conclusions when using the latter [35–37].

6. Conclusions

The use of reduced doses is being actively explored for booster vaccinations and several trials have already reported findings. The largest of these, the COV-BOOST trial, assessed the safety and immunogenicity of seven COVID-19 vaccines as a third dose following two doses of ChAdOx1 or BNT162b2 [38]. This included three vaccines which were studied both as a full dose and as a half dose: BNT162b2, NVX-CoV2373, and Valneva (a whole, inactivated virus). The reduced doses of BNT162b2 and NVX-CoV2373 produced potent immune response, with only a minimal decrease in anti-spike IgG and neutralising antibody levels. Also, the FDA approved a 50-μg half dose of mRNA-1273 when used as a homologous booster injection, based on a phase-2 study of 344 participants, in whom the lower dose boosted neutralizing titres significantly above the phase-3 benchmark.[39].

In summary, our review has highlighted limitations in the design of the early-phase COVID-19 vaccine trials, suggesting that that current licenced doses may be higher than necessary. Trials of reduced doses should be widened to include the priming injection as well as booster injections [3,4]. The experience with COVID-19 vaccines mirrors that in therapeutic drug medicine, where the initially marketed dose is frequently found to be unnecessarily high [26]. The high barrier to achieving a licensure change in dosage highlights the importance of carefully designed dose-finding trials to determine the optimal dose as early as possible.

Authorship

All authors attest they meet the ICMJE criteria for authorship.

DTD conceived the study, conducted the analyses, and drafted the manuscript. RG, SMc, and LMc made important comments on the draft manuscript.

Data availability

No data was used for the research described in the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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