

Changes in COVID-19-related mortality across key demographic and clinical subgroups

Protocol Amendment

The original protocol for this study was written in January 2022. Due to data restrictions at that time, the study defined three waves. In this amendment, we add two waves to the protocol: wave 3, Omicron and wave 4. We additionally describe a descriptive analysis using data on vaccination status.

Additional waves

The following start dates and end dates will be used to define two additional waves:

Wave 3, Omicron: 15 December 2021 - 29 April 2022

Wave 4: 24 June 2022 - 3 August 2022

These dates are chosen based on reported R values and growth rates by the UK Health Security Agency [1].

The start date of wave 3 (Omicron) will be 15 December 2021 as Omicron became the dominant variant on that date (see original protocol). The end date of wave 3 (Omicron) will be 29 April 2022 as in the week commencing that date, the R value was below 1 (0.7;0.9) and the growth rate was negative (-6;-3).

29 April 2022 was not the first date on which an R value of below 1 and a negative growth rate were reported since the start of wave 3 (28 May 2021). On 28 January 2022, reports show that the R value was below 1 (0.7;0.9) and the growth rate was negative (-6;-2). However, the R value was above 1 and the growth rate was positive again one week after 28 January 2022 (4 February 2022). Because the R value stayed below 1 and the growth rate stayed negative for nearly 2 months after 29 April 2022, we will use 29 April as the end date of wave 3 (Omicron). Of note, to our knowledge, no values were reported between 27 May and 24 June 2022.

The start date of wave 4 will be 24 June 2022. The end date of wave 4 will be 3 August 2022, as in the week commencing that date, the R value was not above 1 (0.8;1.0) and the growth rate was negative (-5;-2).

COVID-19 genomic surveillance data of the Wellcome Sanger institute [2] show that (approximately) the week after 12 February 2022, Omicron BA.2 became more prevalent than Omicron BA.1.1. Omicron B.1.1.529 and B.A.1.1 were the dominant variants before 12 February 2022 (from 15 December 2021 onwards). The week after 4 June 2022, Omicron BA.5 became more prevalent than Omicron BA.2. The week after 18 June 2022, Omicron BA.4 became more prevalent than Omicron BA.2 (while Omicron BA.5 was still more prevalent than Omicron BA.4). We can therefore conclude that in the defined period for wave

3, Omicron, Omicron B.1.1.529, BA.1 and BA.2 were dominant. In the defined period for wave 4, Omicron BA.4 and BA.5 were dominant.

Vaccination analysis

We hypothesised that the observed changes in absolute and relative death rates are likely to be largely driven by vaccination coverage. The patterns seen in the fold changes for wave 3 vs wave 1 in COVID-19-related mortality were largely following the same patterns as the prioritisation of vaccines in several subgroups. For example, larger falls were observed in death rates in the older age groups compared to younger age groups in wave 3. In contrast, in some population subgroups, death rates remained stable *despite* high known vaccination coverage (e.g. the immunocompromised).

Vaccination was introduced midway through wave 2 and prioritised to the high risk groups and was offered to other groups in a stepwise manner. Figure S1 provides an overview of the eligibility criteria for the first vaccination dose. As a consequence, vaccination status is a complex covariate to measure; it is time varying with people having different numbers of doses at different times; and the time since the most recent dose also varying. Our study was set out to compare absolute and relative COVID-19-related mortality risks throughout the course of the first three years of the pandemic in clinical and demographic population subgroups. Changing immunity levels via vaccination (and/or previous infections) are inherent to these population subgroups. Determining the cause of the vulnerability of specific groups (e.g. the immunocompromised) is beyond our scope and better tackled in a focused study on e.g. vaccination effectiveness. That is, thorough investigations of the *impact* of vaccination on COVID-19-related mortality in different subgroups are best considered using subgroups analyses in appropriately designed vaccine effectiveness studies.

To contextualise immunity levels by vaccination status during each wave, we will add the following descriptives to our study. Starting from wave 2, we will include a breakdown of vaccination status at the start of each wave (not for wave 2) and the end of follow-up (end of the wave or COVID-19-related death or death by other causes, whichever came first). We will additionally calculate the vaccination-dose incidence for each wave starting from wave 2 by counting the number of individuals on each dose per 1,000 person-years (wave 2: 0, 1, 2 or 3 doses; wave 3 (Delta): 0, 1, 2, 3 or 4 doses; wave 3 (Omicron) and wave 4: 0, 1, 2, 3, 4 or 5 doses). We will use a 2-week lag before updating vaccination-dose status. Individuals with more than the maximum number of doses will be classified as having had 3, 4 or 5 doses in wave 2, wave 3 (Delta) and wave 3 (Omicron) or wave 4, respectively. The maximum number of doses in our categorisation was based on the theoretical maximum of doses in the immunocompromised and non-immunocompromised. The initial SARS-CoV-2 vaccination course from December 2020 entailed 3 doses for the immunocompromised and 2 doses for the non-immunocompromised. In September 2021, a booster dose was offered to all individuals aged 16 years and over, and in February 2022, a seasonal spring booster was offered to some people, including those aged 50 years or over, those at high risk from COVID-19 or who are pregnant, and frontline health and social care workers [3].

References

- [1] 'The R value and growth rate', *GOV.UK*.
<https://www.gov.uk/guidance/the-r-value-and-growth-rate> (accessed Aug. 24, 2022).
- [2] 'Lineages (raw) | COVID-19 Genomic Surveillance – Wellcome Sanger Institute'.
https://covid19.sanger.ac.uk/lineages/raw?cases_type=line&show=A%2CB%2CB.1.1.7%2CB.1.617.2%2CB.1.1.529%2CBA.1.1%2CBA.2%2CBA.4%2CBA.5 (accessed Aug. 24, 2022).
- [3] 'How to get a booster dose of the coronavirus (COVID-19) vaccine', *nhs.uk*, Feb. 21, 2022.
<https://www.nhs.uk/conditions/coronavirus-covid-19/coronavirus-vaccination/how-to-get-a-coronavirus-vaccine/how-to-get-a-booster-dose/> (accessed Dec. 05, 2022).
- [4] E. M. F. Horne *et al.*, 'Waning effectiveness of BNT162b2 and ChAdOx1 covid-19 vaccines over six months since second dose: OpenSAFELY cohort study using linked electronic health records', *BMJ*, vol. 378, p. e071249, Jul. 2022, doi: 10.1136/bmj-2022-071249.

Supplementary Material

Supplementary Methods

Supplementary Table 1: Vaccination phases and priority groups for primary vaccination advised by the Joint Committee on Vaccination and Immunisation

Vaccination phase	Priority group	Risk group
1	1	Residents in a care home for older adults
		Staff in a care home for older adults
	2	All those 80 years of age and over
		Frontline health and social care workers
	3	All those 75 years of age and over
	4a	All those 70 years of age and over
	4b	Individuals aged 16 to 69 in a high risk group ^a
	5	All those 65 years of age and over
	6	Individuals aged 16 to 65 years in an at-risk group ^a
2	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
	10	All those 40 years of age and over
	11	All those 30 years of age and over
	12	All those 18 years of age and over

^a See COVID-19: the green book, chapter 14a for definitions of the high-risk and at-risk groups.

Supplementary Table 2: Eligibility dates for first vaccine dose

Grouped eligibility date	Exact eligibility date	JCVI groups	Age range	Reference
2020-12-08	2020-12-08	1, 2	-	source
2021-01-18	2021-01-18	3, 4a, 4b	-	source
2021-02-15	2021-02-15	5, 6	-	source
2021-02-22	2021-02-22	7	64	source
2021-03-01	2021-03-01	7	60-63	source
2021-03-08	2021-03-08	8	56-59	source
	2021-03-09	8	55	source
2021-03-19	2021-03-19	9	50-54	source
2021-04-13	2021-04-13	10	45-49	source
2021-04-26	2021-04-26	10	44	source
	2021-04-27	10	42-43	source
	2021-04-30	10	40-41	source
2021-05-13	2021-05-13	11	38-39	source
	2021-05-19	11	36-37	source
2021-05-21	2021-05-21	11	34-35	source
	2021-05-25	11	32-33	source
	2021-05-26	11	30-31	source
2021-06-08	2021-06-08	12	25-29	source
2021-06-15	2021-06-15	12	23-24	source
	2021-06-16	12	21-22	source
	2021-06-18	12	18-20	source

JCVI: Joint Committee on Vaccination and Immunisation

Figure S1. Overview of eligibility criteria for first vaccine dose, copied from Horne et al. [4].