# COVID-19 vaccines: what happened to evidence-based medicine?

The UK government recently decided to extend the interval between the first dose of the Pfizer-BioNTech and AstraZeneca COVID-19 vaccines from 3 weeks to 12 weeks to maximise the number of people receiving the initial dose, despite the trials only providing vaccine efficacy data based on a schedule of 21 days between doses. This editorial discusses whether there is evidence to support this policy change.

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## Introduction

Since the beginning of the COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), there have been over 92 million confirmed cases and over 2 million deaths worldwide (World Health Organization, 2021). The need to contain the pandemic has meant that vaccine development and authorisation timelines have been significantly accelerated. On 2 December 2020, the UK became the first country to licence a vaccine against COVID-19 after it granted approval for the Pfizer-BioNTech vaccine, later giving emergency authorisation to the AstraZeneca (Oxford) and Moderna vaccines.

The original recommendation was to deliver the booster dose of the Pfizer vaccine 21 days after the first dose had been given, in accordance with timings used in the trials. However, as a second surge of cases threatened to overwhelm NHS hospitals, on 30 December the UK Chief Medical Officers issued a statement saying that the interval for the booster dose for the Pfizer and AstraZeneca vaccines would be extended to 12 weeks, to 'protect as many at risk people overall in the shortest possible time and have the greatest impact on reducing mortality, severe disease and hospitalisations' (Department of Health and Social Care, 2020).

This editorial highlights the differing medical and scientific opinions on this policy decision and discusses whether this is the right approach to take.

## Which COVID-19 vaccines are being rolled out for use in the UK?

Three main vaccines have emerged as the front runners from over 48 human clinical trials being held worldwide. Pfizer-BioNTech concluded their phase III trial randomising over 43 000 participants to receive two doses, 21 days apart, of a nucleoside-modified RNA (mRNA) vaccine or a placebo (Polack et al, 2020). The primary end-point was efficacy against confirmed symptomatic COVID-19, with onset at least 7 days after the administration of the second dose. Eight cases were recorded in the vaccine group compared to 162 cases in the placebo group, corresponding to a reported 95% efficacy (confidence interval 90.3–97.6).

The AstraZeneca (Oxford) vaccine consists of a chimpanzee adenovirus viral vector containing the SARS-CoV-2 spike protein gene. Notably, compared to the Pfizer vaccine, which needs to be stored at -70°C, the AstraZeneca vaccine can be stored at commercial fridge temperatures and therefore poses fewer logistical challenges in terms of storage and distribution. The study pooled data from trials in the UK and Brazil that enrolled 11 636 subjects (Voysey et al, 2021). Participants received two doses, with the interval ranging from between 4 and 26 weeks. Overall, there were 30 (0·5%) cases among 5807 participants in the vaccine arm and 101 (1·7%) cases among 5829 participants in the control group, resulting in vaccine efficacy of 70·4% (95·8% confidence interval 54·8–80·6).

The Moderna group has also developed an mRNA vaccine. The trial enrolled 30 420 participants, including those over 65 years old and patients with chronic disease who were randomised to receive two doses of a vaccine or placebo on days 1 and 29 (Baden et al, 2020). Vaccine efficacy was found to be 94.1% (11 cases in the vaccine group vs 185 cases in the placebo group).

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## Why did the government decide to delay the second dose?

Amid the emergence of a new highly transmissible variant that saw the number of cases in the UK soar, the pressure to rapidly deploy a mass vaccination programme intensified. A major concern influencing the decision was limitation of vaccine supply. The Joint Committee on Vaccination and Immunisation published a statement on increasing the short-term impact of the vaccine roll-out: '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' (Department of Health and Social Care, 2021).

## What is the evidence to support the extended interval between doses?

In the trial data published by Pfizer (Polack et al, 2020), the efficacy was 52.4% when there were 21 days between the first and second dose. A Public Health England (2020) report to the Joint Committee on Vaccination and Immunisation calculated things slightly differently, asserting that efficacy was 92% after the first dose, by focussing only on cases between days 15 to 28. They presumed that the vaccine only takes effect after 14 days based on divergence in COVID cases between the vaccine and placebo cohorts after this point, and that efficacy 7 days after the second dose can still be attributed to protection conferred by the first dose. During this period, there were four cases in the vaccine group vs 42 in the placebo cohort, and it was therefore argued that first dose vaccine efficacy was 92%.

Importantly, the median follow-up time for the participants was only 28 days, so there are still no trial data to support the notion that protection afforded by the first dose alone will persist for 12 weeks, or that the second dose is equally or more effective when delayed. Pfizer have released a statement cautioning that 'There is no data to demonstrate that protection after the first dose is sustained after 21 days' (Boseley, 2021). Notably, other prominent international health bodies have not followed suit. The Food and Drug Administration (2021) released a statement with a warning that 'at this time, suggesting changes to the FDA-authorized dosing or schedules of these vaccines is premature and not rooted solidly in the available evidence'. Similarly, the World Health Organization Strategic Advisory Group of Experts on Immunisation continued to recommend administration of two doses between 21 and 28 days apart, up to a maximum of 6 weeks.

Immunogenicity data from trials have suggested a more robust antibody response after the booster vaccination. A preprint study in 48 participants measured S1-binding IgG, SARS-CoV-2 neutralising titres, $CD4^+$ and $CD8^+$ T cells elicited by a prime-boost regimen of the Pfizer vaccine at different dose strengths (administered at 0 and 21 days) (Sahin et al, 2020). They found that, 21 days after the first dose, geometric mean concentrations of S1-binding IgG increased in all participants in the range 49–1161 U/ml, and 7 days after the booster dose saw a much stronger antibody response, ranging from 691 to 8279 U/ml. Similarly, neutralising antibody titres increased modestly in only a proportion of participants after the prime dose, but increased substantially 7 days after the booster dose.

Initial reports are also emerging from an as-yet unpublished serological trial examining antibody response in 102 medical personnel who received the Pfizer vaccine (Firstwordpharma, 2021). They have purportedly found that, a week before receiving the second dose, only 50% of participants had antibody levels considered sufficient for protection, compared to 98% 1 week after the booster vaccination.

In the Oxford AstraZeneca trial, there was slightly more evidence to support the move. Subgroup analyses found that efficacy 14 days after the second dose was 65.4% (confidence interval 41.1–79.6) in the cohort given the booster at more than 6 weeks after the first dose, compared to 53.4% (confidence interval 2.5–78.8) in those given the booster at less than 6 weeks after the first dose. It should be noted that, across these smaller subsets, case numbers were relatively low, with relatively wide confidence intervals for vaccine efficacy.

## What are the potential implications of delaying the second dose?

The chair of the British Medical Association GP committee, Dr Richard Vautrey, called this decision 'grossly and patently unfair to tens of thousands of our most at-risk patients' (British Medical Association, 2020). Aside from highlighting the logistical problems this poses in the cancellation and rescheduling of thousands of appointments, many GPs raised concerns about the upset this could cause vulnerable patients who have already spent much of the year shielding and now face a more prolonged period of not being able to see their loved ones. Many raised concerns that they would find it difficult to justify the decision to patients, given the incomplete nature of the evidence so far.

Some doctors are concerned that, if there is a potential that efficacy does wane during this period and a higher number of people develop symptomatic COVID, despite having had the vaccination, this could decrease public confidence in the vaccines. There are also worries about whether providing only partial protection to a large number of people for a prolonged period of time could encourage the development of vaccine-resistant strains of the virus.

However, a number of prominent groups, including the British Society of Immunology (2021), agreed that 'a pragmatic approach is needed in the short term…we need to protect as many vulnerable people from severe COVID-19 disease'.

## Is it safe to receive two different types of vaccines?

Public Health England's (2021) Green Book guidance to healthcare professionals stated that, although it was preferable for patients to receive the same vaccine type, it was 'reasonable to offer one dose of the locally available product to complete the schedule'. Dr Mary Ramsay, head of immunisations at Public Health England, clarified that this should be considered only in 'extremely rare occasions where the same vaccine is not available, or where it is not known what vaccine the patient received' (Mahase, 2021). Kate Bingham, outgoing chair of the UK vaccines taskforce, said the government planned to start trials 'mixing and matching' vaccines (BBC News, 2020). It is theorised that this approach could augment immunogenicity, as has been observed in heterologous prime-boost trials for other vaccines. However, at the time of writing, there are no available results from trials testing interchangeability of different COVID vaccines.

## Conclusions

In challenging times, where infection and deaths continue to rise and the NHS is facing unprecedented pressure on services, it is understandable that urgent public health policies need to be made. However, caution should be exercised in any decisions, as a number of questions remain unanswered about the strength or duration of protection afforded by the first dose of the vaccines alone. The evidence for the efficacy of the vaccination to date is based on second administration of the booster within the timeframe delineated by the clinical trials. Until such time as this is evaluated further, the authors believe that those at high risk and frontline workers should receive the second dose as per the studies. They also advocate that the vaccines are not mixed until there is evidence that efficacy is maintained. It is important for the government to release any unpublished data to justify their decisions, both to bolster the confidence of the public and healthcare workers, and to actually protect the NHS. Robust data must now be collected and trials established to compare vaccine efficacy using the 3-week vs 12-week schedule, allowing policy that is not supported by current evidence to be more rigorously evaluated.

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## Key points

- Proven efficacy of the Pfizer vaccine is based on randomised controlled trial data with a dosing interval of 21 days between first and second doses. There is currently not the evidence to support the booster dose being given at 12 weeks.
- It is essential that data are collected and trials are established to compare vaccine efficacy using the 12-week schedule proposed by the government.
- Until this is more rigorously evaluated, the authors advocate that the second dose should be administered to high-risk individuals and frontline workers as per the timeframe tested in the clinical trials.

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