Bwrdd Iechyd Prifysgol Hywel Dda University Health Board

CYFARFOD BWRDD PRIFYSGOL IECHYD
UNIVERSITY HEALTH BOARD MEETING

DYDDIAD Y CYFARFOD: **DATE OF MEETING:**	28 January 2021
TEITL YR ADRODDIAD: **TITLE OF REPORT:**	Joint Committee on Vaccination and Immunisation/Chief Medical Officer Announcement to Defer Second Dose Pfizer Vaccine to up to 12 weeks
CYFARWYDDWR ARWEINIOL: **LEAD DIRECTOR:**	Dr Phil Kloer, Deputy CEO and Medical Director Mr Steve Moore, Chief Executive Officer
SWYDDOG ADRODD: **REPORTING OFFICER:**	Mr John Evans, Assistant Director, Medical Directorate

Pwrpas yr Adroddiad (dewiswch fel yn addas) **Purpose of the Report** (select as appropriate)
Ar Gyfer Penderfyniad/For Decision

ADRODDIAD SCAA
SBAR REPORT

Sefyllfa / Situation

At the same time the announcement was made that the Oxford / AstraZeneca vaccine had been approved by the Medicines and Healthcare products Regulatory Agency (MHRA), the Joint Committee on Vaccination and Immunisation (JCVI) also recommended vaccinating people with the first dose as a priority above offering individuals their second dose, extending the time period between first and second dose for the Pfizer-BioNTech vaccine from 21-28 days to 12 weeks (Appendix 1). The same interval between the two doses was recommended for the Oxford / AstraZeneca vaccine. This decision was endorsed by the four UK CMOs and Welsh Government subsequently issued a statement to implement this policy nationally. Written Statement: COVID-19 Vaccine Deployment Data in Wales (4 January 2021) | GOV.WALES

The announcement of approval of the second (Oxford / AstraZeneca) vaccine, and now third vaccine (with Moderna having been approved) is excellent news; however, NHS services and the staff providing them are under immense pressure in their professional lives, and – in common with everyone – are managing change and uncertainty in their personal lives. The announcement has caused concern among some staff who were expecting their second dose much sooner, and the Health Board has received letters expressing these concerns from representatives of the Staff Partnership Forum, the Local Medical Committee (LMC), the Local Negotiating Committee (LNC) and the Withybush Medical Staff Committee (MSC). The announcement from the JCVI / UK CMOs has also prompted concerns amongst individual staff members who have expressed them both to the Board privately in writing and at our staff event, and also publically on social media.

This paper seeks to provide the background and supporting evidence for the JCVI/CMO decision, outline the concerns raised by colleagues and external partners, and detail the risks of adopting the national policy.

The Health Board also considered the ethical implications of the announcement at the Health Board's Ethics Panel on 13th January 2021, and held a Microsoft Teams session, attended by the Chief Executive, Chair and the Executive Team and made available to all staff, to listen to and answer as many concerns as possible.

Cefndir / Background

On 30th December 2020, the MHRA and JCVI advised on the safety of the AstraZeneca and Pfizer-BioNTech vaccines, stating that both vaccines provided high-levels of protection against coronavirus (COVID-19) disease, including severe cases.

The JCVI recommended that vaccinating more people with the first dose should be prioritised above offering individuals their second dose, as this will provide the greatest public health benefits in the short-term and save more lives. This will also offer more people protection, with significant immunity obtained around two weeks after the first vaccine dose.

The JCVI has set out a prioritised list by age and risk factor, categorised into 9 groups on the basis of the latest evidence on who is most vulnerable to COVID-19 (Appendix 2). As a result, the current recommendation is that residents in a care home for older adults and their carers (priority group 1) will be vaccinated first, followed by people over the age of 80 and frontline health and social care workers (priority group 2). The programme will then be rolled out to the rest of the population sequentially based on the JCVI's priority list. This initial phase of the vaccine programme is estimated to cover around 99% of preventable COVID-19 deaths.

On 11th January 2021, the Minister for Health and Social Services in Wales announced the vaccination strategy for Wales, which included a milestone to complete first vaccination dose for priority groups 1-4 by mid-February 2021, and a milestone to complete first dose for priority groups 5-9 by the end of March 2021. Hywel Dda University Health Board is producing its own plans to meet these delivery milestones as a minimum.

The advice from JCVI and the four UK CMOs is that the second dose of the Pfizer-BioNTech vaccine can be offered between 3 and 12 weeks after the first. They also advise that for the AstraZeneca vaccine, the second dose can be offered four to 12 weeks after the first dose. Some data from the AstraZeneca vaccine trials suggests that extending the time to the second dose up to 12 weeks may be better than having the second dose earlier. Missing the second dose is not advised, as this is likely to be important for longer lasting protection; however, exact durations of protection are currently unknown.

The four UK Chief Medical Officers agree with the JCVI that at this stage of the pandemic, prioritising the first doses of vaccine for as many people as possible on the priority list will protect the greatest number of at risk people overall in the shortest possible time. They suggest that this will have the greatest impact on reducing mortality, severe disease, hospitalisations and in protecting the NHS and equivalent health services. Operationally, this will mean that second doses of both vaccines will be administered towards the end of the recommended vaccine dosing schedule of 12 weeks. This will maximise the number of people getting the vaccine and therefore receiving protection in the next 12 weeks.

Based on the JCVI's expert advice, it is the Chief Medical Officers' joint clinical advice that delivery plans should prioritise delivering first vaccine doses to as many people on the JCVI Phase 1 priority list in the shortest possible timeframe. Consequently, the administration of second doses will be completed over the longer timeframes, in line with conditions set out by the independent regulator, the MHRA and advice from the JCVI. This will maximise the impact of the vaccine programme in its primary aims of reducing mortality and hospitalisations and protecting the NHS and equivalent health services.

Asesiad / Assessment

1. JCVI / CMO rationale for its decision

The JCVI produced a short statement on their rationale and the four UK CMOs published a letter to all medical professionals outlining the reasons for their advice (Appendix 3).

2. Welsh Government Policy decision

Welsh Government has confirmed that the revision to second dose cycle are policy decisions, endorsed by Ministers, reflecting the expert advice signed off by the MHRA, JCVI and UK CMOs. They have confirmed that it is not a matter for local review or local policy and all health organisations will be required to comply with this national policy. These decisions have been made on a consistent basis across the UK, to maximise public health protection and to ensure the broadest and quickest protection of both population and healthcare staff, in line with the JCVI advice.

3. Staff concerns

Concerns have been raised in writing by a variety of individuals, groups and organisations including representatives of the Staff Partnership Forum, the LMC, the LNC and Withybush MSC. Similar concerns were raised at the staff meeting held on 14th January 2021. Not all correspondence and discussion at the staff was unsupportive of the revised policy, and indeed some have been strongly supportive.

The key broad areas of concern include:

- Concerns over extending the timing of the Pfizer-BioNTech second dose outside the schedule that the manufacturer recommends and, in relation to this, concerns over the evidence base, given that the trial data did not include a 12 week interval; uncertainty over the protection offered until 12 weeks and effectiveness of the second dose after 12 weeks; and that the vaccine uses relatively new technology (mRNA), and other evidence base related concerns
- Concerns that employees who have already had the first dose will be delayed in receiving full protection from a second dose, with particular concerns for individuals working in high exposure areas, or undertaking aerosol-generating procedures
- Concerns that some shielding individuals, who would potentially be willing and able to return to work if they had the second dose, will be delayed in doing so and that this will risk a longer period of staffing fragility than necessary in some service areas
- That staff consented to have the first dose Pfizer-BioNTech vaccine on the basis that they would receive their second dose in 3-4 weeks

4. Response to LNC from CEO and Medical Director (similar responses provided to LMC and Withybush MSC)

Attached at Appendix 4

5. Organisations providing statement and comment on the UK's revised policy decision

Explanatory Video from Public Health Wales

- **Dr Richard Roberts (PHW) video** Covid-19 vaccinations dosage intervals on Vimeo

Supportive organisations

- **Academy of Medical Royal Colleges** https://www.aomrc.org.uk/statements/covid-19-vaccination-and-second-doses-academy-statement/
- **British Society of Immunologists** https://www.immunology.org/policy-and-public-affairs/briefings-and-position-statements/COVID-19-vaccine-dosing-schedules
- **Royal Pharmaceutical Society advice** https://www.rpharms.com/resources/pharmacy-guides/coronavirus-covid-19/covid-19-vaccines/vaccine-dose-interval-changes
- **Royal College of General Practitioners** (statement attached at Appendix 5)

Organisations challenging the decision

- **British Medical Association** BMA says decision to delay follow-up dose of Pfizer vaccine 'grossly unfair' to thousands of at-risk patients in England, as appointments are rescheduled - BMA media centre - BMA
- **World Health Organisation media statement** WHO warns against UK strategy of delaying second Covid vaccine dose | The Independent
- **U.S. Food & Drug Administration** FDA Statement on Following the Authorized Dosing Schedules for COVID-19 Vaccines | FDA

6. Legal advice

The Health Board obtained legal advice in relation to the concerns raised about consent and any implications arising from this, and also to test the implications for the Heath Board in not following National Policy. The legal advice was clear, in that Health Boards are obliged to follow National Policy, that it is not optional and that there could be legal implications for the Health Board if it did not follow National Policy as directed by Welsh Government.

7. Ethics Panel advice (13th January 2021)

The Ethics Panel was asked by Gold Command to consider the question "Advise the Board on the ethical issues that arise and need to be taken into account in its decision making relating to the change in advice from the JCVI and Joint UK CMOs to defer the second dose of Pfizer vaccine from 3-4 weeks to 12 weeks".

The advice is attached at Appendix 6.

The Ethics Panel strongly advised that wasting doses is ethically impermissible and that vaccinators should do all they can to ensure that vaccines are given to the most high-risk individual available. Reserve lists will be in place for vaccinators to call on; however, given the short time lines that the vaccine is usable for, vaccinators need to be able to use their discretion to deliver the vaccine to the most appropriate person possible.

The Ethics panel also advised that, where an individual is unavailable during the 11th/12th week to receive the second dose for genuine reasons of exceptionality, the decision to allow the second dose to be administered earlier, but as close to the advised time as possible, should be made. There is no evidence as to the efficacy of the vaccine if it is given after 12 weeks and

this could lead to a need to restart the vaccine schedule and thus waste the first dose already administered. The Health Professionals Forum (HPF) have also written to the Executive Medical Director in support of the view that the Health Board should adopt a "no wastage policy". Each case is considered by the Executive Medical Director and he is supported by a small panel of experts including the Director of Public Health.

The Ethics Panel considered other at risk groups and how they might be prioritised however the National Policy is as stated that 1st doses must be prioritised and clinical discretion is not currently part of the National Policy.

8. Summary

The Board needs to recognise the significant concerns raised by our staff, and the context and nature of their concerns, which come at a time when services and our staff are under pressure. The paper sets out the range of views, both nationally and internationally, around the policy decision on the second dosing schedule. Where there are conflicting views, it is understandable that staff and public will be concerned about what the best course of action is. The legal advice is clear that the Health Board is obliged to follow the National Policy and, if it does not, then there could be legal implications for the Board.

The rapidly changing situation, conflicting sources of advice and concerns raised by large numbers of staff make it more important than ever that the Health Board continues to make arrangements to extensively and continuously listen to its staff, hear the messages and communicate its own messages clearly through every avenue available.

Argymhelliad / Recommendation

The Board is requested to:

- Recognise the significant concerns of some Health Board staff to the change in the second dose scheduling;
- Request that the Medical Director continue to raise these concerns with Welsh Government in its considerations regarding the second dose schedule for the Pfizer Vaccine;
- To issue guidance to staff that, should members on the reserve list be unavailable, to use their discretion to deliver the vaccine to the most appropriate person possible to avoid any wastage.

Amcanion: (rhaid cwblhau) **Objectives: (must be completed)**	
Cyfeirnod Cofrestr Risg Datix a Sgôr Cyfredol: Datix Risk Register Reference and Score:	1030 - Reputational risk if the Health Board is perceived to not deliver the mass vaccination programme Risk Score 12
Safon(au) Gofal ac Iechyd: Health and Care Standard(s): Hyperlink to NHS Wales Health & Care Standards	All Health & Care Standards Apply
Amcanion Strategol y BIP: UHB Strategic Objectives: Hyperlink to HDdUHB Strategic Objectives	All Strategic Objectives are applicable

Amcanion Llesiant BIP: UHB Well-being Objectives: Hyperlink to HDdUHB Well-being Objectives Annual Report 2018-2019	2. Develop a skilled and flexible workforce to meet the changing needs of the modern NHS 4. Improve Population Health through prevention and early intervention, supporting people to live happy and healthy lives 8. Transform our communities through collaboration with people, communities and partners

Gwybodaeth Ychwanegol: Further Information:	
Ar sail tystiolaeth: Evidence Base:	Included within the body of the report
Rhestr Termau: Glossary of Terms:	Contained within the body of the report
Partïon / Pwyllgorau â ymgynhorwyd ymlaen llaw y Cyfarfod Bwrdd Iechyd Prifysgol: Parties / Committees consulted prior to University Health Board:	Quality, Safety and Experience Assurance Committee Ethics Panel

Effaith: (rhaid cwblhau) Impact: (must be completed)	
Ariannol / Gwerth am Arian: Financial / Service:	No additional financial implications
Ansawdd / Gofal Claf: Quality / Patient Care:	Assessment includes impact upon the workforce and, in turn, patient care
Gweithlu: Workforce:	Assessment includes impact upon the workforce and, in turn, patient care
Risg: Risk:	Risks of the policies adopted included within each attachment
Cyfreithiol: Legal:	Legal impact included within Assessment above
Enw Da: Reputational:	Policy provided by Welsh Government
Gyfrinachedd: Privacy:	None
Cydraddoldeb: Equality:	Not applicable

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.

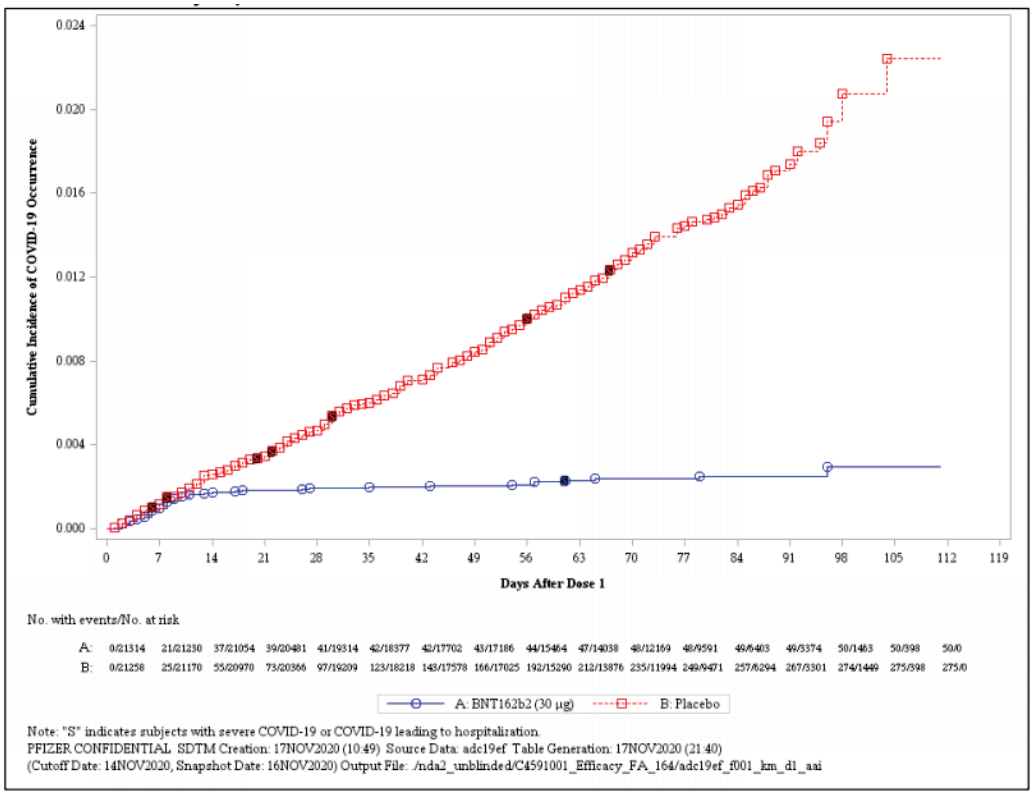
	Pfizer vaccine		Placebo		VE (95% CI)
Post dose 1 interval	N	N	N	N	
15-21 days	2	20481	18	20366	89% (52-97)
22-28 days	2	20481	24	20366	92% (65-98)
15-28 days	4	20481	42	20366	91% (74-97)

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

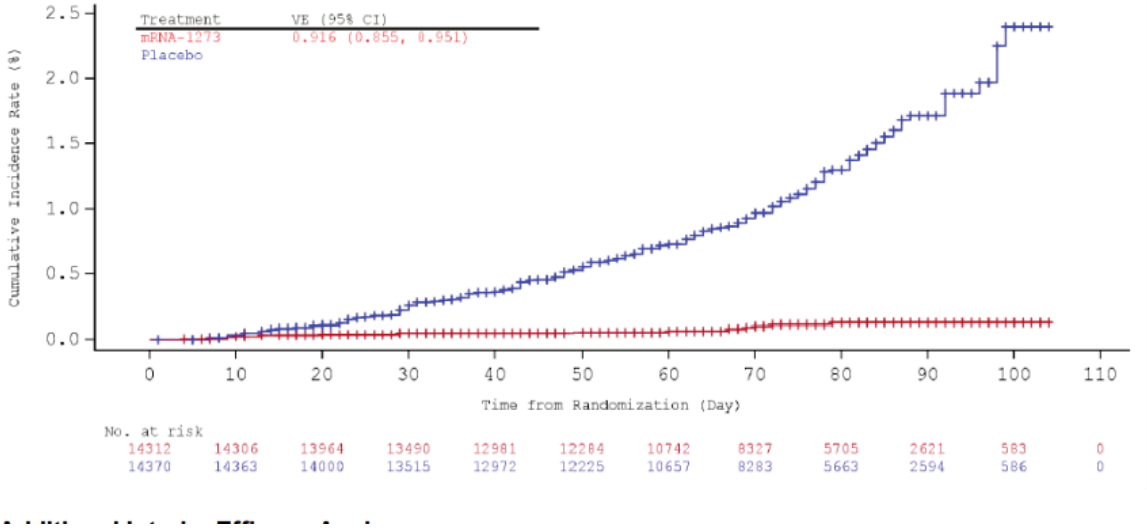
First COVID-19 Occurrence After Dose 1	Vaccine Group N=996 Case n (%)	Placebo Group N=1079 Case n (%)	VE (%) (95% CI)*
After dose 1	7/996 (87.5)	39/1079 (96.7)	80.2% (55.2%, 92.5%)
After dose 1 to 14 days after dose 1	5/996 (38.0)	11/1079 (41.1)	50.8% (-53.6%, 86.6%)
>14 days after dose 1**	2/983 (87.2)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

Joint Committee on Vaccination and Immunisation: advice on priority groups for COVID-19 vaccination

30 December 2020

Introduction

This advice is provided to facilitate the development of policy on COVID-19 vaccination in the UK.

JCVI advises that the first priorities for the current COVID-19 vaccination programme should be the prevention of COVID-19 mortality and the protection of health and social care staff and systems. Secondary priorities could include vaccination of those at increased risk of hospitalisation and at increased risk of exposure, and to maintain resilience in essential public services. This document sets out a framework for refining future advice on a national COVID-19 vaccination strategy.

This advice has been developed based on a review of UK epidemiological data on the impact of the COVID-19 pandemic so far (1), data on demographic and clinical risk factors for mortality and hospitalisation from COVID-19 (2-3), data on occupational exposure(4-7), a review on inequalities associated with COVID-19 (8), Phase I, II and III data on the Pfizer-BioNTech mRNA vaccine and the AstraZeneca vaccine, Phase I and II data on other developmental COVID-19 vaccines (9-20), and mathematical modelling on the potential impact of different vaccination programmes (21).

Considerations

Pfizer-BioNTech vaccine

The Committee has reviewed published and unpublished Phase I/II/III safety and efficacy data for the Pfizer BioNTech mRNA vaccine. The vaccine appears to be safe and well-tolerated, and there were no clinically concerning safety observations. The data indicate high efficacy

in all age groups (16 years and over), including protection against severe disease and encouraging results in older adults. The Committee advises that this vaccine be used in the first phase of the programme, according to the priority order set out below. While there is some evidence to indicate high levels of short-term protection from a single dose of vaccine, a two-dose vaccine schedule is currently advised as this is likely to offer longer lasting protection. (See below).

AstraZeneca vaccine

The Committee has reviewed published and unpublished Phase I/II/III safety and efficacy data for the AstraZeneca vaccine. The vaccine appears to have a good safety profile, and the data indicate high efficacy in adults aged 18 years and over, including protection against severe disease and encouraging results in older adults. Existing data are consistent with high levels of short-term protection following the first dose of vaccine, with further protection obtained following the second dose of vaccine which may be given between 4 – 12 weeks after the first dose. The Committee advises that this vaccine be used in the first phase of the programme, according to the priority order set out below. A two-dose vaccine schedule is currently advised as this is likely to offer longer lasting protection. (See below)

Vaccine schedule

For both Pfizer-BioNTech and AstraZeneca vaccines, a two-dose schedule is advised.

In the context of the epidemiology of COVID-19 in the UK in late 2020, the JCVI places a high priority on promoting rapid, high levels of vaccine uptake amongst vulnerable persons. Therefore, given data indicating high efficacy from the first dose of both Pfizer-BioNTech and AstraZeneca vaccines, the Committee advises that delivery of the first dose to as many eligible individuals as possible should be initially prioritised over delivery of a second vaccine dose. This should maximise the short-term impact of the programme. The second dose of the Pfizer-BioNTech vaccine may be given between 3 to 12 weeks following the first dose. The second dose of the AstraZeneca vaccine may be given between 4 to 12 weeks following the first dose.

JCVI advises that the second vaccine dose should be with the same vaccine as for the first dose. Switching between vaccines or missing the second dose is not advised as this may affect the duration of protection.

Vaccine choice

There have been no clinical trials directly comparing the Pfizer-BioNTech and AstraZeneca vaccines. In Phase III trials of the respective vaccines, efficacy against symptomatic disease for the Pfizer-BioNTech vaccine was higher than for the AstraZeneca vaccine. Differences in study setting, study design, study population (age, ethnicity, social demographics, etc), and efficacy endpoints may account for some of the observed differences. Both vaccines give very high protection against severe disease, which is the primary aim of the first phase of the programme, and both vaccines have good safety profiles.

The logistical challenges posed by the storage and distribution requirements for the Pfizer-BioNTech vaccine mean that in some populations, the AstraZeneca vaccine is the only vaccine which can be deployed rapidly, and without substantial vaccine wastage.

JCVI does not advise a preference for either vaccine in any specific population. For operational and programmatic reasons, such as to enable more extensive and timely vaccine coverage, one vaccine may be offered in certain settings in preference over another vaccine.

This statement will be updated following consideration of Phase III safety and efficacy data on other COVID-19 vaccines.

Direct protection vs transmission reduction

JCVI has considered a number of different vaccination strategies, including those targeting transmission and those targeted at providing direct protection to persons most at risk.

In order to interrupt transmission, mathematical modelling indicates that we would need to vaccinate a large proportion of the population with a vaccine which is highly effective at preventing infection (transmission). At the start of the vaccination programme, good evidence on the effects of vaccination on transmission will not be available, and vaccine availability will be more limited. The best use of

available vaccine will also, in part, be dependent on the point in the pandemic the UK is at.

Given the current epidemiological situation in the UK, the best option for preventing morbidity and mortality in the initial phase of the programme is to directly protect persons most at risk of morbidity and mortality.

Age

Current evidence strongly indicates that the single greatest risk of mortality from COVID-19 is increasing age and that the risk increases exponentially with age (1-3). Mathematical modelling indicates that the optimal strategy for minimising future deaths or quality adjusted life year (QALY) losses is to offer vaccination to older age groups first. These models assume an available vaccine is both safe and effective in older adults (21). Data also indicate that the absolute risk of mortality is higher in those over 65 years than that seen in the majority of younger adults with an underlying health condition (see below). Accordingly, the Committee's advice largely prioritises based on age.

Age-based programmes are usually easier to implement and therefore achieve higher vaccine uptake. An age-based programme is also likely to increase uptake in those with clinical risk factors as the prevalence of these increases with age.

Older adults resident in care homes

There is clear evidence that those living in residential care homes for older adults have been disproportionately affected by COVID-19 (22-25) as they have had a high risk of exposure to infection and are at higher clinical risk of severe disease and mortality. Given the increased risk of outbreaks, morbidity and mortality in these closed settings, these adults are considered to be at very high risk. The Committee's advice is that this group should be the highest priority for vaccination. Vaccination of residents and staff at the same time is considered to be a highly efficient strategy within a mass vaccination programme with the greatest potential impact (see below).

Health and social care workers

Frontline health and social care workers are at increased personal risk of exposure to infection with COVID-19 and of transmitting that infection

to susceptible and vulnerable patients in health and social care settings. The Committee considers frontline health and social care workers who provide care to vulnerable people a high priority for vaccination. Protecting them protects the health and social care service and recognises the risks that they face in this service. Even a small reduction in transmission arising from vaccination would add to the benefits of vaccinating this population, by reducing transmission from health and social care workers to multiple vulnerable patients and other staff members. This group includes those working in hospice care and those working temporarily in the COVID-19 vaccination programme who provide face-to-face clinical care.

There is evidence that infection rates are higher in residential care home staff (22-25), than in those providing domiciliary care or in healthcare workers. Care home workers are therefore considered a very high priority for vaccination.

Prioritisation amongst health and social care workers

Frontline health and social care workers at high risk of acquiring infection, at high individual risk of developing serious disease, or at risk of transmitting infection to multiple vulnerable persons or other staff in a healthcare environment, are considered of higher priority for vaccination than those at lower risk. This prioritisation should be taken into account during vaccine deployment.

Clinically Extremely Vulnerable (Shielding patients)

Individuals considered extremely clinically vulnerable have been shielding for much of the pandemic (26). This means that available data are likely to underestimate the risk in this group. Many of those who are clinically extremely vulnerable are in the oldest age groups and will be among the first to receive vaccine. Considering data from the first wave in the UK, the overall risk of mortality for clinically extremely vulnerable younger adults is estimated to be roughly the same as the risk to persons aged 70 – 74 years. Given the level of risk seen in this group as a whole, JCVI advises that persons aged less than 70 years who are clinically extremely vulnerable should be offered vaccine alongside those aged 70-74 years of age. There are two key exceptions to this, pregnant women with heart disease and children (see below).

Many individuals who are clinically extremely vulnerable will have some degree of immunosuppression or be immunocompromised and may not respond as well to the vaccine. Therefore, those who are clinically extremely vulnerable should continue to follow Government advice on reducing their risk of infection. Consideration has been given to vaccination of household contacts of immunosuppressed individuals. However, at this time there are no data on the size of the effect of COVID-19 vaccines on transmission. Evidence is expected to accrue during the course of the vaccine programme, and until that time the committee is not in a position to advise vaccination solely on the basis of indirect protection. Once sufficient evidence becomes available the committee will consider options for a cocooning strategy for immunosuppressed individuals, including whether any specific vaccine is preferred in this population.

Women who are pregnant

There is no known risk associated with giving non-live vaccines during pregnancy. These vaccines cannot replicate, so they cannot cause infection in either the woman or the unborn child.

Although the available data do not indicate any safety concern or harm to pregnancy, there is insufficient evidence to recommend routine use of COVID-19 vaccines during pregnancy.

JCVI advises that, for women who are offered vaccination with the Pfizer-BioNTech or AstraZeneca COVID-19 vaccines, vaccination in pregnancy should be considered where the risk of exposure to Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV2) infection is high and cannot be avoided, or where the woman has underlying conditions that put them at very high risk of serious complications of COVID-19. In these circumstances, clinicians should discuss the risks and benefits of vaccination with the woman, who should be told about the absence of safety data for the vaccine in pregnant women.

JCVI does not advise routine pregnancy testing before receipt of a COVID-19 vaccine. Those who are trying to become pregnant do not need to avoid pregnancy after vaccination.

Women who are breastfeeding

There is no known risk associated with giving non-live vaccines whilst breastfeeding. JCVI advises that breastfeeding women may be offered vaccination with the Pfizer-BioNTech or AstraZeneca COVID-19 vaccines.

The developmental and health benefits of breastfeeding should be considered along with the woman's clinical need for immunisation against COVID-19, and the woman should be informed about the absence of safety data for the vaccine in breastfeeding women.

Children less than 16 years of age

Following infection, almost all children will have asymptomatic infection or mild disease. There are very limited data on vaccination in adolescents, with no data on vaccination in younger children, at this time. The Committee advises that only those children at very high risk of exposure and serious outcomes, such as older children with severe neuro-disabilities that require residential care, should be offered vaccination with either the Pfizer-BioNTech or the AstraZeneca vaccine. Clinicians should discuss the risks and benefits of vaccination with a person with parental responsibility, who should be told about the paucity of safety data for the vaccine in children aged < 16 years. More detail on vaccination in children is set out in the Green Book – Immunisation Against Infectious Disease.

Persons with underlying health conditions

There is good evidence that certain underlying health conditions increase the risk of morbidity and mortality from COVID-19. When compared to persons without underlying health conditions, the absolute increased risk in those with underlying health conditions is considered generally to be lower than the increased risk in persons over the age of 65 years (with the exception of the clinically extremely vulnerable – see above). The Committee's advice is to offer vaccination to those aged 65 years and over followed by those in clinical risk groups aged 16 years and over. The main risk groups identified by the Committee are set out below.

- Chronic respiratory disease, including chronic obstructive pulmonary disease (COPD), cystic fibrosis and severe asthma
- Chronic heart disease (and vascular disease)
- Chronic kidney disease

- Chronic liver disease
- Chronic neurological disease including epilepsy
- Down's syndrome
- Severe and profound learning disability
- Diabetes
- Solid organ, bone marrow and stem cell transplant recipients
- People with specific cancers
- Immunosuppression due to disease or treatment
- Asplenia and splenic dysfunction
- Morbid obesity
- Severe mental illness

Other groups at higher risk, including those who are in receipt of a carer's allowance, or those who are the main carer of an elderly or disabled person whose welfare may be at risk if the carer falls ill, should also be offered vaccination alongside these groups.

Individuals within these risk groups who are clinically extremely vulnerable are discussed separately (see above). Further advice on risk groups, including clear definitions, are set out in the Green Book - Immunisation Against Infectious Disease.

Mitigating inequalities

Multiple social and societal drivers are recognised to contribute towards increased risk from COVID-19. JCVI considered it important to understand the factors underlying health inequalities in COVID-19 giving due consideration to relevant scientific evidence, ethical principles and vaccine programme deliverability. The issues considered are set out in Annex A.

There is clear evidence that certain Black, Asian and minority ethnic (BAME) groups have higher rates of infection, and higher rates of serious disease, morbidity and mortality. There is no strong evidence that ethnicity by itself (or genetics) is the sole explanation for observed differences in rates of severe illness and deaths. What is clear is that certain health conditions are associated with increased risk of serious disease, and these health conditions are often overrepresented in certain Black, Asian and minority ethnic groups. It is also clear that societal factors, such as occupation, household size, deprivation, and access to healthcare can increase susceptibility to COVID-19 and worsen

outcomes following infection. These factors are playing a large role in the inequalities being seen with COVID-19.

Good vaccine coverage in Black, Asian and minority ethnic groups will be the most important factor within a vaccine programme in reducing inequalities for this group. Prioritisation of persons with underlying health conditions (see above) will also provide for greater vaccination of BAME communities who are disproportionately affected by such health conditions.

The Committee's advice is for NHS England and Improvement, the Department of Health and Social Care, Public Health England and the devolved administrations to work together to ensure that inequalities are identified and addressed in implementation. This could be through culturally competent and tailored communications and flexible models of delivery, aimed at ensuring everything possible is done to promote good uptake in Black, Asian and minority ethnic groups and in groups who may experience inequalities in access to, or engagement with, healthcare services. These tailored implementation measures should be applied across all priority groups during the vaccination programme.

Occupational vaccination (other than frontline health and social care workers)

The Committee considered evidence on the risk of exposure and risk of mortality by occupation. Under the priority groups advised below, those over 50 years of age, and all those 16 years of age and over in a risk group, would be eligible for vaccination within the first phase of the programme. This prioritisation captures almost all preventable deaths from COVID-19, including those associated with occupational exposure to infection. As such, JCVI does not advise further prioritisation by occupation during the first phase of the programme.

Occupational prioritisation could form part of a second phase of the programme, which would include healthy individuals from 16 years of age up to 50 years of age, subject to consideration of the latest data on vaccine safety and effectiveness.

The impact of vaccine delivery on non-pharmaceutical interventions.

In a situation of constrained vaccine supply, population level protection will not be achievable immediately.

Once we have evidence of the impact of the programme on morbidity and mortality amongst vulnerable persons, the initial phase of the vaccination programme could allow the subsequent relaxation of non-pharmaceutical interventions in some sectors of the population. Government advice on non-pharmaceutical interventions should continue to be followed.

Vaccine priority groups: advice on 30 December 2020

Phase 1 – direct prevention of mortality and supporting the NHS and social care system

JCVI advises that the first priorities for the COVID-19 vaccination programme should be the prevention of mortality and the maintenance of the health and social care systems. As the risk of mortality from COVID-19 increases with age, prioritisation is primarily based on age. The order of priority for each group in the population corresponds with data on the number of individuals who would need to be vaccinated to prevent one death, estimated from UK data obtained from March to June 2020 (3)

1	Residents in a care home for older adults and their carers
2	All those 80 years of age and over Frontline health and social care workers
3	All those 75 years of age and over
4	All those 70 years of age and over Clinically extremely vulnerable individuals*
5	All those 65 years of age and over
6	All individuals aged 16 years** to 64 years with underlying health conditions which put them at higher risk of serious disease and mortality***
7	All those 60 years of age and over
8	All those 55 years of age and over
9	All those 50 years of age and over

*	Clinically extremely vulnerable individuals are described here. This advice on vaccination does not include all pregnant women or those under the age of 16 years (see above)
**	The Pfizer-BioNTech vaccine is authorised in those aged 16 years and over. The AstraZeneca vaccine is only authorised for use in those aged 18 years of age and over
***	This also includes those who are in receipt of a carer's allowance, or those who are the main carer of an elderly or disabled person whose welfare may be at risk if the carer falls ill.

It is estimated that taken together, these groups represent around 99% of preventable mortality from COVID-19.

JCVI advises that implementation of the COVID-19 vaccine programme should aim to achieve high vaccine uptake. An age-based programme will likely result in faster delivery and better uptake in those at the highest risk. Implementation should also involve flexibility in vaccine deployment at a local level with due attention to:

- mitigating health inequalities, such as might occur in relation to access to healthcare and ethnicity;
- vaccine product storage, transport and administration constraints;
- exceptional individualised circumstances; and
- availability of suitable approved vaccines e.g. for specific age cohorts.

JCVI appreciates that operational considerations, such as minimising wastage, may require a flexible approach, where decisions are taken in consultation with national or local public health experts. To be assured that outcome is maximised however, JCVI would like to see early and regular comprehensive vaccine coverage data so that the Committee can respond if high priority risk groups are unable to access vaccination in a reasonable time frame.

The next phase – further reduction in hospitalisation and targeted vaccination of those at high risk of exposure and/or those delivering key public services

As the first phase of the programme is rolled out in the UK, additional data will become available on the safety and effectiveness of COVID-19 vaccines. These data will provide the basis for consideration of vaccination in groups that are at lower risk of mortality from COVID-19. The Committee is currently of the view that the key focus for the second phase of vaccination could be on further preventing hospitalisation.

Vaccination of those at increased risk of exposure to SARS-CoV-2 due to their occupation could also be a priority in the next phase. This could include first responders, the military, those involved in the justice system, teachers, transport workers, and public servants essential to the pandemic response. Priority occupations for vaccination are considered an issue of policy, rather than for JCVI to advise on. JCVI asks that the Department of Health and Social Care consider occupational vaccination in collaboration with other Government departments.

Wider use of COVID-19 vaccines will provide a better understanding of whether they can prevent infection and onward transmission in the population. Data on vaccine impact on transmission, along with data on vaccine safety and effectiveness, will potentially allow for consideration of vaccination across the rest of the population.

As trials in children and pregnant women are completed, we will also gain a better understanding of the safety and effectiveness of the vaccines in these persons.

Further work

JCVI will continually monitor data on vaccines in development. As more Phase III data become available on candidate COVID-19 vaccines the Committee will be able to prepare further advice for policy makers in the UK.

JCVI will review data on vaccine coverage, in particular focussing on inequalities, and the impact of actions being undertaken to mitigate inequalities. Vaccine safety will be continually monitored by the MHRA and PHE, and JCVI will regularly review data on vaccine safety as the programme rolls out. Vaccine efficacy and any potential impacts on transmission will be monitored by PHE. Data will be considered at the earliest opportunity to facilitate discussions on prioritisation after the first phase of the programme.

Background

JCVI met to consider COVID-19 vaccination on 7 May, 3 June, 6 July, 1 September, 29 November, 30 November, 1 December, 22 December and

29 December 2020. Between 24 September 2020 and 22 December 2020, a JCVI COVID-19 sub-committee met most weeks to consider key issues in greater depth. The advice provided is to support the government in development of a vaccine strategy for the procurement and delivery of a vaccination programme to the population.

SARS-CoV-2 (COVID-19)

COVID-19 disease first emerged as a cause of severe respiratory infection in Wuhan, China in late 2019. The first two cases in the UK were seen in late January 2020. In March 2020, the WHO declared a SARS-Cov-2 pandemic.

In adults, the clinical picture varies widely. A significant proportion of individuals are likely to have mild symptoms and may be asymptomatic at the time of diagnosis. Symptoms are commonly reported as a new onset of cough and fever, but may include headache, loss of smell, nasal obstruction, lethargy, myalgia, rhinorrhoea, taste dysfunction, sore throat, diarrhoea, vomiting and confusion. Fever may not be reported in all symptomatic individuals. Progression of disease, multiple organ failure and death will occur in some individuals.

As with other Coronaviruses, SARS-CoV-2 is an RNA virus which encodes four major structural proteins. Most vaccine candidates focus on immunisation with the spike glycoprotein, which is the main target for neutralising antibodies following infection. Neutralising antibodies that block viral entry into host cells by preventing interaction between the spike protein and the host cell are expected to be protective.

Pfizer-BioNTech vaccine

The Pfizer/BioNTech vaccine is a lipid nanoparticle-formulated mRNA vaccine. The mRNA encodes the SARS-CoV-2 full length spike protein. The mRNA in the vaccine is translated and transcribed by the body to produce the spike protein. The protein then acts as an intracellular antigen to stimulate the immune response. The mRNA in the vaccine is normally degraded within a few days and cannot incorporate into the host genome. Data from the Pfizer/BioNTech vaccine trials undertaken in over 40,000 individuals indicate high vaccine efficacy, with no serious safety concerns observed.

AstraZeneca COVID-19 vaccine

The AstraZeneca COVID-19 vaccine uses a replication deficient chimpanzee adenovirus as a vector that encodes the full-length SARS-CoV2 spike protein. Chimpanzee adenoviruses are non-enveloped viruses, meaning that the glycoprotein antigen is not present on the surface of the vector, but is only expressed at high levels once the vector enters the target cells. Genes are deleted from the adenovirus to render the virus replication incompetent, and to enhance immunogenicity. Once the vector is in the nucleus, mRNA encoding the spike protein is produced that then enters the cytoplasm. This leads to translation of the target protein which acts as an intracellular antigen. Data from vaccine trials undertaken indicate high vaccine efficacy, with no serious safety events related to the vaccine.

Other vaccines in development

Other COVID-19 vaccines are in development, with some in late stage trials. When sufficient data on vaccine safety and efficacy are available, these will be considered by JCVI and this statement will be updated.

References

1. National COVID-19 surveillance reports
2. Williamson EJ, Walker AJ, Bhaskaran K, *et al.* Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020 Aug;584(7821):430-436.
3. Clift AK, Coupland CAC, Keogh RH *et al*. Living risk prediction algorithm (QCOVID) for risk of hospital admission and mortality from coronavirus 19 in adults: national derivation and validation cohort study. BMJ. 2020 Oct 20;371:m3731.
4. Coronavirus (COVID-19) related deaths by occupation, before and during lockdown, England and Wales: deaths registered between 9 March and 30 June 2020, Office for National Statistics
5. Meyerowitz EA, Richterman A, Gandhi RT *et al*. Transmission of SARS-CoV-2: A Review of Viral, Host, and Environmental Factors. Ann Intern Med. 2020 Sep 17:M20-5008.
6. Lally C. COVID-19 and occupational risk

7. Mutambudzi M, Niedzwiedz C, Macdonald *et al*. Occupation and risk of severe COVID-19: prospective cohort study of 120,075 UK Biobank participants medRxiv 2020.05.22.20109892; doi: https://doi.org/10.1101/2020.05.22.20109892
8. Public Heath England report - Beyond the data: Understanding the impact of COVID-19 on BAME groups
9. Voysey M, Clemens SAC, Madhi SA, *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:
10. Polack FP, Thomas SJ, Kitchin N *et al*. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020 Dec 10.
11. Jackson LA, Anderson EJ, Rouphael NG *et al*. An mRNA Vaccine against SARS-CoV-2 - Preliminary Report. N Engl J Med. 2020 Nov 12;383(20):1920-1931.
12. Corbett KS, Flynn B, Foulds KE *et al*. Evaluation of the mRNA-1273 Vaccine against SARS-CoV-2 in Nonhuman Primates. N Engl J Med. 2020 Oct 15;383(16):1544-1555.
13. Anderson EJ, Rouphael NG, Widge AT *et al*. mRNA-1273 Study Group. Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Older Adults. N Engl J Med. 2020 Sep 29.
14. van Doremalen N, Lambe T, Spencer A et al. ChAdOx1 nCoV-19 vaccine prevents SARS-CoV-2 pneumonia in rhesus macaques. Nature. 2020 Jul 30.
15. Folegatti PM, Ewer KJ, Aley PK *et al*. Oxford COVID Vaccine Trial Group. 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 Aug 15;396(10249):467-478.
16. Ramasamy M, Minassian A, Ewer K *et al*. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. Lancet Nov 18 2020.
17. Mulligan MJ, Lyke KE, Kitchin N *et al*. Phase 1/2 study of COVID-19 RNA vaccine BNT162b1 in adults. Nature. 2020 Aug 12.

18. Sahin U, Muik A, Derhovanessian E *et al*. Concurrent human antibody and T H 1 type T-cell responses elicited by a COVID-19 RNA vaccine. medRxiv [Preprint]. 2020 July 20.
19. Walsh EE, Frenck R, Falsey AR *et al*. RNA-Based COVID-19 Vaccine BNT162b2 Selected for a Pivotal Efficacy Study. medRxiv [Preprint]. 2020 Aug 20.
20. Keech C, Albert G, Cho I et al. Trial of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine. N Engl J Med. 2020 Sep 2.
21. Moore S, Hill E, Dyson L et al. Modelling optimal vaccination strategy for SARS-CoV-2 in the UK. MedRxiv 2020.09.22.20194183; doi: https://doi.org/10.1101/2020.09.22.20194183
22. Ladhani SN, Chow JY, Janarthanan R et al. Investigation of SARS-CoV-2 outbreaks in six care homes in London, April 2020. EClinicalMedicine. 2020 Sep 9:100533.
23. Ladhani SN, Chow JY, Janarthanan R et al. London Care Home Investigation Team. Increased risk of SARS-CoV-2 infection in staff working across different care homes: enhanced CoVID-19 outbreak investigations in London care Homes. J Infect. 2020 Jul 29;81(4):621–4.
24. Graham NSN, Junghans C, Downes R, et al. SARS-CoV-2 infection, clinical features and outcome of COVID-19 in United Kingdom nursing homes. J Infect. 2020 Sep;81(3):411-419.
25. Vivaldi 1: coronavirus (COVID-19) care homes study report
26. https://www.gov.uk/government/publications/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19

31 December 2020

A letter to the profession from the UK Chief Medical Officers, regarding the UK COVID-19 vaccination programmes

Dear Colleagues,

Thank you for your remarkable commitment to the health of our nation in the most difficult of circumstances; the COVID-19 pandemic is undoubtedly the biggest health crisis in a generation, and certainly in our professional lifetimes. We are at a critical point in the pandemic as the emergence of a novel variant of SARS-CoV-2 with a markedly higher growth rate is rapidly shifting the epidemiological curve in the wrong direction across much of the UK in the middle of winter.

Authorisation of first the Pfizer and now the AZ vaccine (AZD1222) for use is incredibly welcome. Both are highly effective vaccines from clinical trial data and are anticipated to have sizeable effects on preventing severe disease and hospitalisation. Getting vaccines deployed as rapidly as possible into as many older, clinically vulnerable patients, and also frontline health and social care workers is essential. The Joint Committee on Vaccination and Immunisation (JCVI) has put forward a prioritisation scheme, attached, of which you will all be aware.

We wanted to lay out to you the scientific and public health rationale for the dosing schedule for the AZ vaccine and the change to the dosing schedule for the second dose of the Pfizer vaccine. As with all decisions during this pandemic it is about balance of risks and benefits.

1) We have to ensure that we maximise the number of eligible people who receive the vaccine. Currently the main barrier to this is vaccine availability, a global issue, and this will remain the case for several months and, importantly, through the critical winter period. The availability of the AZ vaccine reduces, but does not remove, this major problem. Vaccine shortage is a reality that cannot be wished away.
2) We are confident that based on publicly available data as well as data available to the JCVI, the statutory independent body, that the first dose of either Pfizer or AZ vaccine provides substantial protection within 2-3 weeks of vaccination for clinical disease, and in particular severe COVID disease. The JCVI has issued a new evidence statement today and this is attached. [1]
3) The second vaccine dose is likely to be very important for duration of protection, and at an appropriate dose interval may further increase vaccine efficacy. In the short term, the additional increase of vaccine efficacy from the second dose is likely to be modest; the great majority of the initial protection from clinical disease is after the first dose of vaccine.[1]
4) In terms of protecting priority groups, a model where we can vaccinate twice the number of people in the next 2-3 months is obviously much more preferable in public health terms than one where we vaccinate half the number but with only slightly greater protection.
5) This is why the JCVI has recommended that first doses of vaccine are prioritised for as many people as possible on the Phase 1 JCVI priority list, in advance of second doses which will subsequently provide more assured longer-term protection. It is a classic public health approach centred on doing as much good for as many people in the shortest possible

[1] The JCVI statement can be accessed through the JCVI minutes, available on GOV.UK https://www.gov.uk/government/groups/joint-committee-on-vaccination-and-immunisation#minutes

Direct link to statement: https://app.box.com/s/uwwn2dv4o2d0ena726gf4403f3p2acnu

timeframe, within the available vaccine supplies, against a background of immediate disease activity and still high population sero-susceptibility (despite the disease burden seen).

6) The JCVI is confident 12 weeks is a reasonable dosing interval to achieve good longer-term protection.

7) The position is strongly supported by the UK Chief Medical Officers on public health grounds of maximising benefit.

We recognise that the request to re-schedule second appointments is operationally very difficult, especially at short notice, and will distress patients who were looking forward to being fully immunised. However, we are all conscious that for every 1000 people boosted with a second dose of COVID-19 vaccine in January (who will as a result gain marginally on protection from severe disease), 1000 new people can't have substantial initial protection which is in most cases likely to raise them from 0% protected to at least 70% protected. Whilst the NHS, through all of your work, has so far vaccinated over 1 million UK patients with a first dose, approximately 30 million UK patients and health and social care workers eligible for vaccination in Phase 1 remain totally unprotected and many are distressed or anxious about the wait for their turn. These unvaccinated people are far more likely to end up severely ill, hospitalised on in some cases dying without vaccine. Halving the number vaccinated over the next 2-3 months because of giving two vaccines in quick succession rather than with a delay of 12 weeks does not provide optimal public health impact.

We have to follow public health principles and act at speed if we are to beat this pandemic which is running rampant in our communities and we believe the public will understand and thank us for this decisive action. We hope this has your support.

We attach a statement from the JCVI laying out their thinking in more detail.

Once again, many thanks.

Yours sincerely,

Llywodraeth Cymru
Welsh Government

Dr. Frank Atherton
Chief Medical Officer,
Wales

Department of Health
An Roinn Sláinte
Männystrie O Poustie
www.health-ni.gov.uk

Dr. Michael McBride
Chief Medical Officer,
Northern Ireland

The Scottish Government
Riaghaltas na h-Alba

Dr. Gregor Smith
Chief Medical Officer,
Scotland

Department of Health & Social Care

Prof. Chris Whitty
Chief Medical Officer,
England

Prof. Jonathan Van-Tam
Deputy Chief Medical Officer,
England

Bwrdd Iechyd Prifysgol
Hywel Dda
University Health Board

Ein cyf/Our ref:
Gofynnwch am/Please ask for: Dr Phil Kloer
Rhif Ffôn /Telephone: 01267 239670
E-bost/E-mail: Philip.Kloer@wales.nhs.uk
Dyddiad/Date: 12th January 2021

Swyddfeydd Corfforaethol, Adeilad Ystwyth
Hafan Derwen, Parc Dewi Sant, Heol Ffynnon Job
Caerfyrddin, Sir Gaerfyrddin, SA31 3BB

Corporate Offices, Ystwyth Building
Hafan Derwen, St Davids Park, Job's Well Road,
Carmarthen, Carmarthenshire, SA31 3BB

Dr. Chris James
Chair, Local Negotiating Committee
Hywel Dda UHB

By email: Christopher.James@wales.nhs.uk

Dear Chris,

Thank you for your email on 5th January We really appreciate just how much concern the announcement from the JCVI and four CMOs has caused amongst some of our staff who have received their first dose of the Pfizer vaccine and were expecting the second dose to be given shortly. We are sorry that this has caused additional stress, whether the concerns are in relation to getting additional protection against the virus, to allow colleagues to participate more fully in the work place, or other issues, and we know it is at a time when staff are under additional pressure due to how busy our services are.

Welsh Government has confirmed that this is a policy decision and there could be legal implications for the Health Board if we were not to follow the national policy. We are therefore obliged to prioritise the vaccines for first dose rather than the second dose vaccination as was previously planned, and do not have a choice in this matter unless further directives are provided.

There are a number of documents that set out the evidence in favour of the decision, and we have attached some of these. We have also included the link below to a video from Public Health Wales and to statements from the Academy of Medical Royal Colleges and British Society of Immunologists and the Royal Pharmaceutical Society, which help explain the thinking behind the decision and their support for the decision. However, we do recognise that there are those who have a different view.

- **Academy of Medical Royal Colleges** https://www.aomrc.org.uk/statements/covid-19-vaccination-and-second-doses-academy-statement/
- **British Society of Immunologists** https://www.immunology.org/policy-and-public-affairs/briefings-and-position-statements/COVID-19-vaccine-dosing-schedules
- **Royal Pharmaceutical Society advice** https://www.rpharms.com/resources/pharmacy-guides/coronavirus-covid-19/covid-19-vaccines/vaccine-dose-interval-changes
- **Dr Richard Roberts (PHW) video** Covid-19 vaccinations dosage intervals on Vimeo

The statements and information contained highlight that the 52.4% efficacy figure includes cases of COVID-19 where exposure could have occurred before the vaccination. Looking at the data for days 15-21, a full incubation period after vaccination, efficacy of a single dose of vaccine against symptomatic COVID-19 is 89%.

The CMOs also outline that whilst there is individual gain in prioritising second doses, the advice is that the first dose gives good protection and prioritising being able to give more first doses will protect the greatest number of at risk people overall in the shortest possible time.

We continue to have discussions with Welsh Government, and have highlighted the strength of feeling locally and raising the concerns that you and other colleagues have written about. We are holding a meeting for all staff on Teams this week, which we will attend to update on the vaccination programme and listen to staff concerns; Thursday 14th January 5:30 – 6:30pm. In addition, we will be discussing the issue at the Health Board's Ethics Panel on 13th January 2021 and at the next Health Board meeting on 28th January 2021. The Public Board meeting will be live streamed; a link to the Teams Meeting is: MS Teams live link to HDdUHB Public Board meeting 9.30am 28th January 2021

We know that this announcement has come at a difficult time when colleagues have been working tirelessly in caring for people affected by the Covid pandemic, at the same time as protecting themselves from it; this will have caused additional anxiety. We are working to ensure that we are able to offer second vaccines as soon as is possible, and in keeping with the ethos outlined, where first doses must be prioritised.

The 12-week interval between doses is the maximum and not a target, and as soon as we have worked through the initial prioritised groups in line with the JCVI advice, we will be calling staff for second vaccinations, earlier than 12 weeks if we are given the freedom to do so.

Yours sincerely

Dr Phil Kloer
Medical Director / Deputy CEO

Mr Steve Moore
CEO

Urgent update on COVID vaccine arrangements

1 January 2021

I'm taking the unusual step of writing to you on New Year's Day following NHS England's instruction to cancel second Pfizer doses from Monday in order to retain stocks to give first doses to a larger number of people.

This is not the start to 2021 we would have wanted, especially when GP workloads are already at unbelievable levels and you're stretched to your limits.

I understand how frustrating this is for you and your teams, especially when you were following the original guidance and supporting your patients in making these appointments. I also understand that this is not just going to be a case of cancelling some patients and then rebooking a new cohort for their first jab – and that the task of explaining these changes to vulnerable and elderly patients cannot be underestimated.

I want to share more information about the **case put forward by the Joint Committee for Vaccination and Immunisation, supported by the four Chief Medical Officers of the UK (940 KB PDF)**. It clearly sets out the reasons that have swung the decision for the new arrangements.

This might feel uncomfortable and it will be hard work, but it is the right thing to do for our patients and the health of the wider population.

So much of what we do in general practice is in the interests of our patients' long-term health and lives but these are effective interventions with immediate impact.

The current infection surge – and its impact on the NHS and patients' lives - makes it imperative to protect as many people as possible, as quickly as possible. People will still need to receive two doses but releasing the 'reserved for second dose' vaccine will release, we are told, close to a million more doses, which means we can give more first doses to higher numbers of our vulnerable patients and get healthcare workers vaccinated more quickly.

The modelling shows you need to vaccinate 250 people aged over 80 with the first dose in order to save one life. The decision to delay the second dose is particularly important when we can't guarantee that the Oxford/AstraZeneca vaccine will be available at high volumes straight away.

England Deputy Chief Medical Officer Jonathan Van-Tam has also urged a closer look at protection/effectiveness data - the cited efficacy rates of 54% for the first dose of the Pfizer vaccine include infections in the first 9-10 days which would have happened before the vaccine became effective. Remove these from the data and first dose protection for the Pfizer vaccine is around 89-91%, only marginally below that for two doses (though we are told the protection will last for longer with two doses).

I hope this provides you with more background on the issues. NHS England's guidance does allow for some clinical discretion for practices to go ahead with second vaccinations where necessary and, of course, there will be some who decide to do this and their decision must be respected.

The next few weeks were always going to be difficult and we now have an additional hurdle to overcome, but I really hope you can persevere because the ambitious COVID vaccination programme will not be successful without general practice playing its part.

Whilst it may not feel like it from where we're standing at the moment, we are making progress - as demonstrated by the announcement of the Oxford/AstraZeneca vaccine and the brilliant work by practices over the country in delivering the Pfizer vaccine over the last few weeks.

We know we need a larger workforce in order to achieve what is necessary and so the College is also campaigning hard to overcome the unnecessary red tape that thousands of retired GPs are facing in trying to return to the frontline.

I've written this opinion piece for today's Daily Mail. We had no say over the headline but I hope the article itself conveys the important message that at a time when GPs need all the support they can get, it's ridiculous that the skills and expertise of highly qualified doctors are being under-used or going to waste.

On behalf of the College, I thank you again for everything you are doing for your patients and for our profession.

Very best wishes for the year ahead, the NHS will overcome this virus - thanks in large part to the contribution of general practice and the efforts of hardworking and dedicated GPs.

Post written by

Professor Martin Marshall, Chair of RCGP Council

Professor Martin Marshall is Chair of the Royal College of General Practitioners and a GP in Newham, East London. He is also Professor of Healthcare Improvement at UCL in the Department of Primary Care and Population Health. Previously he was Programme Director for Population Health and Primary Care at UCLPartners (2014-2019), Director of Research & Development at the Health Foundation (2007-2012), Deputy Chief Medical Officer for England and Director General in the Department of Health (2006-2007), Professor of General Practice at the University of Manchester (2000-2006) and a Harkness Fellow in Healthcare Policy.

He is a Fellow of the Royal College of Physicians of London and of the Faculty of Public

Health Medicine and was a non-executive director of the Care Quality Commission until 2012. He has advised governments in Singapore, Egypt, Canada and New Zealand, has over 230 publications in the field of quality improvement and health service redesign and his primary academic interest is in maximising the impact of research on practice. In 2005 he was awarded a CBE in the Queen's Birthday Honours for Services to Health Care.

A co-founder and driving force of the Rethinking Medicine movement, Martin has a passionate commitment to the values of the NHS, patient care and ensuring the GP voice is central in a time of great change. When he's not working, he likes being outside, preferably on a mountain or a coastal path with his wife Sue and their puppy.

Ethics Panel Response to Strategic Ethical Question (discussed at Panel Meeting 13/01/2021)

"Advise the Board on the ethical issues that arise and need to be taken into account in its decision making relating to the change in advice from the JCVI and Joint UK CMOs to defer the 2nd dose of Pfizer vaccine from 3-4 weeks to 12 weeks"

National Principles	Panel Responses
Respect	➢ Despite the decision being made nationally, many staff feel undervalued, unsupported and that the risks they are being exposed to in these challenging times are not being respected. ➢ Those who went to have the first dose of the vaccine were told they would have the second dose 28 days later. Respect for autonomous decision making in relation dosing schedule has been taken away for those who consented to the first dose before the change in National policy and the implied promise has weight and could be considered an ethical breach.
Minimising the overall harm from the pandemic	➢ The CMOs letter clearly states the reason for delaying the second dose is to "protect the greatest number of at-risk people overall in the shortest possible time". ➢ At the peak of a pandemic, which is our current situation, there is a strong argument for providing protection to the largest number of people as rapidly as possible, and therefore reduce most mortality and harm ➢ It is unclear as to how much of the individual benefit derived from having the vaccine will be lost as a consequence of delaying the second dose. It is therefore difficult to assess the impact upon the risk/benefit balance.
Fairness	➢ It could be argued that giving some significant protection to many rather than maximum protection to a few is fair however, the levels of risk to staff from Covid varies. Relative risk of exposure to Covid is not always easily defined. For example, ITU staff are at a high risk but are protected by PPE, whereas there may be other staff, such as community-based staff, who are not knowingly dealing with the virus and may be just as much at risk, especially when considering that they are unlikely to have the same level of PPE. ➢ If discretion was available then the panel considered how at risk staff groups could be prioritised. It was agreed that there was no system of prioritisation that would satisfy everyone, but that the staff risk assessment would be a helpful indicator ➢ If a 2nd dose is given to staff who are shielding, including those who are willing and able to participate more fully in the work if they have the 2nd dose, then this offers benefit not only to the individual but also potentially to the public through their work, and also to their colleagues where staffing is fragile. This benefit, over and above individual benefit suggests that shielding staff who are willing and able to return to work could be prioritised if discretion was permitted. Caution was raised that there was the potential for individuals to feel pressure in this situation to return to work, and potential other issues that might arise from this strategy. ➢
Working Together	➢ The 4 CMOs and the scientific advisors worked together to produce the national guidance but further engagement with stakeholders was lacking. This decision has been perceived very much as a top down decision may with no consultation with affected staff groups. ➢ Information from the ethics panel discussions should be shared with other forums and professional colleagues, including the CMO and other advisors, to help inform any further changes in national policy.
Reciprocity	➢
Keeping things in proportion	➢ We still have no curative treatments for COVID-19 and there are untold direct and indirect health and economic consequences worldwide that will occur for decades. ➢ This is the biggest public health emergency since the 1918 Spanish Flu. Improving the efficiency of the vaccination programme would enable people to move through the system much faster and everyone would be able to have the second doses within shorter timescales. ➢ Despite Pfizer's recommendation against the new dosing strategy, it is clear that Pfizer would want as many vaccines to be purchased as possible. It was raised that it may turn out that only one vaccine is needed so their recommendations may not be governed by evidence. ➢ Flu vaccinations are around 50% effective – therefore getting more people vaccinated with 1 dose of Covid vaccine at 50% may be more proportionate than fewer vaccinated at a higher efficacy rate, but with risks of more people becoming ill overall. ➢ Views were expressed that vaccines are safe and protective when done according to scientific

	research and MHRA/manufacturer recommendations, although in this case the recommendations deviate from each other
Flexibility	➢ It is ethically impermissible to waste or dispose of any vaccinations and so, in the event that there may be spare vaccines, perhaps due to individuals not turning up for appointments, staff should prioritise as best they can at the time. A reserve list of higher risk individuals should be compiled for the vaccination staff to call upon ➢ Employers have a duty to give the second dose of the vaccine within the 12-week period. In the absence of national guidance and operational clarity, where an individual is unavailable during the 11th- 12th week to have the second dose for genuine reasons of exceptionality, the decision to allow the second dose to be administered earlier, but as close to the advised time as possible, should be made. There is no evidence as to the efficacy of the vaccine if it is given after 12 weeks and this could lead to a need to restart the vaccine schedule and thus waste the first dose that has already been given.
Good decision-making	➢ All decisions should comply with the law and existing ethical and clinical guidance. ➢
Resources	➢ It is ethically impermissible to waste or dispose of any vaccinations. ➢ One of the most important resource considerations we are facing in combatting Covid presently is a lack of frontline staff. The decision to vaccinate twice as many may ameliorate the worst of the winter bed crisis and help to 'flatten the curve' (even to achieve limited herd immunity for a short time), but not providing maximum protection to our most frontline staff could lead to increased workforce pressures through sickness, isolation, shielding and stress. ➢ Ethically, the Health Board needs to be comfortable with a decision where a limited resource, such as the vaccine, is used to control spread of Covid amongst the general population when other options, such as lockdown, are effective. Frontline staff cannot stay at home so have no other protective option apart from Infection control measures, PPE and vaccination