Optimising the COVID-19 vaccination programme for maximum short-term impact

Short statement from the Joint Committee on Vaccination and Immunisation (JCVI)

31 December 2020

Summary

- There has been a rapid increase in COVID-19 cases in the UK in December 2020
- Two vaccines now have MHRA Regulation 174 authorisation (Pfizer-BioNTech and AstraZeneca)
- Rapid delivery of the vaccines is required to protect those most vulnerable
- Short term vaccine efficacy from the first dose of the Pfizer-BioNTech vaccine is calculated at around 90%, short term vaccine efficacy from the first dose of the AstraZeneca vaccine is calculated at around 70% (efficacy estimates are not directly comparable between the two vaccines)
- Given the high level of protection afforded by the first dose, models suggest that initially vaccinating a greater number of people with a single dose will prevent more deaths and hospitalisations than vaccinating a smaller number of people with two doses
- The second dose is still important to provide longer lasting protection and is expected to be as or more effective when delivered at an interval of 12 weeks from the first dose

Introduction

A new variant of COVID-19 has been identified in the UK, which has been associated with an increase in COVID -19 cases. Given this, the Joint Committee on Vaccination and Immunisation (JCVI) has considered options for increasing the short-term impact of the vaccination programme.

Considerations

When considering vaccination schedules JCVI often considers first principles, and regularly advises schedules which differ from the marketing authorisation. In every case, the advice of JCVI is aimed at maximising protection in the population.

Published efficacy between dose 1 and 2 of the Pfizer vaccine was 52.4% (95% CI 29.5-68.4%). Based on the timing of cases accrued in the phase 3 study, most the vaccine failures in the period between doses occurred shortly after vaccination, the period before any immune response is expected. Using data for those cases observed between day 15 and 21, efficacy against symptomatic COVID-19 was estimated at 89% (95% CI 52-97%), suggesting that short term protection from dose 1 is very high from day 14 after vaccination. Similar findings were seen with the Moderna mRNA vaccine out to 108 days after the first dose (see Annex A).

The level of protection gained from a single dose of the AstraZeneca vaccine was assessed in an exploratory analysis. Vaccine efficacy from 22 days post dose 1 was 73% (95% CI 48.79-85.76). High protection against hospitalisation was seen from 21 days after dose 1 until two weeks after the second dose, suggesting that a single dose of the AstraZeneca will provide high short-term protection against severe disease. Protective immunity from the first dose likely lasts for a duration of 12 weeks (unpublished data).

With most vaccines an extended interval between the prime and booster doses leads to a better immune response to the booster dose. There is evidence that a longer interval between the first and second doses promotes a stronger immune response with the AstraZeneca vaccine.

There is currently no strong evidence to expect that the immune response from the Pfizer-BioNTech vaccine would differ substantially from the AstraZeneca and Moderna vaccines.

The rate of vaccine delivery in the UK is currently limited by vaccine supply rather than by workforce capacity. An extended interval between vaccine doses together with initial prioritisation of the first vaccine dose would increase the flow of vaccine supply in the short term. This will allow for more first doses to be delivered to more people earlier.

Conclusion

Given the epidemiology of COVID-19 in the UK in late 2020 there is a need for rapid, high levels of vaccine uptake amongst vulnerable persons.

The Committee supports a two-dose vaccine schedule for the Pfizer-BioNTech and AstraZeneca vaccines. Given the data available, and evidence from the use of many other vaccines, JCVI advises a maximum interval between the first and second doses of 12 weeks for both vaccines. It can be assumed that protection from the first dose will wane in the medium term, and the second dose will still be required to provide more durable protection.

The Committee advises initially prioritising delivery of the first vaccine dose as this is highly likely to have a greater public health impact in the short term and reduce the number of preventable deaths from COVID-19.

Annex A

Report to JCVI on estimated efficacy of a single dose of Pfizer BioNTech (BNT162b2 mRNA) vaccine and of a single dose of ChAdOx1 vaccine (AZD1222).

Public Health England

1. Introduction

This report outlines the estimated single dose vaccine efficacy (VE) of the Pfizer and ChAdOx1 Covid-19 vaccines as discussed at the JCVI COVID-19 sub-group meeting of December 22nd December 2020. The ChAdOx1 estimates were presented by the Oxford team to the JCVI COVDI-19 sub-committee in a presentation and also in a clinical overview document. The Pfizer estimates were verbally given by PHE during discussion and were based on data previously provided to the sub-committee.

2. Pfizer single dose VE

In the published phase III efficacy paper [1] the VE primary end point for Covid-19 at least 7 days after a second dose was 95.0% (95% Confidence Interval: 90.3-97.6) and when including those with evidence of prior infection at baseline 94.6% (89.9-97.3).

In Figure 3 single dose VE at any time after dose 1 and before dose 2 was given as 52.4% (29.5-68.4) [39 events in the vaccine arm and 82 placebo]. For the period 2 to 7 days after dose 2 it was given as 90.5% (61.0-98.8) [2 events vs 21].

The 52.4% figure, however, includes COVID-19 infections occurring shortly after the first dose, an interval within which this dose would not be expected to have had an effect (i.e prior to the recipient mounting an immune response). Figure 3 clearly shows that from approximately 10 days after the first dose the cumulative incidence in the vaccine and Placebo groups diverge. It would therefore be appropriate to calculate the VE of a single dose in a period after this 10 day period.

A reasonable interval to use for post first dose VE would therefore be from >14 days to the time of the second dose (scheduled 21 days after the first dose) or to 7 days after the second dose base on the assumption the second dose would not have induced a response in this interval. Unfortunately, this analysis is not presented in the paper. The fact that the slope of the placebo and vaccine arms appears similar in figure 3 as person time moves from 10 days post 1 to post 2 doses suggests that VE is fairly similar from at least 10 days post dose 1 and post dose2.

The numbers at each 7-day cumulative interval behind figure 3 of the published paper are given in Figure 1 below which is taken from the *Emergency Use Authorization for Pfizer-BioNTech COVID-19 Vaccine Review Memo (fda.gov)*. These were as follows at days 14, 21- and 28-days post dose 1:

	Cumulative cases	
Days after dose 1	**Vaccine n/N**	**Placebo n/N**
14	37/21054	55/20970
21	39/20481	73/20366
28	41/19314	97/19209

VE of a single dose for the intervals 15-21, 22-28 and 15-28 days after the first dose is therefore as given in table 1 below (using the denominator at the day 21 time point).

Table1: VE in intervals post the first dose where protection from only this dose may be expected.

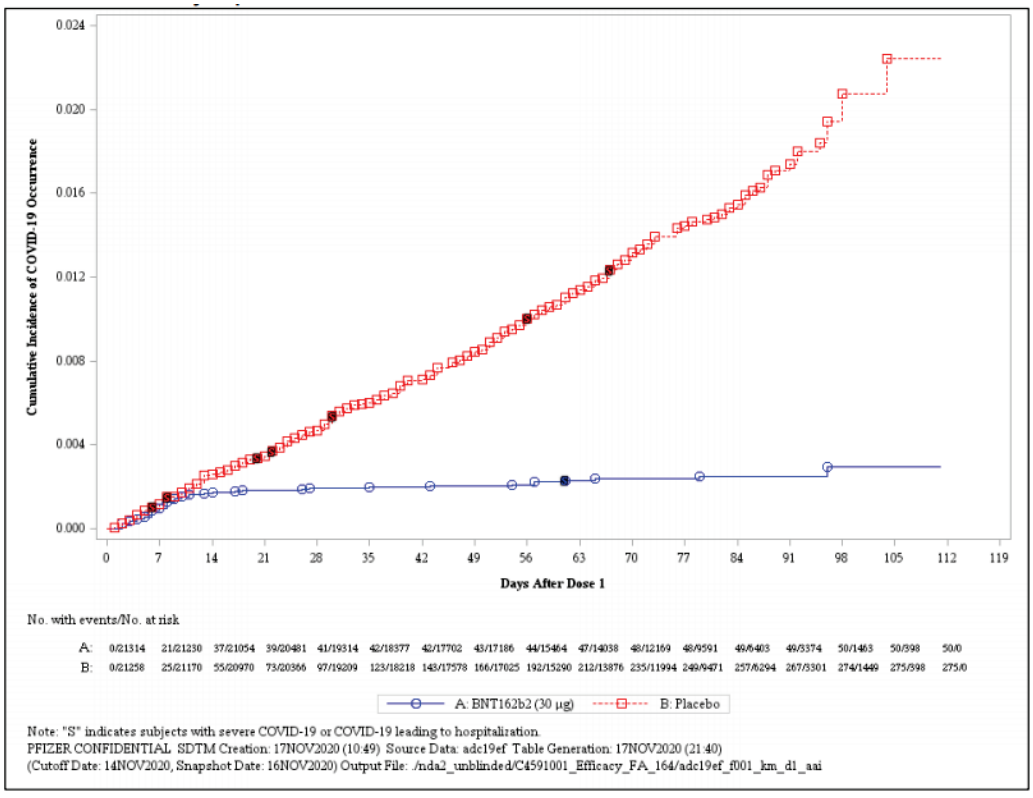
	Pfizer vaccine		Placebo		VE (95% CI)
Post dose 1 interval	N	N	N	N	
15-21 days	2	20481	18	20366	89% (52-97)
22-28 days	2	20481	24	20366	92% (65-98)
15-28 days	4	20481	42	20366	91% (74-97)

Note that the 15-21 day interval is prior to the scheduled second dose. The 22-28 day interval is in a period where the second dose will have been given to many participants but is prior to the time protection may be expected from the second dose. The numbers for this 22-28 day interval are similar to the reported numbers of 2 v 21 given in Figure 3 of the publication for the interval 2 to 7 days after dose2.

This analysis therefore indicates a VE of about 90% from 2 weeks after the first dose and for the following 2 weeks. It does not indicate VE beyond this time point as participants had received a second dose. Assuming the period up to 7 days post the second dose is still dose 1 protection then the VE is at least 74% (bottom end of 95%CI). This estimate of ~ 90% is much higher than the 52.4% reported in the paper where the early cases post the first dose were included.

Figure 1 – Cumulative incidence curves for the first COVID-19 occurrence after dose 1

Taken from [Emergency Use Authorization for Pfizer-BioNTech COVID-19 Vaccine Review Memo (fda.gov)]



3. ChadOx1 single dose VE

MHRA Information for Healthcare Professionals on COVID-19 Vaccine AstraZeneca states:

The level of protection gained from a single dose of COVID-19 Vaccine AstraZeneca was assessed in an exploratory analysis that included participants who had received one dose. Participants were censored from the analysis at the earliest time point of when they received a second dose or at 12 weeks post dose 1. [62% of the population had at least 6 weeks between vaccine doses (Voysey *et al*)] In this population, vaccine efficacy from 22 days post dose 1 was 73.00% (95% CI: 48.79; 85.76 [COVID-19 Vaccine AstraZeneca 12/7,998 vs control 44/7,982]).

Exploratory analyses showed that increased immunogenicity was associated with a longer dose interval. Efficacy is currently demonstrated with more certainty for dose intervals from 8 to 12 weeks. Data for intervals longer than 12 weeks are limited.

4. Moderna

The details below are taken from Vaccines and Related Biological Products Advisory Committee December 17, 2020 Meeting Briefing Document - FDA.

This shows that from 15 days after the first dose to the time of the second dose VE was 92.1% (68.8%-99.1%). Cumulative cases show a divergence between the vaccine and placebo groups from about 14 days after the first dose (Figure 2)

Additional Interim Efficacy Analyses

Additional analyses were done to assess efficacy against COVID-19 after one dose of mRNA1273. In participants in the mITT set who only received one dose of the vaccine at the time of the interim analysis, VE after one dose was 80.2% (95% CI 55.2%, 92.5%). These participants had a median follow-up time of 28 days (range: 1 to 108 days). The small, non-random sample and short median follow-up time limits the interpretation of these results. There appears to be some protection against COVID-19 disease following one dose; however, these data do not provide sufficient information about longer term protection beyond 28 days after a single dose.

Table - Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 From Dose 1 by Time Period in Participants Who Only Received One Dose, mITT Set

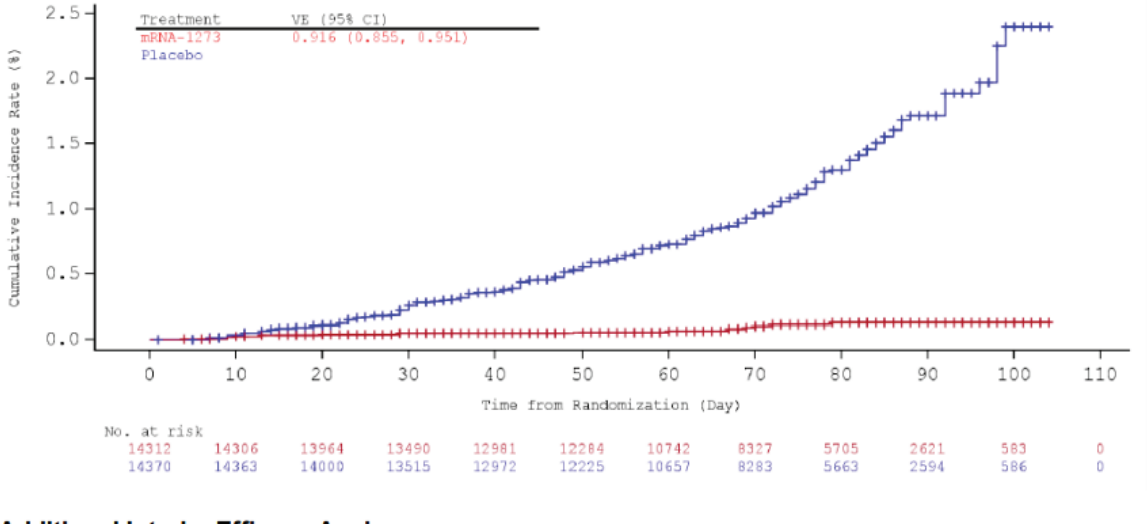
First COVID-19 Occurrence After Dose 1	Vaccine Group N=996 Case n (%)	Placebo Group N=1079 Case n (%)	VE (%) (95% CI)*
After dose 1	7/996 (87.5)	39/1079 (96.7)	80.2% (55.2%, 92.5%)
After dose 1 to 14 days after dose 1	5/996 (38.0)	11/1079 (41.1)	50.8% (-53.6%, 86.6%)
>14 days after dose 1**	2/983 (87.2)	28/1059 (96.2)	92.1% (68.8%, 99.1%)

Surveillance time in person years for given endpoint across all participants within each group at risk for the endpoint
* VE is calculated as 1-ratio of incidence rates (mRNA-1273/Placebo). The 95% CI of VE is calculated using the exact method conditional upon the total number of cases, adjusting for person-years
**Participants who were not at risk (cases or censored at prior time period) are excluded from this analysis
[a] Based on interim analysis: Novemer 7, 2020 efficacy data cutoff.

Figure 2 – Cumulative incidence curves for the first COVID-19 occurrence after randomisation

Taken from Vaccines and Related Biological Products Advisory Committee December 17, 2020 Meeting Briefing Document - FDA

Figure 2. Cumulative Incidence Curves for the First COVID-19 Occurrence After Randomization, mITT Set



[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 Dec 10:NEJMoa2034577. doi: 10.1056/NEJMoa2034577.

[2] Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, Angus B, 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. 2020 Dec 8:S0140-6736(20)32661-1. doi: 10.1016/S0140-6736(20)32661-1.

[3] Emergency Use Authorization for Pfizer-BioNTech COVID-19 Vaccine Review Memo (fda.gov)

[4] Vaccines and Related Biological Products Advisory Committee December 17, 2020 Meeting Briefing Document - FDA

[5] https://www.gov.uk/government/publications/regulatory-approval-of-covid-19-vaccine-astrazeneca/information-for-healthcare-professionals-on-covid-19-vaccine-astrazeneca