Severe COVID-19 outcomes after full vaccination of primary schedule and initial boosters: pooled analysis of national prospective cohort studies of 30 million individuals in England, Northern Ireland, Scotland, and Wales

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Summary

Background Current UK vaccination policy is to offer future COVID-19 booster doses to individuals at high risk of serious illness from COVID-19, but it is still uncertain which groups of the population could benefit most. In response to an urgent request from the UK Joint Committee on Vaccination and Immunisation, we aimed to identify risk factors for severe COVID-19 outcomes (ie, COVID-19-related hospitalisation or death) in individuals who had completed their primary COVID-19 vaccination schedule and had received the first booster vaccine.

Methods We constructed prospective cohorts across all four UK nations through linkages of primary care, RT-PCR testing, vaccination, hospitalisation, and mortality data on 30 million people. We included individuals who received primary vaccine doses of BNT162b2 (tozinameran; Pfizer–BioNTech) or ChAdOx1 nCoV-19 (Oxford–AstraZeneca) vaccines in our initial analyses. We then restricted analyses to those given a BNT162b2 or mRNA-1273 (elasomeran; Moderna) booster and had a severe COVID-19 outcome between Dec 20, 2021, and Feb 28, 2022 (when the omicron (B.1.1.529) variant was dominant). We fitted time-dependent Poisson regression models and calculated adjusted rate ratios (aRRs) and 95% CIs for the associations between risk factors and COVID-19-related hospitalisation or death. We adjusted for a range of potential covariates, including age, sex, comorbidities, and previous SARS-CoV-2 infection. Stratified analyses were conducted by vaccine type. We then did pooled analyses across UK nations using fixed-effect meta-analyses.

Findings Between Dec 8, 2020, and Feb 28, 2022, 16 208 600 individuals completed their primary vaccine schedule and 13 836 390 individuals received a booster dose. Between Dec 20, 2021, and Feb 28, 2022, 59 510 (0·4%) of the primary vaccine group and 26 100 (0·2%) of those who received their booster had severe COVID-19 outcomes. The risk of severe COVID-19 outcomes reduced after receiving the booster (rate change: 8·8 events per 1000 person-years to 7·6 events per 1000 person-years). Older adults (≥80 years *vs* 18–49 years; aRR 3·60 [95% CI 3·45–3·75]), those with comorbidities (≥5 comorbidities *vs* none; 9·51 [9·07–9·97]), being male (male *vs* female; 1·23 [1·20–1·26]), and those with certain underlying health conditions—in particular, individuals receiving immunosuppressants (yes *vs* no; 5·80 [5·53–6·09])—and those with chronic kidney disease (stage 5 *vs* no; 3·71 [2·90–4·74]) remained at high risk despite the initial booster. Individuals with a history of COVID-19 infection were at reduced risk (infected ≥9 months before booster dose *vs* no previous infection; aRR 0·41 [95% CI 0·29–0·58]).

Interpretation Older people, those with multimorbidity, and those with specific underlying health conditions remain at increased risk of COVID-19 hospitalisation and death after the initial vaccine booster and should, therefore, be prioritised for additional boosters, including novel optimised versions, and the increasing array of COVID-19 therapeutics.

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See **Comment** page 1282

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Introduction

COVID-19 vaccination programmes have been rolled out globally as the key strategy to control and minimise the impact of the COVID-19 pandemic.[1] Three vaccines have mainly been used in the UK—namely, BNT162b2 (tozinameran; Pfizer–BioNTech), ChAdOx1 nCoV-19 (Oxford–AstraZeneca), and mRNA-1273 (elasomeran; Moderna).[2] In the UK, the primary vaccination schedule is

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Research in context

Evidence before this study

We searched PubMed, medRxiv, and SSRN on June 27, 2022, for English studies investigating severe COVID-19 outcomes after vaccination using the search terms "COVID-19 breakthrough infections (MeSH)", "COVID-19 vaccines (MeSH)", and "COVID-19 (MeSH)". Our searches identified 133 studies. Previous evidence has consistently shown that vaccination with the first booster dose reduces the risk of SARS-CoV-2 infection, and COVID-19-related hospitalisation and death. An analysis of national data from Israel estimated first booster dose of BNT162b2 mRNA vaccine effectiveness of 92% (95% CI 82–97) against severe COVID-19. Another national study from Qatar in the omicron era estimated vaccine effectiveness of BNT162b2 against severe COVID-19 as 77% (95% CI 56–88). We have previously reported on risk factors for severe COVID-19 outcomes after first and second vaccine doses of the primary schedule, but there is little population-based evidence about the factors associated with COVID-19-related hospitalisation and death after the first booster dose in the omicron era.

Added value of this study

We found an increased risk of severe COVID-19 outcomes beginning 10 weeks after completing the primary vaccination schedule, with this risk reducing after the first booster dose. This UK-wide analysis, in addition to confirming some of the previously identified risk factors for severe COVID-19 outcomes such as older age and use of immunosuppressants, has also highlighted additional risk factors, such as chronic kidney disease, neurological disorders, heart failure, and chronic obstructive pulmonary disease. Most importantly, we demonstrate a substantive increased risk associated with high multimorbidity.

Implications of all the available evidence

As the pandemic continues to evolve, vaccination programmes and mitigation strategies need to evolve to prioritise those at highest risk of severe COVID-19 outcomes. This UK-wide population-based investigation has found that, after the first vaccine booster, older people, those with high multimorbidity, and those with certain underlying health conditions remain at highest risk of COVID-19-related hospitalisation and death. The UK's Joint Commission on Vaccination and Immunisation should consider prioritising these individuals for the forthcoming autumn booster dose programme, ideally with novel optimised vaccines, and COVID-19 therapeutics.

two doses for the majority of the population or three doses for people who are immunosuppressed. Booster doses have been offered in the UK since September, 2021, initially for groups at high risk of serious illness from COVID-19. However, the rapid emergence of the more transmissible omicron (B.1.1.529) variant of concern (relative to delta [B.1.617.2])—which was first seen in the UK in late November, 2021, and became the dominant variant by mid-December—led to considerable concern in public, professional, and government circles, resulting in a policy initiative to fast-track the roll-out of the booster vaccine, including to younger people (all those aged 40 years and older), in an attempt to prevent yet another UK-wide lockdown over Christmas, 2021. From Nov 29, 2021, booster doses were then extended to those aged 18 years and over, with a recommended gap of 3 months after primary vaccination.[3–5]

Although the primary vaccination schedule and subsequent booster offer considerable protection against COVID-19-related hospitalisation and death, emerging data suggest that some individuals remain at particularly high risk.[6] Work in Israel showed that, although a booster reduced the risk of severe COVID-19 outcomes (ie, COVID-19-related hospitalisation or death), these events continued at a rate of 1·68 events per 1000 person-years.[7] In another study done in Israel,[8] vaccine effectiveness of the first booster dose against severe COVID-19 illness was estimated to be 92%. In a study by Arbel and colleagues,[9] compared with individuals who were not boosted, COVID-19 mortality was reduced by 90% in individuals who received a booster dose. Although these studies suggest that the first booster dose has been beneficial, there is little evidence about factors associated with severe COVID-19 outcomes in the boosted population.

Our previous Scotland-wide analysis[10] reported that older age, multimorbidity, hospitalisation in the 4 weeks before vaccination, working in a high-risk occupation, being a care home resident, socioeconomic deprivation, being male, and being an ex-smoker increased the risk of severe COVID-19 outcomes after the first dose of the primary vaccination schedule. However, this analysis was done when the alpha (B.1.1.7) variant was dominant. It is crucial to characterise factors associated with increased risk for individuals after the first booster dose so that they can be prioritised for future boosters and potentially also be offered COVID-19 therapeutics.[11] Current UK vaccination policy is to offer future booster doses to individuals at high risk, but it is still uncertain which groups of the population could benefit most.[12]

In response to an urgent request from the UK's Joint Commission on Vaccination and Immunisation (JCVI), we sought to describe the clinical and demographic characteristics of individuals associated with increased risk of COVID-19-related hospitalisation and mortality at 14 days or more after receiving the booster dose of the BNT162b2 or mRNA-1273 vaccine. Working with population-based data from across the UK's four nations offered us the opportunity to populate data gaps in individual country datasets (eg, for HIV) and generate precise estimates for rare risk groups.

Methods

Study design and population

A statistical analysis plan was developed before we did the analysis and was published on the EAVE II website.[13] We used Reporting of Studies Conducted using Observational Routinely-collected Data (also termed RECORD) and Strengthening the Reporting of Observational Studies in Epidemiology (also termed STROBE) checklists to guide transparent reporting (appendix pp 3–7).[14,15]

We used four near real-time nationwide health-care datasets stored in separate secure Trusted Research Environments (TREs) in England, Northern Ireland, Scotland, and Wales. Each of these datasets included information on clinical and demographic characteristics of each individual, their vaccination status and type of vaccine used, and information on positive SARS-CoV-2 infection from RT-PCR and subsequent COVID-19-related hospitalisation or death. We were unable to report on infection in the community setting based on home-antigen testing that was not confirmed with RT-PCR.

Our cohorts consisted of individuals aged 18 years and older who had completed their primary vaccine schedule (first and second doses) with BNT162b2 or ChAdOx1 nCoV-19 vaccines only or had subsequent booster doses of BNT162b2 or mRNA-1273 vaccines between Dec 8, 2020, and Feb 28, 2022. The majority of primary vaccination schedules used BNT162b2 or ChAdOx1 nCoV-19 because these vaccines were the first to be licensed for use in the UK. The mRNA-1273 vaccine became available more than 4 months later and was, therefore, almost exclusively used in individuals aged 40 years or younger. The small numbers in strata for the groups would be insufficiently powered for robust estimates, so the individuals who received mRNA-1273 as their primary vaccine were excluded from this analysis. For individuals aged 12 years or older with primary or acquired immunodeficiency, receiving immunosuppressive or immunomodulating therapy, with chronic immune-mediated inflammatory disease, or receiving high-dose steroids, the primary vaccine schedule included a third half-vaccine dose.[2] Follow-up was from 14 days after completing the primary vaccination schedule until COVID-19-related hospitalisation, COVID-19-related death, or the end of the study period (ie, Feb 28, 2022). We excluded events that occurred within the first 14 days after completion of the primary vaccination schedule to allow time for a full immune response to be mounted.[10] For the same reason, the 14-day period after a booster dose was counted as the exposure period after the primary vaccine dose.

We sought to describe the clinical and demographic characteristics and estimate risk factors for individuals who had severe COVID-19 outcomes after completing the primary vaccination schedule or subsequent booster dose during the period when the omicron variant was dominant. Therefore, we included events that occurred between Dec 20, 2021, and Feb 28, 2022. Two separate analyses were performed to achieve this. For the first analysis, we included all individuals who completed their primary vaccine schedule of BNT162b2 or ChAdOx1 nCoV-19. Many of these individuals then went on to receive the booster dose. For the second analysis, we therefore included all individuals who also received the first booster dose of BNT162b2 or mRNA-1273 vaccines. As part of this second analysis, we also estimated the risk of severe COVID-19 outcome associated with any of 36 underlying clinical conditions identified using the Qcovid risk algorithm.[16]

See Online for appendix

In England, ethical approval was granted by the Health Research Authority London Central Research Ethics Committee (reference number REC reference 21/HRA/2786; integrated research application system number 30174). In Northern Ireland, study approval was granted by the Honest Broker Service (HBS) Governance Board (project number 064; the HBS process does not require separate National Research Ethics Service governance approval). In Scotland, ethical approval was granted by the National Research Ethics Service Committee (Southeast Scotland 02; reference number 12/SS/0201), and the approval for data linkage was granted by the Public Benefit and Privacy Panel for Health and Social Care (reference number 1920–0279). In Wales, research conducted within the Secure Anonymised Information Linkage Databank was done with the permission and approval of the independent Information Governance Review Panel (project number 0911). Individual written patient consent was not required for this study.

Study datasets

Our analytical approach was to conduct separate, equivalent analyses within each nation, and then generate pooled estimates using fixed-effect meta-analyses for the UK as a whole. In England, we used the Oxford-Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) database, one of Europe's oldest sentinel networks that has a near real-time feed of primary care data and is nationally representative, covering around 32% of the English population (N>19 million). The RSC supports the UK Health Security Agency's immunisation and vaccine-preventable disease and real-time syndromic surveillance. Data were pseudonymised in the Oxford RCGP Clinical Informatics Digital Hub (ORCHID) TRE. Pseudonymisation was conducted using a National Health Service (NHS) Digital-approved process, allowing pseudonymised NHS numbers (unique national IDs) to link individual patient-level data to other datasets to supplement primary care data; these datasets included the second generation surveillance system for Pillar 1 (laboratory testing within NHS facilities) and Pillar 2 (community test facilities set up during the pandemic) COVID-19 infection results, the national immunisation management service for vaccine

uptake, Hospital Episode Statistics for hospitalisation and intensive care unit admissions, and Office for National Statistics data for certificated cause of death.[17]

In Northern Ireland, vaccination data from the Vaccine Management System were linked to relevant datasets using an anonymised study identifier that replaced each individual's unique health and care number to construct the cohort, covering 1·9 million individuals (entire population). These datasets were: population data from the National Health Authority Information System (recording eligibility for health care in Northern Ireland, which included date of death); medications dispensed by community pharmacists from the enhanced prescribing database (more details are available in the appendix [p 10]); and COVID-19 testing data from the Northern Ireland centralised testing register, which included Pillar 1, Pillar 2, and other sources (such as travel and point-of-care testing). COVID-19-related hospital admissions were identified using the Patient Administration System, which captured all acute hospital sites in Northern Ireland. Primary care consultation and diagnostic data were not available for Northern Ireland; therefore, medication dispensation was used as a proxy measure for comorbidities.

In Scotland, the Early Pandemic Evaluation and Enhanced Surveillance of COVID-19 (EAVE II) platform[18] used the Community Health Index number, which is a unique identifier used in all health-care contacts across Scotland, to deterministically link primary care data on 5·4 million people (around 99% of the population) from 940 general practices, secondary care data from Scottish Morbidity Record 01 and Rapid Preliminary Inpatient Data, laboratory data from Electronic Communication of Surveillance in Scotland, vaccination status data from the Turas Vaccination Management Tool, and mortality data from National Records of Scotland.

In Wales, the Secure Anonymised Information Linkage Databank platform[19,20] used Anonymised Information Linkage Field, covering 3·2 million individuals (entire population), which is a pseudonymised unique identifier used in all health-care contacts across Wales, to link population-level primary care records of 329 (84%) of 391 General Practitioner practices across Wales, all hospital admissions, and RT-PCR testing results for the entire population from a cohort designed for studying COVID-19-related outcomes.

Outcomes

Our primary outcome of interest was severe COVID-19 outcomes, defined as COVID-19-related hospital admission or death, 14 days or more after completing the primary vaccine schedule or after the first booster dose. A COVID-19-related hospital admission was defined as a hospital admission with either a positive SARS-CoV-2 RT-PCR test within 14 days before admission and any reason of admission, or COVID-19 as reason for admission or a positive SARS-CoV-2 RT-PCR test result during an admission, in which COVID-19 was not the reason for admission (appendix p 1). COVID-19-related mortality was defined as either death for any reason within 28 days of a positive SARS-CoV-2 RT-PCR test or if COVID-19 was recorded as the primary reason for death on the death certificate (appendix p 1).

Population characteristics and covariates

Characteristics of interest were defined at baseline and included age, sex, ethnicity, urban or rural place of residence (which is a measure of rurality based on residential settlement),[10] BMI, SARS-CoV-2 infection before the primary dose of the vaccine (classified as <3 months, 3–5 months, 6–8 months, and ≥9 months before the vaccine dose), being in a high-risk occupational group (defined by the number of previous RT-PCR tests, a proxy for high-risk occupations, classified as 0, 1, 2, 3–4, 5–9, and >10 tests), the interval between first and second vaccine doses (classified as 3–6 weeks, 7–8 weeks, 9–10 weeks, 11–12 weeks, and >13 weeks), health-care administrative areas (NHS regions in England, local councils in Northern Ireland, and health boards in Scotland and in Wales; results for administrative areas are not shown in this Article), socioeconomic deprivation status (based on quintiles of Index of Multiple Deprivation in England, Northern Ireland Multiple Deprivation Measure in Northern Ireland, Scottish Index of Multiple Deprivation in Scotland, and Welsh Index of Multiple Deprivation in Wales[21,22]), and the number of pre-existing comorbidities previously known to be associated with severe COVID-19 outcome (the differences in measurement between nations are detailed in the Methods section in the appendix [p 10]).[23] The complete list of comorbidities included in the number of pre-existing comorbidities and included as part of the second analysis is listed in the appendix (pp 8–9). We examined time since vaccination in periods of 3–9 weeks, 10–19 weeks, and ≥20 weeks from completion of the primary vaccination schedule, and 3–5 weeks, 6–8 weeks, and 9 weeks or more for the booster doses separately. To allow for variation in background levels of community infection, we split the data by calendar week. We examined RT-PCR test results to determine what proportion of SARS-CoV-2-positive tests each day were due to the omicron variant. Data suggested that omicron was dominant after Dec 14, 2021 (appendix p 2). We then included all the events (severe COVID-19 outcomes) after Dec 20, 2021, to allow for the known lag between infection and severe outcomes.

Statistical analysis

Data governance arrangements did not permit the sharing of individual-level data between the four TREs. Therefore, we first performed the analysis in each TRE and then pooled the estimates using fixed-effect meta-analyses. We calculated the frequency and rate per 1000 person-years of severe COVID-19 outcomes for all demographic and clinical factors. We used generalised linear models, assuming a Poisson distribution with person-time as an

	Both vaccines		ChAdOx1 nCoV-19		BNT162b2	
	Total vaccination n (%)	Severe COVID-19 outcome, n (rate per 1000 person-years)	Total vaccination, n (%)	Severe COVID-19 outcome, n (rate per 1000 person-years)	Total vaccination, n (%)	Severe COVID-19 outcome, n (rate per 1000 person-years)
Sex						
Male	7 740 320 (47·8%)	29 230 (9·1)	4 237 980 (49·2%)	17 820 (10·1)	3 502 340 (46·1%)	11 420 (7·9)
Female	8 468 280 (52·2%)	30 280 (8·5)	4 381 540 (50·8%)	17 730 (9·7)	4 086 740 (53·9%)	12 550 (7·2)
Age						
18–49 years	7 416 410 (45·8%)	11 630 (3·9)	2 780 360 (32·3%)	6220 (5·4)	4 636 050 (61·1%)	5420 (2·9)
50–54 years	1 516 010 (9·4%)	3080 (4·9)	1 174 370 (13·6%)	2340 (5·1)	341 640 (4·5%)	730 (4·4)
55–59 years	1 555 030 (9·6%)	3610 (5·6)	1 199 080 (13·9%)	2720 (5·7)	355 950 (4·7%)	890 (5·2)
60–64 years	1 366 560 (8·4%)	3950 (6·9)	1 030 000 (11·9%)	2960 (7·1)	336 560 (4·4%)	990 (6·2)
65–69 years	1 160 690 (7·2%)	4370 (8·8)	729 940 (8·5%)	3140 (11·0)	430 740 (5·7%)	1230 (5·8)
70–74 years	1 155 870 (7·1%)	6180 (12·3)	677 080 (7·9%)	4280 (14·2)	478 800 (6·3%)	1910 (9·4)
75–79 years	867 070 (5·3%)	6940 (17·7)	481 700 (5·6%)	4290 (18·7)	385 370 (5·1%)	2640 (16·3)
≥80 years	1 170 980 (7·2%)	19 730 (37·3)	547 000 (6·3%)	9580 (36·0)	623 980 (8·2%)	10 150 (38·5)
Ethnicity*						
White	10 145 220 (77·9%)	44 080 (12·0)	5 506 010 (80·4%)	25 690 (13·0)	4 639 210 (75·2%)	18 390 (10·8)
Asian	871 160 (6·7%)	2710 (8·5)	386 280 (5·6%)	1630 (11·3)	484 880 (7·9%)	1080 (6·2)
Black	291 310 (2·2%)	1110 (9·5)	142 910 (2·1%)	680 (11·2)	148 410 (2·4%)	430 (7·7)
Mixed	156 860 (1·2%)	440 (7·7)	66 920 (1·0%)	250 (10·0)	89 950 (1·5%)	180 (5·8)
Other	144 210 (1·1%)	440 (8·2)	62 300 (0·9%)	260 (10·6)	81 910 (1·3%)	180 (6·2)
Unknown	1 412 960 (10·9%)	4400 (8·9)	687 940 (10·0%)	2460 (10·3)	725 020 (11·8%)	1940 (7·6)
Socioeconomic deprivation status						
1 (most deprived)	2 709 510 (16·7%)	12 800 (10·8)	1 405 720 (16·3%)	8180 (13·0)	1 303 790 (17·2%)	4620 (8·3)
2	3 088 270 (19·1%)	12 040 (9·2)	1 597 060 (18·5%)	7450 (10·9)	1 491 200 (19·6%)	4600 (7·4)
3	3 263 370 (20·1%)	11 790 (8·6)	1 738 250 (20·2%)	6920 (9·6)	1 525 120 (20·1%)	4870 (7·6)
4	3 446 240 (21·3%)	11 610 (8·1)	1 851 780 (21·5%)	6700 (8·9)	1 594 460 (21·0%)	4910 (7·3)
5 (least deprived)	3 682 060 (22·7%)	11 220 (7·5)	2 017 380 (23·4%)	6260 (7·9)	1 664 680 (21·9%)	4960 (7·2)
Unknown	19 150 (0·1%)	40 (3·0)	9330 (0·1%)	20 (4·3)	9820 (0·1%)	10 (2·0)
BMI†						
<18·5	422 940 (2·6%)	1920 (12·7)	140 600 (1·6%)	1120 (20·7)	282 340 (3·7%)	800 (8·2)
18·5–24·9	4 576 050 (28·3%)	15 690 (9·4)	2 269 640 (26·4%)	8320 (10·1)	2 306 410 (30·5%)	7370 (8·7)
25·0–29·9	6 124 700 (37·9%)	18 220 (7·5)	3 443 140 (40·0%)	10 410 (7·7)	2 681 560 (35·4%)	7800 (7·2)
30·0–34·9	2 385 270 (14·8%)	10 370 (11·3)	1 414 430 (16·4%)	6620 (12·4)	970 840 (12·8%)	3750 (9·8)
35·0–39·9	943 010 (5·8%)	4770 (13·1)	559 880 (6·5%)	3180 (14·8)	383 130 (5·1%)	1590 (10·7)
≥40·0	549 830 (3·4%)	3480 (16·1)	351 210 (4·1%)	2540 (18·3)	198 620 (2·6%)	940 (12·1)
Unknown	1 169 140 (7·2%)	2760 (6·9)	420 840 (4·9%)	1480 (10·0)	748 300 (9·9%)	1270 (5·1)
Number of risk groups†						
0	8 416 050 (52·0%)	9680 (3·1)	4 206 130 (48·9%)	5400 (3·4)	4 209 920 (55·6%)	4280 (2·7)
1	4 136 300 (25·6%)	11 040 (6·9)	2 306 800 (26·8%)	6730 (7·6)	1 829 500 (24·2%)	4320 (6·1)
2	1 858 350 (11·5%)	10 300 (14·3)	1 080 220 (12·6%)	6330 (15·1)	778 130 (10·3%)	3970 (13·2)
3	922 330 (5·7%)	8720 (24·5)	536 440 (6·2%)	5210 (25·3)	385 890 (5·1%)	3520 (23·3)
4	451 500 (2·8%)	6780 (38·5)	258 200 (3·0%)	3990 (39·8)	193 300 (2·6%)	2800 (36·8)
≥5	386 400 (2·4%)	10 660 (70·8)	211 950 (2·5%)	6030 (74·4)	174 450 (2·3%)	4640 (66·7)
Number of risk groups by British National Formulary chapters‡						
0	15 740 (41·8%)	310 (1·1)	5940 (30·1%)	180 (1·7)	9790 (54·7%)	130 (0·8)
1	6580 (17·5%)	200 (1·6)	3380 (17·1%)	140 (2·4)	3200 (17·9%)	50 (0·9)
2	4890 (13·0%)	250 (2·9)	2950 (14·9%)	200 (4·0)	1940 (10·8%)	50 (1·3)
3	3800 (10·1%)	340 (5·3)	2590 (13·1%)	300 (7·0)	1210 (6·8%)	40 (2·0)
4	2630 (7·0%)	340 (7·9)	1910 (9·7%)	300 (10·0)	720 (4·1%)	40 (3·2)
5	1860 (4·9%)	350 (12·9)	1380 (7·0%)	290 (15·1)	470 (2·6%)	50 (7·1)
≥6	2170 (5·8%)	530 (18·7)	1620 (8·2%)	450 (22·2)	560 (3·1%)	80 (10·0)

(Table 1 continues on next page)

	Both vaccines		ChAdOx1 nCoV-19		BNT162b2	
	Total vaccination n (%)	Severe COVID-19 outcome, n (rate per 1000 person-years)	Total vaccination, n (%)	Severe COVID-19 outcome, n (rate per 1000 person-years)	Total vaccination, n (%)	Severe COVID-19 outcome, n (rate per 1000 person-years)
(Continued from previous page)						
Urban-rural index						
Urban	12 512 340 (77·2%)	48 140 (9·4)	6 517 020 (75·6%)	28 640 (10·7)	5 995 320 (79·0%)	19 500 (8·0)
Rural	3 677 090 (22·7%)	11 340 (6·9)	2 093 160 (24·3%)	6880 (7·5)	1 583 930 (20·9%)	4460 (6·1)
Unknown	19 150 (0·1%)	40 (3·0)	9330 (0·1%)	20 (4·3)	9820 (0·1%)	10 (2·0)
Interval between primary vaccine doses						
3–6 weeks	860 170 (5·3%)	4030 (9·9)	137 770 (1·6%)	840 (14·2)	722 400 (9·5%)	3190 (9·1)
7–8 weeks	3 349 850 (20·7%)	5820 (4·5)	1 094 000 (12·7%)	3280 (7·3)	2 255 850 (29·7%)	2550 (3·1)
9–10 weeks	5 431 620 (33·5%)	20 080 (7·7)	3 141 610 (36·4%)	12 410 (8·4)	2 290 010 (30·2%)	7670 (6·7)
11–12 weeks	5 762 820 (35·6%)	25 460 (11·7)	3 879 580 (45·0%)	16 380 (11·3)	1 883 240 (24·8%)	9080 (12·4)
≥13 weeks	804 150 (5·0%)	4070 (14·2)	366 570 (4·3%)	2590 (17·5)	437 580 (5·8%)	1480 (10·7)
Number of previous RT-PCR tests						
0	13 491 070 (83·2%)	52 490 (9·7)	7 331 710 (85·1%)	30 730 (10·5)	6 159 360 (81·2%)	21 760 (8·8)
1	1 266 650 (7·8%)	2430 (3·6)	644 330 (7·5%)	1760 (5·0)	622 320 (8·2%)	670 (2·0)
2	821 850 (5·1%)	1610 (4·2)	376 790 (4·4%)	1090 (6·1)	445 060 (5·9%)	520 (2·6)
3–4	366 830 (2·3%)	1340 (7·2)	173 590 (2·0%)	920 (10·6)	193 240 (2·5%)	420 (4·2)
5–9	125 180 (0·8%)	960 (13·8)	59 110 (0·7%)	640 (21·2)	66 080 (0·9%)	320 (8·2)
≥10	137 010 (0·8%)	680 (9·4)	33 980 (0·4%)	410 (24·7)	103 030 (1·4%)	260 (4·8)
History of SARS-CoV-2 infection						
No previous infection	15 745 170 (97·1%)	58 920 (9·0)	8 406 910 (97·5%)	35 170 (10·1)	7 338 260 (96·7%)	23 750 (7·7)
<3 months	158 740 (1·0%)	210 (3·0)	64 310 (0·7%)	120 (4·1)	94 430 (1·2%)	90 (2·2)
3–5 months	124 400 (0·8%)	260 (4·1)	76 610 (0·9%)	200 (5·4)	47 790 (0·6%)	60 (2·3)
6–8 months	105 030 (0·6%)	100 (1·8)	46 120 (0·5%)	60 (2·4)	58 910 (0·8%)	40 (1·3)
≥9 months	75 250 (0·5%)	60 (1·8)	25 550 (0·3%)	20 (1·9)	49 700 (0·7%)	40 (1·7)

Rates are per 1000 person-years. *England and Wales. †England, Scotland, and Wales. ‡Northern Ireland only.

Table 1: **Combined sample characteristics and rates of severe COVID-19 outcomes for individuals who received primary vaccine doses across England (N=11·4 million), Northern Ireland (N=40 000), Scotland (N=3·1 million), and Wales (N=1·6 million)**

offset that represented the time at risk, as an approximation to a Cox proportional hazards model to derive rate ratios (RRs) with 95% CIs for the association between demographic and clinical factors and COVID-19-related hospitalisation or death. The adjusted RRs (aRRs) for time since receiving the vaccine dose were estimated for all vaccines combined, as well as for each vaccine separately. The models were adjusted for age, sex, socioeconomic deprivation status, urban versus rural place of residence, BMI, number of pre-existing comorbidities, the gap between the first and second vaccine doses, history of SARS-CoV-2 infection, number of previous RT-PCR tests, health board (data not shown), and weekly prevalence of SARS-CoV-2 infection in the community. We selected these potentially important demographic and clinical characteristics of interest based on our previous work,[10] conditions previously identified by QCOVID as high risk,[16] and the availability of data within each national dataset. To calculate the RRs for 36 individual comorbidities (in England, Scotland, and Wales), separate models were fitted. These models adjusted for all the aforementioned variables except for the number of pre-existing comorbidities.

For more information on **R** see https://www.r-project.org/

For both analyses, separate results (log RRs and their standard errors) from each nation were meta-analysed using fixed-effect analyses with a generic inverse variance approach.[24]

All statistical analyses were done using the statistical software R: in England, R version 4.2.0 was used; in Northern Ireland, R version 4.1.0 was used; in Scotland, R version 3.6.3 was used; and in Wales, R version 4.1.2 was used. Statistical analyses were performed in England by JO (and independently checked by SB and UA), in Northern Ireland by LP (and independently checked by DTB), in Scotland by UA (and independently checked by CR), and in Wales by SB (and independently checked by FT).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

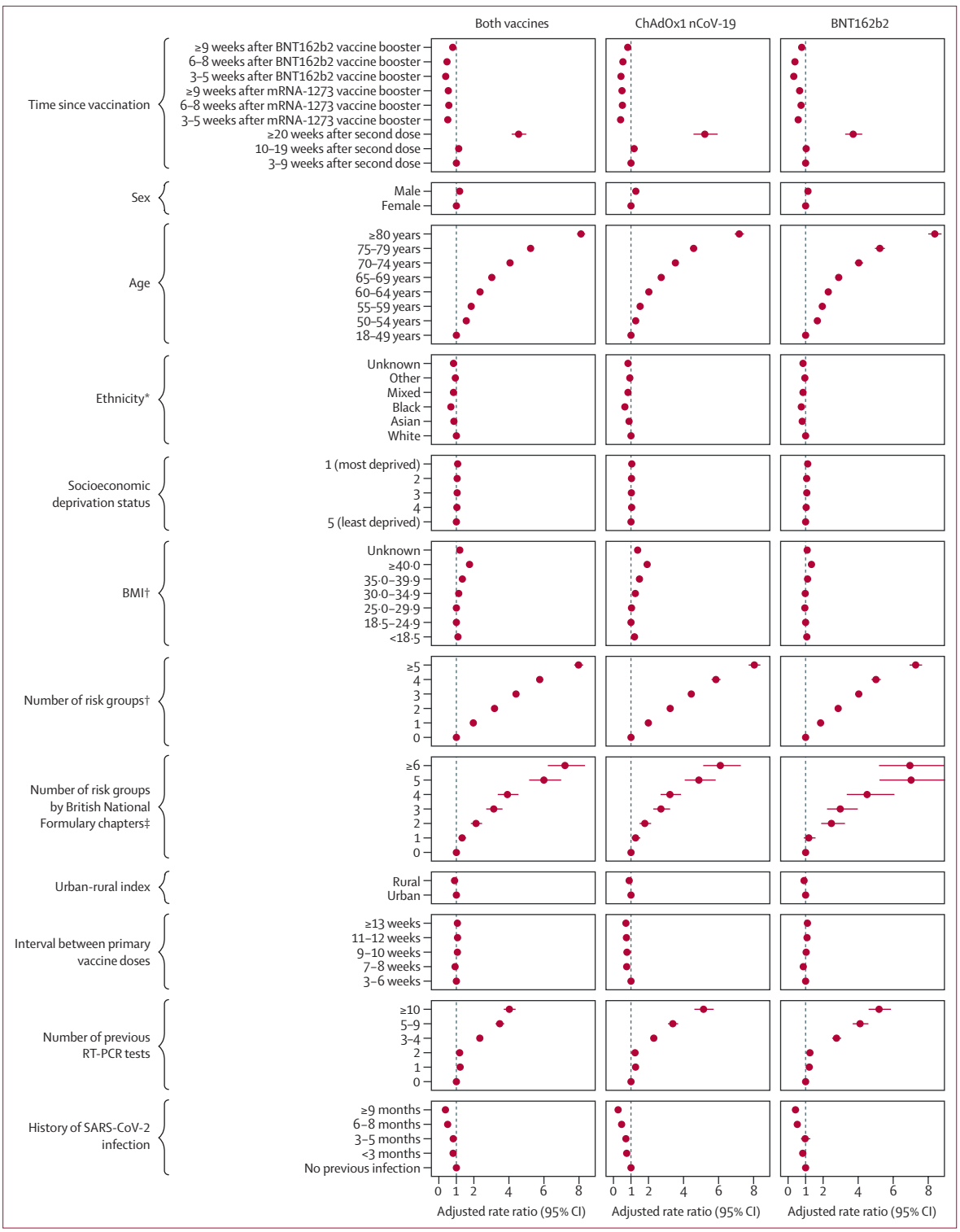

Figure 1: **Pooled analyses of Poisson-adjusted rate ratios for demographic and clinical characteristics associated with COVID-19-related hospitalisation or death among individuals who received primary vaccine doses only or subsequent booster**

Overall estimates are shown and those stratified by type of vaccine at second dose. Due to small numbers of individuals with unknown socioeconmic deprivation status and unknown urban-rural index, these data were omitted from this figure. *England and Wales. †England, Scotland, and Wales. ‡Northern Ireland only.

Results

16 208 600 individuals aged 18 years and older had received primary doses of COVID-19 vaccines in England, Northern Ireland, Scotland, or Wales between Dec 8, 2020, and Feb 28, 2022, and were followed up until hospitalisation, death, or the end of the study period. Among these individuals, 59 510 (0·4%; 8·8 events per 1000 person-years) had a severe COVID-19 outcome between Dec 20, 2021, and Feb 28, 2022. 7 589 080 individuals received primary doses of BNT162b2 and 8 619 520 received primary doses of ChAdOx1 nCoV-19. The rate of severe COVID-19 outcomes was higher among individuals who received the ChAdOx1 nCoV-19 vaccine (35 550 events at the rate of 9·9 events per

	Both vaccines		mRNA-1273		BNT162b2	
	Total vaccination n (%)	Severe COVID-19 outcome (n, rate per 1000 person-years)	Total vaccination n (%)	Severe COVID-19 outcome (n, rate per 1000 person-years)	Total vaccination n (%)	Severe COVID-19 outcome (n, rate per 1000 person-years)
Sex						
Male	6 529 700 (47·2%)	12 650 (7·9)	1 719 700 (50·6%)	1110 (2·8)	4 810 000 (46·1%)	11 540 (9·6)
Female	7 306 690 (52·8%)	13 450 (7·3)	1 676 870 (49·4%)	1250 (3·2)	5 629 820 (53·9%)	12 200 (8·4)
Age						
18–49 years	5 652 310 (40·9%)	4410 (3·5)	1 792 720 (52·8%)	750 (2·0)	3 859 580 (37·0%)	3650 (4·2)
50–54 years	1 353 300 (9·8%)	1210 (3·6)	408 140 (12·0%)	180 (1·8)	945 160 (9·1%)	1030 (4·3)
55–59 years	1 423 540 (10·3%)	1410 (3·9)	419 250 (12·3%)	200 (2·0)	1 004 290 (9·6%)	1210 (4·7)
60–64 years	1 277 210 (9·2%)	1570 (4·6)	340 090 (10·0%)	210 (2·4)	937 120 (9·0%)	1370 (5·4)
65–69 years	1 107 600 (8·0%)	1860 (6·1)	199 730 (5·9%)	220 (4·0)	907 870 (8·7%)	1640 (6·5)
70–74 years	1 110 210 (8·0%)	2610 (8·4)	114 140 (3·4%)	190 (5·7)	996 070 (9·5%)	2420 (8·7)
75–79 years	834 560 (6·0%)	3250 (13·8)	61 810 (1·8%)	200 (10·3)	772 760 (7·4%)	3050 (14·1)
≥80 years	1 077 660 (7·8%)	9770 (32·3)	60 680 (1·8%)	410 (22·9)	1 016 980 (9·7%)	9360 (32·9)
Ethnicity*						
White	8 893 590 (80·4%)	18 530 (8·6)	2 154 680 (80·8%)	1360 (2·8)	6 738 910 (80·3%)	17 170 (10·3)
Asian	637 580 (5·8%)	860 (5·7)	144 790 (5·4%)	80 (2·3)	492 790 (5·9%)	790 (6·7)
Black	172 990 (1·6%)	290 (7·1)	34 010 (1·3%)	30 (3·4)	138 980 (1·7%)	270 (8·0)
Mixed	115 950 (1·0%)	160 (6·0)	28 460 (1·1%)	20 (3·2)	87 490 (1·0%)	140 (6·9)
Other	99 750 (0·9%)	150 (6·6)	26 500 (1·0%)	20 (3·2)	73 250 (0·9%)	130 (7·7)
Unknown	1 142 490 (10·3%)	1820 (6·5)	279 340 (10·5%)	130 (1·9)	863 150 (10·3%)	1690 (7·9)
Socioeconomic deprivation status						
1 (most deprived)	2 051 520 (14·8%)	4670 (9·5)	515 790 (15·2%)	470 (4·1)	1 535 730 (14·7%)	4200 (11·1)
2	2 519 160 (18·2%)	5080 (8·2)	634 650 (18·7%)	520 (3·6)	1 884 510 (18·1%)	4560 (9·6)
3	2 818 550 (20·4%)	5260 (7·5)	647 110 (19·1%)	420 (2·8)	2 171 430 (20·8%)	4840 (8·8)
4	3 063 000 (22·1%)	5430 (7·0)	707 360 (20·8%)	470 (2·8)	2 355 640 (22·6%)	4960 (8·2)
5 (least deprived)	3 368 540 (24·3%)	5640 (6·6)	887 270 (26·1%)	470 (2·2)	2 481 280 (23·8%)	5170 (8·0)
Unknown	15 620 (0·1%)	30 (7·7)	4400 (0·1%)	10 (7·8)	11 220 (0·1%)	20 (7·6)
BMI†						
<18·5	309 610 (2·2%)	840 (12·0)	79 920 (2·4%)	60 (3·2)	229 690 (2·2%)	790 (14·9)
18·5–24·9	3 895 910 (28·2%)	7460 (8·0)	953 870 (28·1%)	610 (2·9)	2 942 040 (28·2%)	6850 (9·5)
25·0–29·9	5 347 220 (38·7%)	8610 (6·8)	1 307 860 (38·6%)	740 (2·6)	4 039 360 (38·8%)	7870 (8·0)
30·0–34·9	2 104 790 (15·2%)	4180 (8·2)	496 820 (14·7%)	380 (3·5)	1 607 970 (15·4%)	3800 (9·5)
35·0–39·9	831 480 (6·0%)	1720 (8·7)	202 160 (6·0%)	140 (3·3)	629 320 (6·0%)	1570 (10·2)
≥40·0	477 750 (3·5%)	1070 (9·3)	114 440 (3·4%)	110 (4·4)	363 310 (3·5%)	960 (10·7)
Unknown	845 540 (6·1%)	1100 (5·6)	233 960 (6·9%)	90 (1·7)	611 580 (5·9%)	1010 (7·1)
Number of risk groups†						
0	6 996 930 (50·7%)	3880 (2·4)	1 992 940 (58·8%)	580 (1·4)	5 003 990 (48·0%)	3300 (2·8)
1	3 589 070 (26·0%)	4720 (5·5)	866 490 (25·6%)	520 (2·7)	2 722 580 (26·1%)	4210 (6·3)
2	1 651 780 (12·0%)	4690 (11·3)	320 740 (9·5%)	370 (4·9)	1 331 030 (12·8%)	4330 (12·7)
3	827 980 (6·0%)	4040 (18·9)	129 160 (3·8%)	260 (8·1)	698 820 (6·7%)	3780 (20·7)
4	406 010 (2·9%)	2990 (28·1)	49 910 (1·5%)	170 (13·5)	356 100 (3·4%)	2820 (30·0)
≥5	340 540 (2·5%)	4640 (51·6)	29 780 (0·9%)	240 (33·6)	310 760 (3·0%)	4400 (53·2)

(Table 2 continues on next page)

	Both vaccines		mRNA-1273		BNT162b2	
	Total vaccination n (%)	Severe COVID-19 outcome (n, rate per 1000 person-years)	Total vaccination n (%)	Severe COVID-19 outcome (n, rate per 1000 person-years)	Total vaccination n (%)	Severe COVID-19 outcome (n, rate per 1000 person-years)
(Continued from previous page)						
Number of risk groups by British National Formulary chapters‡						
0	8690 (36·1%)	90 (1·7)	2820 (37·4%)	20 (1·4)	5870 (35·5%)	70 (1·8)
1	4390 (18·2%)	80 (2·7)	1440 (19·1%)	20 (2·2)	2950 (17·8%)	60 (2·9)
2	3440 (14·3%)	150 (6·0)	1140 (15·1%)	20 (2·6)	2300 (13·9%)	130 (7·5)
3	2680 (11·1%)	160 (8·5)	830 (11·0%)	40 (7·0)	1850 (11·2%)	130 (9·0)
4	1960 (8·1%)	170 (12·4)	560 (7·4%)	30 (7·7)	1400 (8·5%)	140 (14·1)
5	1340 (5·6%)	180 (20·9)	350 (4·7%)	30 (14·3)	990 (6·0%)	150 (23·2)
≥6	1590 (6·6%)	280 (29·5)	410 (5·4%)	50 (23·6)	1190 (7·2%)	220 (31·4)
Urban-rural index						
Urban	10 519 740 (76·0%)	20 590 (7·9)	2 662 240 (78·4%)	1840 (3·0)	7 857 490 (75·3%)	18 750 (9·4)
Rural	3 301 040 (23·9%)	5490 (6·5)	729 930 (21·5%)	520 (2·9)	2 571 110 (24·6%)	4970 (7·5)
Unknown	15 620 (0·1%)	30 (7·7)	4400 (0·1%)	10 (7·8)	11 220 (0·1%)	20 (7·6)
Interval between primary vaccine doses						
3–6 weeks	737 470 (5·3%)	1670 (9·3)	92 600 (2·7%)	50 (2·5)	644 860 (6·2%)	1620 (10·2)
7–8 weeks	2 744 850 (19·8%)	2500 (4·2)	816 770 (24·0%)	340 (2·0)	1 928 080 (18·5%)	2170 (5·0)
9–10 weeks	4 824 110 (34·9%)	9540 (7·3)	1 128 170 (33·2%)	810 (2·9)	3 695 940 (35·4%)	8730 (8·6)
11–12 weeks	5 147 600 (37·2%)	11 080 (8·6)	1 252 880 (36·9%)	1000 (3·4)	3 894 720 (37·3%)	10 070 (10·2)
≥13 weeks	382 380 (2·8%)	1160 (14·5)	106 150 (3·1%)	160 (7·7)	276 230 (2·6%)	1000 (16·8)
Number of previous RT-PCR tests						
0	11 642 910 (84·1%)	22 410 (7·7)	2 732 530 (80·4%)	1800 (2·8)	8 910 380 (85·3%)	20 610 (9·1)
1	1 046 660 (7·6%)	1110 (4·6)	340 690 (10·0%)	190 (2·8)	705 970 (6·8%)	920 (5·4)
2	637 420 (4·6%)	770 (5·1)	193 230 (5·7%)	130 (3·1)	444 190 (4·3%)	640 (5·9)
3–4	290 460 (2·1%)	710 (10·6)	86 710 (2·6%)	110 (6·3)	203 750 (2·0%)	610 (12·0)
5–9	102 110 (0·7%)	510 (18·9)	25 110 (0·7%)	80 (16·1)	77 000 (0·7%)	430 (19·5)
≥10	116 830 (0·8%)	410 (12·6)	18 300 (0·5%)	40 (11·5)	98 530 (0·9%)	370 (12·7)
Previous history of SARS-CoV-2 infection						
No prior infection	13 474 880 (97·4%)	25 820 (7·7)	3 280 550 (96·6%)	2320 (3·0)	10 194 330 (97·6%)	23 500 (9·0)
<3 months	122 150 (0·9%)	110 (4·3)	34 710 (1·0%)	20 (3·0)	87 440 (0·8%)	90 (4·8)
3–5 months	100 480 (0·7%)	120 (4·7)	31 760 (0·9%)	20 (2·7)	68 720 (0·7%)	100 (5·5)
6–8 months	80 580 (0·6%)	60 (3·6)	33 080 (1·0%)	20 (2·8)	47 500 (0·5%)	40 (4·1)
≥9 months	58 310 (0·4%)	50 (4·1)	16 470 (0·5%)	10 (4·5)	41 840 (0·4%)	40 (4·0)

Rates are per 1000 person-years. *England and Wales. †England, Scotland, and Wales. ‡Northern Ireland only.

Table 2: **Combined sample characteristics and rates of severe COVID-19 outcomes for individuals who received a booster dose, across England (N=9·7 million), Northern Ireland (N=24 000), Scotland (N=2·7 million), and Wales (N=1·4 million)**

1000 person-years) compared with individuals who had received the BNT162b2 vaccine (23 970 events at the rate of 7·5 events per 1000 person-years). A detailed description of the characteristics of the whole population is shown in Table 1.

There was an increased risk of severe COVID-19 outcomes 10 weeks after completing the primary doses of BNT162b2 or ChAdOx1 nCoV-19 (≥20 weeks *vs* 3–9 weeks; aRR 4·55 [95% CI 4·16–4·99]). Individuals with a greater number of comorbidities (≥5 comorbidities *vs* none; 7·98 [7·73–8·24]; appendix p 11), who were older (aged ≥80 years *vs* 18–49 years; 8·12 [7·89–8·35]), who had a higher BMI (≥40 *vs* 18·5–24·9; 1·75 [1·69–1·82]), or who were male (male *vs* female; 1·19 [1·17–1·21]) were also associated with increased risk of severe COVID-19 outcomes (figure 1, appendix pp 11–13). Individuals with a history of SARS-CoV-2 infection (infected ≥9 months before the booster dose *vs* no previous infection) were found to be at reduced risk of severe COVID-19 outcomes (0·38 [0·29–0·49]; figure 1, appendix pp 11–13). The risk of severe COVID-19 reduced after receiving the booster dose (≥9 weeks after mRNA-1273 booster *vs* 3–9 weeks after completing primary schedule, aRR 0·54 [95% CI 0·48–0·60]; ≥9 weeks after BNT162b2 booster *vs* 3–9 weeks after primary schedule, 0·80 [0·72–0·88]; figure 1, appendix pp 11–13).

	Both vaccines adjusted rate ratio (95% CI)	mRNA-1273 adjusted rate ratio (95% CI)	BNT162b2 adjusted rate ratio (95% CI)
Time since vaccination			
3–5 weeks after booster dose	1·00 (ref)	1·00 (ref)	1·00 (ref)
6–8 weeks after booster dose	1·09 (0·97–1·23)	0·96 (0·77–1·20)	1·10 (0·95–1·27)
≥9 weeks after booster dose	1·20 (1·07–1·35)	1·11 (0·87–1·41)	1·11 (0·98–1·27)
Sex			
Female	1·00 (ref)	1·00 (ref)	1·00 (ref)
Male	1·23 (1·20–1·26)	1·04 (0·95–1·13)	1·26 (1·23–1·29)
Age			
18–49 years	1·00 (ref)	1·00 (ref)	1·00 (ref)
50–54 years	0·90 (0·85–0·96)	0·81 (0·68–0·96)	0·91 (0·85–0·97)
55–59 years	0·91 (0·85–0·97)	0·85 (0·72–1·01)	0·90 (0·84–0·96)
60–64 years	1·01 (0·95–1·07)	0·97 (0·82–1·15)	0·98 (0·92–1·04)
65–69 years	1·21 (1·14–1·28)	1·50 (1·27–1·78)	1·10 (1·03–1·17)
70–74 years	1·46 (1·39–1·53)	1·91 (1·60–2·28)	1·31 (1·24–1·38)
75–79 years	1·95 (1·86–2·05)	2·98 (2·49–3·58)	1·73 (1·65–1·82)
≥80 years	3·60 (3·45–3·75)	5·52 (4·73–6·43)	3·19 (3·06–3·33)
Ethnicity*			
White	1·00 (ref)	1·00 (ref)	1·00 (ref)
Asian	0·89 (0·83–0·96)	1·02 (0·80–1·31)	0·88 (0·82–0·94)
Black	0·99 (0·88–1·10)	1·20 (0·80–1·81)	0·95 (0·84–1·07)
Mixed	0·99 (0·85–1·15)	1·35 (0·85–2·16)	0·94 (0·80–1·11)
Other	1·21 (1·03–1·41)	1·36 (0·81–2·27)	1·16 (0·98–1·38)
Unknown	0·94 (0·89–0·98)	0·78 (0·65–0·94)	0·95 (0·90–1·00)
Socioeconomic deprivation status†			
5 (least deprived)	1·00 (ref)	1·00 (ref)	1·00 (ref)
4	1·07 (1·04–1·11)	1·21 (1·06–1·38)	1·06 (1·02–1·10)
3	1·14 (1·10–1·18)	1·14 (0·99–1·30)	1·13 (1·08–1·17)
2	1·20 (1·15–1·24)	1·32 (1·16–1·51)	1·18 (1·13–1·22)
1 (most deprived)	1·35 (1·29–1·40)	1·45 (1·26–1·66)	1·33 (1·27–1·38)
BMI‡			
<18·5	1·42 (1·32–1·52)	1·01 (0·76–1·33)	1·46 (1·35–1·57)
18·5–24·9	1·00 (ref)	1·00 (ref)	1·00 (ref)
25·0–29·9	0·87 (0·84–0·90)	0·82 (0·73–0·92)	0·88 (0·85–0·90)
30·0–34·9	0·88 (0·85–0·92)	0·92 (0·80–1·05)	0·88 (0·85–0·92)
35·0–39·9	0·97 (0·92–1·02)	0·92 (0·76–1·10)	0·97 (0·92–1·02)
≥40·0	1·13 (1·06–1·21)	1·08 (0·87–1·34)	1·13 (1·05–1·20)
Unknown	1·54 (1·44–1·64)	1·08 (0·86–1·36)	1·60 (1·50–1·71)
Number of risk groups‡			
0	1·00 (ref)	1·00 (ref)	1·00 (ref)
1	1·98 (1·90–2·06)	1·82 (1·61–2·06)	1·97 (1·88–2·06)
2	3·35 (3·21–3·50)	2·83 (2·46–3·25)	3·34 (3·19–3·50)
3	4·78 (4·56–5·00)	4·04 (3·45–4·73)	4·75 (4·53–4·99)
4	6·34 (6·03–6·66)	5·98 (4·98–7·18)	6·24 (5·92–6·57)
≥5	9·51 (9·07–9·97)	10·03 (8·40–11·99)	9·34 (8·89–9·81)
Number of risk groups by British National Formulary British National Formulary chapters§			
0	1·00 (ref)	1·00 (ref)	1·00 (ref)
1	1·25 (0·91–1·72)	1·22 (0·66–2·26)	1·27 (0·88–1·83)
2	2·33 (1·75–3·09)	1·46 (0·77–2·76)	2·58 (1·86–3·56)
3	2·68 (2·01–3·57)	2·76 (1·55–4·91)	2·66 (1·90–3·71)
4	3·72 (2·78–4·98)	2·79 (1·51–5·16)	4·08 (2·93–5·69)
5	5·58 (4·17–7·46)	4·92 (2·65–9·13)	5·70 (4·09–7·95)
≥6	6·46 (4·87–8·58)	7·26 (4·07–12·97)	6·28 (4·53–8·70)

(Table 3 continues on next page)

13 836 390 individuals received a booster vaccine of BNT162b2 or mRNA-1273 and were followed up until hospitalisation, death, or the end of the study period on Feb 28, 2022. In the period after booster vaccination, 26 100 (0·2%; 7·6 events per 1000 person-years) individuals had severe COVID-19 outcomes. 10 439 820 individuals received the booster dose of BNT162b2 and 3 396 570 individuals received the booster dose of mRNA-1273, leading to 2360 and 23 740 severe COVID-19 outcomes, respectively. The rate of events among individuals who received mRNA-1273 (3·0 events per 1000 person-years) as the booster dose was lower than that for individuals who received BNT162b2 (9·0 events per 1000 person-years) booster; a detailed description of the characteristics of the population is shown in table 2.

Risk factors associated with severe COVID-19 outcomes after receiving a booster dose were similar to those associated with worse outcomes after completion of the primary vaccination schedule. There was an increased risk of severe COVID-19 outcomes 9 weeks or more after receiving a booster dose of BNT162b2 or mRNA-1273 vaccine (≥9 weeks *vs* 3–5 weeks; aRR 1·20 [95% CI 1·07–1·35]). Individuals with a greater number of comorbidities (≥5 comorbidities *vs* none; 9·51 [9·07–9·97]), who were older (aged ≥80 years *vs* 18–49 years; 3·60 [3·45–3·75]), or who were male (male *vs* female; 1·23 [1·20–1·26]) were also associated with increased risk of severe COVID-19 outcomes.

There was a protective effect among individuals with a history of SARS-CoV-2 infection (infected ≥9 months before booster dose *vs* no previous infection; aRR 0·41 [95% CI 0·29–0·58]). Individuals with increasing multimorbidity were associated with increased risk of severe COVID-19 outcomes (two *vs* none, aRR 3·35 [95% CI 3·21–3·50]; three *vs* none, 4·78 [4·56–5·00]; four *vs* none, 6·34 [6·03–6·66]). Further details are shown in table 3 and figure 2.

The presence of any of the underlying conditions of interest was associated with an increased risk of severe COVID-19 outcomes. This risk was particularly high among those receiving immunosuppressants (yes *vs* no; aRR 5·80 [95% CI 5·53–6·09]), individuals with a history of a rare neurological condition (yes *vs* no; 5·30 [4·90–5·74]), and individuals with chronic kidney disease (chronic kidney disease stage 5 *vs* no; 3·71 [2·90–4·74]; figure 3, appendix pp 14–16).

Discussion

This UK-wide analysis has identified those who remain at risk of severe COVID-19 outcomes after the first vaccine booster dose. Our findings identified risk factors that have been previously reported (eg, age and being immunosuppressed), but we also identified a range of additional risk groups and highlighted the substantial increased risk posed by multimorbidity. These risk factors translated into both analyses in a dose-dependent manner. Our results showed that there were benefits of the first

vaccine booster dose, indicated by the reduced rate of severe COVID-19 outcomes after booster doses, changing from 8·8 events per 1000 person-years (59 510 total events) to 7·6 events per 1000 person-years (26 100 total events). Although lower, this risk is still appreciable in public health terms, necessitating consideration of further booster doses, beginning with those at highest risk. These insights now need to be factored into plans for the roll-out of the autumn COVID-19 booster programme and those who should be prioritised for COVID-19 therapeutics.

To our knowledge, this is the first national study in the UK to estimate and characterise the risk of severe COVID-19 events in the UK population who have received a booster dose. Our analysis has several key strengths. The data used were based on government-mandated reporting from NHS providers, which provided rapid access to data on vaccination status and clinical outcomes from routinely collected electronic health records for around one-third of the population from England and almost the entire populations of Northern Ireland, Scotland, and Wales.[18,25] Our decision to analyse population-based cohorts across different UK nations offered the opportunity to fill data gaps present in individual nations (eg, HIV exceptionalism in the devolved administrations). Additional strengths included our ability to adjust for a range of covariates, and the pooling of data from across the UK, thereby allowing for precision of estimates for groups of patients with rare conditions. Confining our analysis to the period during which omicron was dominant was an additional strength.

However, this study is not without its limitations. These limitations include undertaking work in the context of an evolving pandemic in which sublineages of omicron have emerged, challenges in harmonising some of the risk groups across UK nations, and the risk of residual confounding. Chronologically, most of the population were completing their primary vaccination schedule during two peaks of infection, whereas booster doses were rolled out when infection numbers were falling and the emerging omicron variant was less likely to cause severe outcomes in infected people.[4] Moreover, a few of the earlier hospital admissions in the study might have not been caused by omicron, considering that no variant has ever been 100% dominant.

Individuals who were considered underweight by BMI (<18·5), living in urban rather than rural settings, and those with a shorter period between vaccine doses in the primary schedule were at increased risk of severe COVID-19 outcomes. By contrast, those with a history of COVID-19 were shown to be at reduced risk. These observations are in keeping with the previous literature.[26] Our findings also suggest that all groups aged 65 years and over were at increased risk of serious outcomes relative to the reference group (aged 18–49 years), indicating the need to consider the second dose of booster in these older adults. Our analysis is in agreement with findings from other work,[7–9] which has shown reduction in severe COVID-19 outcomes after booster. Our findings suggest that there were around 8 severe COVID-19 events per 1000 person-years, which is higher than the figure reported in a study in Israel.[7] However, the timeframe of this study and that of Bar-On and colleagues[7] was different. The increased risk of infection and severe COVID-19 outcomes seen as time elapsed since completion of the primary vaccination schedule was corrected by the booster, and this waning of vaccine effectiveness reflects existing reported work.[27–29]

Although this study, alongside others,[30,31] found that previous SARS-CoV-2 infection was associated with a reduced risk of severe COVID-19, there is a caveat that infection with different variants might not confer the same degree of protection, and the population-scale roll-out of booster vaccines has precluded assessment of previous immunity owing to logistical challenges, which suggests that boosting remains appropriate among individuals with previous SARS-CoV-2 infection for the time being. However, as further evidence accumulates, the risk of severe COVID-19 outcomes among individuals who were previously infected with SARS-CoV-2 virus should be reassessed.

Our data suggested a lower rate of severe COVID-19 outcomes in people who received mRNA-1273 compared with those who received BNT162b2. Our study was not designed to investigate the comparative effectiveness of

	Both vaccines adjusted rate ratio (95% CI)	mRNA-1273 adjusted rate ratio (95% CI)	BNT162b2 adjusted rate ratio (95% CI)
(Continued from previous page)			
Urban-rural index†			
Urban	1·00 (ref)	1·00 (ref)	1·00 (ref)
Rural	0·91 (0·88–0·94)	0·99 (0·89–1·11)	0·91 (0·88–0·94)
Interval between primary vaccine doses			
3–6 weeks	1·00 (ref)	1·00 (ref)	1·00 (ref)
7–8 weeks	0·98 (0·92–1·05)	1·01 (0·75–1·36)	1·01 (0·94–1·08)
9–10 weeks	1·09 (1·03–1·15)	1·08 (0·81–1·43)	1·10 (1·05–1·16)
11–12 weeks	1·10 (1·05–1·16)	1·19 (0·90–1·58)	1·12 (1·06–1·18)
≥13 weeks	1·76 (1·64–1·90)	1·73 (1·25–2·39)	1·82 (1·68–1·96)
Number of previous RT-PCR tests			
0	1·00 (ref)	1·00 (ref)	1·00 (ref)
1	1·29 (1·20–1·39)	1·20 (1·00–1·44)	1·33 (1·23–1·44)
2	1·29 (1·19–1·40)	1·44 (1·16–1·79)	1·28 (1·17–1·40)
3–4	2·56 (2·35–2·80)	2·52 (1·99–3·19)	2·59 (2·36–2·86)
5–9	4·40 (3·98–4·86)	5·83 (4·42–7·69)	4·43 (3·94–4·99)
≥10	4·63 (4·13–5·19)	3·86 (2·59–5·77)	4·67 (4·10–5·31)
History of SARS-CoV-2 infection			
No previous infection	1·00 (ref)	1·00 (ref)	1·00 (ref)
<3 months	0·67 (0·54–0·84)	0·44 (0·21–0·94)	0·69 (0·54–0·87)
3–5 months	0·91 (0·73–1·12)	0·99 (0·49–1·99)	0·89 (0·71–1·12)
6–8 months	0·70 (0·51–0·96)	1·04 (0·45–2·38)	0·75 (0·53–1·06)
≥9 months	0·41 (0·29–0·58)	0·34 (0·08–1·36)	0·41 (0·29–0·58)

Overall estimates are shown as well as those stratified by type of vaccine at second dose. *England and Wales. †Because of the little data on unknown status, these data were omitted. ‡England, Scotland, and Wales. §Northern Ireland only.

Table 3: **Pooled analyses of Poisson-adjusted rate ratios for demographic and clinical characteristics associated with COVID-19-related hospitalisation or death among individuals who received booster doses**

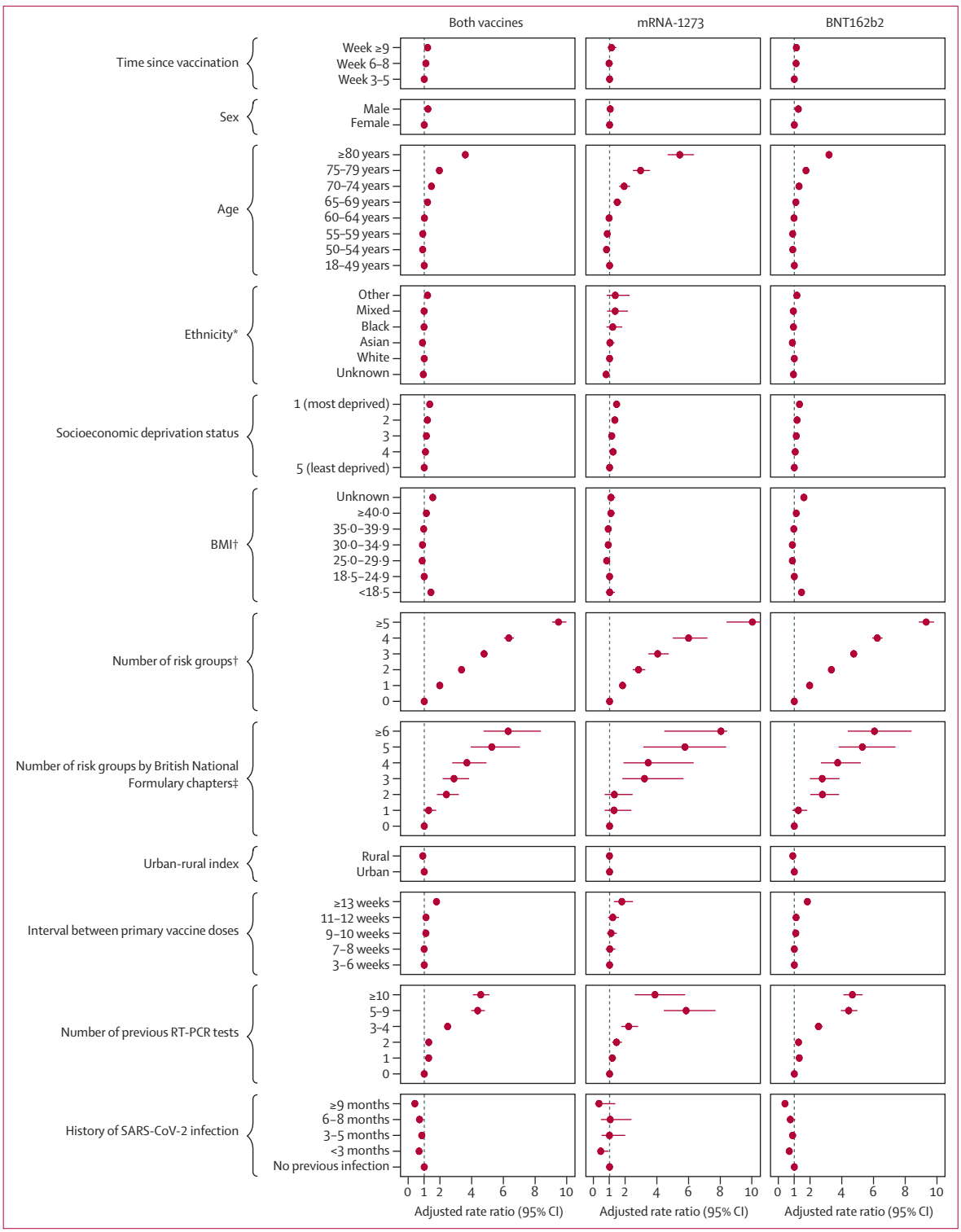

Figure 2: **Pooled analyses of Poisson-adjusted rate ratios for demographic and clinical characteristics associated with COVID-19-related hospitalisation or death among individuals who received booster doses**

Overall estimates are shown as well as those stratified by type of vaccine at booster dose. Due to small numbers of individuals with unknown socioeconmic deprivation status and unknown urban-rural index, these data were omitted from this figure. *England and Wales. †England, Scotland, and Wales. ‡Northern Ireland only.

Figure 3: **Pooled analyses of Poisson-adjusted rate ratios for specific clinical risk factors associated with COVID-19-related hospitalisation or death among individuals who received booster doses of mRNA-1273 or BNT162b2**

Adjusted for non-clinical factors only; reference category for each is absence of the condition. *England and Wales. †Wales only. ‡England only. §Scotland and Wales.

different boosters, so any apparent differences need to be interpreted with care. Emerging evidence suggests that mRNA-1273 boosters might produce a stronger immune response, leading to lower rates of symptomatic infection and severe COVID-19 outcomes than BNT1261b2.[32]

Our observation of increased risk 10 weeks after primary vaccination is supported by previous work,[33] which showed that peak antibody responses were seen in the first month after vaccination but then declined almost four-fold over the following 10 weeks. Similarly, post-booster antibody responses have been shown to peak, but immune waning then occurs rapidly, with one study[34] reporting a 5·5-fold decrease in peak antibody titre within 16 weeks. Because we did not have access to serological data within this study, we could not determine if individuals with specific clinical risk factors mounted a full immune response after a booster, but a previous study[35] has reported suboptimal immunological responses across many of the groups identified in our analysis as being at increased risk of severe COVID-19 outcomes. Thus, there is a need for follow-on work to investigate risks of severe COVID-19 outcomes after booster in those who have been shown to mount a full immunological response.

Our findings indicate a range of demographic and clinical factors associated with increased clinical risk of severe COVID-19 outcomes despite booster vaccination and raise questions regarding future approaches to enhance protection. Increased clinical risk within older people is not unexpected and is likely to reflect underlying frailty, comorbidity, and immune senescence. Indeed, this pattern is seen with other respiratory viruses, despite the introduction of novel adjuvanted vaccine formulations. Immune senescence is a feature common to several risk groups and indicates that, despite strong immunogenicity, current COVID-19 vaccines cannot deliver equivalent protection to all individuals. Future approaches should aim to improve vaccine immunogenicity and involve a range of novel strategies, including variant-specific immunogenic agents, introduction of viral proteins in addition to spike, and the incorporation of immunodominant cellular epitopes. However, these approaches are unlikely to overcome immune suppression in the most vulnerable groups and for that reason additional approaches, such as administration of anti-spike monoclonal antibodies and antivirals, should also be considered.

These findings have been shared with JCVI and the Chief Medical Officers and Chief Scientific Advisers of the UK nations and are now being considered as the UK plans its autumn COVID-19 booster vaccine programme. This analysis has helped to generate timely insights that are now being used to help identify and prioritise individuals most likely to benefit from second vaccine boosters and COVID-19 therapeutics. Policy makers will not only need to consider this evidence (and any other evidence) on risk groups, but also the logistical aspects of administering booster doses to a substantial proportion of the UK's population.

There is a need to investigate immunological responses to vaccination in those who have been identified as being at high risk after a first booster dose. Our plan is to continue to analyse data on uptake and impact of second dose boosters as the vaccine programme proceeds.

In summary, this UK-wide, population-based analysis has found that individuals who received their first booster vaccination were at reduced risk of COVID-19-related hospitalisation or death compared with those who had only completed their primary vaccination schedule. Older age, those with a higher number of comorbid conditions, and those with a range of specific underlying conditions were, however, found to be at increased risk of severe COVID-19 outcomes and might particularly benefit from additional, preferentially novel, COVID-19 boosters, pre-exposure prophylaxis, and COVID-19 therapeutics.

Contributors

AS, CRS, CR, and LR conceived the original EAVE II study. AS conceived this study. UA and CMC led the writing of the paper and edited the final manuscript with help from AS, SB, ZG, and AA-L. SdL and MJ conceived how Research and Surveillance Centre data could support this study and are the guarantors of these data; JO conducted these analyses, JO; and SdL, MJ, and RSMT added the analysis on data from England to the paper. LP and DTB were responsible for data cleaning, and LP contributed to the analysis in Northern Ireland. UA accessed and verified the underlying data and is responsible for data cleaning and analysis in Scotland. SB accessed and verified the underlying data and is responsible for data cleaning and analysis in Wales. CR oversaw all the analyses. All authors contributed to the study design and all authors contributed to drafting the paper and revised the manuscript for important intellectual content. All authors have seen and approved the final text and gave final approval of the version to be published.

Declaration of interests

AS and CR are members of the Scottish Government Chief Medical Officer's COVID-19 Advisory Group. AS is a member of the Scottish Government's Standing Committee on Pandemic Preparedness, the UK Government's New and Emerging Respiratory Virus Threats Advisory Group (known as NERVTAG) Risk Stratification Subgroup, the Department of Health and Social Care's COVID-19 Therapeutics Modelling Group, and was a member of AstraZeneca's COVID-19 Strategic Thrombocytopenia Taskforce. All AS's roles are unfunded. CMC reports research funding from the Medical Research Council, Health Data Research UK, the National Institute for Health and Care Research, and the Scottish Chief Scientist Office. SVK was Co-Chair of the Scottish Government's Expert Reference Group on COVID-19 and ethnicity and is a member of the SAGE subgroup on ethnicity. SVK acknowledges funding from an NRS Senior Clinical Fellowship (SCAF/15/02), the Medical Research Council (MC_UU_00022/2), and the Scottish Government Chief Scientist Office (SPHSU17). CR is a member of the Scientific Pandemic Influenza Group on Modelling, Medicines and Healthcare products Regulatory Agency Vaccine Benefit and Risk Working Group. SdL received funding through his university for vaccine-related research from AstraZeneca, GSK, Sanofi, Seqirus, and Takeda. He has been a member of advisory boards for AstraZeneca, Sanofi, and Seqirus, and is Director of the Research and Surveillance Centre. All other authors declare no competing interests.

Data sharing

A data dictionary covering the data sources used in this study can be found at https://github.com/EAVE-II/EAVE-II-data-dictionary. All codes used in this study are publicly available at https://github.com/EAVE-II/Covid-breakthrough-post-first-booster/. The data used in this study are sensitive and will not be made publicly available.

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