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Effectiveness of BNT162b2, mRNA-1273, and ChAdOx1-S vaccines against severe covid-19 outcomes in a nationwide mass vaccination setting: cohort study

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ABSTRACT

OBJECTIVE To estimate the effectiveness of the three covid-19 vaccines by Pfizer-BioNTech (BNT162b2), Moderna (mRNA-1273), and Oxford-AstraZeneca (ChAdOx1-S) in people after receiving two doses.

DESIGN Cohort study.

SETTING Nationwide, population based data in France, from the French National Health Data System (Système National des Données de Santé), between 27 December 2020 and 30 April 2021.

PARTICIPANTS Adults aged ≥50 years receiving a first dose of BNT162b2, mRNA-1273, or ChAdOx1-S were randomly selected (1:1) and matched on the date of vaccination with one unvaccinated control. Individuals were matched on year of birth, sex, region of residence, and residence in a nursing home (for individuals aged ≥75 years). All individuals were followed up until 20 August 2021.

MAIN OUTCOME MEASURES Primary outcome measure was vaccine effectiveness estimated at least 14 days after the second dose against covid-19 related hospital admission using Cox proportional hazards models adjusted for baseline characteristics and comorbidities. Vaccine effectiveness against covid-19 related death in hospital was also investigated.

RESULTS 11 256 832 vaccinated individuals were included in the study (63.6% (n=7 161 658) with the BNT162b2 vaccine, 7.6% (n=856 599) with the mRNA-1273 vaccine, and 28.8% (n=3 238 575) with the ChAdOx1-S vaccine), along with 11 256 832 matched unvaccinated controls. During follow-up (up to 20 August 2021), 43 158 covid-19 related hospital admissions and 7957 covid-19 related deaths in hospital were registered. Compared with unvaccinated controls, vaccine effectiveness of two doses against covid-19 related hospital admission was 91% (95% confidence interval 91% to 92%), 95% (93% to 96%), and 91% (89% to 94%) for the BNT162b2, mRNA-1273, and ChAdOx1-S vaccines, respectively. Similar results were observed for vaccine effectiveness of two doses against covid-19 related deaths in hospital (BNT162b2, 91% (90% to 93%); mRNA-1273, 96% (92% to 98%); and ChAdOx1 nCoV-19, 88% (68% to 95%)). At 5-6 months after receiving the second dose of vaccine, effectiveness remained high at 94% (92% to 95%) for the BNT162b2 vaccine and 98% (93% to 100%) for the mRNA-1273 vaccine. Vaccine effectiveness of ChAdOx1-S estimated at 3-4 months was 90% (63% to 97%). All three vaccines remained effective at the time of circulation of the delta variant of SARS-CoV-2 between 1 July and 20 August 2021 (effectiveness between 89% and 95%).

CONCLUSIONS These findings provide evidence indicating that two doses of ChAdOx1-S is as effective as two doses of mRNA vaccines in France against the alpha and delta variants of SARS-CoV-2. The effectiveness of ChAdOx1-S should be further examined with a longer follow-up and in the light of the circulation of new SARS-CoV-2 variants of concern.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Several observational studies have been published on the effectiveness of receiving two doses of BNT162b2 and mRNA-1273 vaccines against severe covid-19 outcomes, such as covid-19 related hospital admission or covid-19 related death in hospital

⇒ However, relatively little comparable data for the ChAdOx1-S vaccine are available, especially when compared with other mRNA vaccines in the same country

WHAT THIS STUDY ADDS

⇒ This matched cohort study, based on nationwide population based data in France, included more than 11 million vaccinated individuals aged 50 ≥years, of whom more than 3 million were vaccinated with the ChAdOx1-S vaccine

⇒ Compared with unvaccinated controls, risk reduction in people who received two vaccine doses was 91% for the ChAdOx1-S vaccine versus 91% and 95% for the BNT162b2 mRNA and mRNA-1273 vaccines, respectively

⇒ Effectiveness of ChAdOx1-S still reached 90% at 3-4 months following 2 weeks after the second dose of vaccine, and remained high (91%) at the time of circulation of the delta variant of SARS-CoV-2 in France; similar results were observed for the mRNA vaccines up to 5-6 months after the second dose

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ These findings indicate that the BNT162b2 mRNA, mRNA-1273, and ChAdOx1-S vaccines were highly and equally effective against severe covid-19 outcomes after completing a two dose vaccination schedule

⇒ These results were valid at the time of the alpha and delta variants of SARS-CoV-2 circulation, but cannot be assumed to be entirely transferable to current or future dominant variants of SARS-CoV-2

Introduction

Since December 2020, health authorities facing a rapidly progressing pandemic caused by the highly transmissible SARS-CoV-2 have issued emergency use authorisation for three covid-19 vaccines. Authorisation was based on safety and efficacy data from randomised, placebo controlled, phase 3 trials. The three vaccines are BNT162b2 (Comirnaty by Pfizer-BioNTech),[1] mRNA-1273 (Spikevax by Moderna),[2] and ChAdOx1-S (Vaxzevria by AstraZeneca)[3 4]; their respective efficacy for preventing symptomatic covid-19 was 95%, 94%, and 70% (estimated at the time of circulation of the original strain of SARS-CoV-2).

In France, the mass vaccination campaign started on 27 December 2020, initially with the BNT162b2 and mRNA-1273 vaccines. Vaccine rollout proceeded in phases, starting with individuals who had the highest risk of being infected by SARS-CoV-2. Vaccination was prioritised first to healthcare workers, people living in nursing homes, and people aged ≥75 years, as well as individuals with severe or multiple chronic conditions.[5] From February 2021, the vaccination was extended to people aged ≥50 years with comorbidities. The ChAdOx1-S vaccine was made available in France in February 2021; its use was restricted to individuals aged ≥55 years from 19 March 2021.[6]

A few months after the start of mass vaccination campaigns worldwide, several studies were conducted in real world settings and showed high levels of effectiveness of the BNT162b2,[7–52] mRNA-1273,[12–24 26 29 31 32 34 43 45 47–51 53 54] and ChAdOx1-S[36–40 42 43 46 48 50 52 55–58] vaccines against covid-19 infection or severe covid-19 disease. Vaccine effectiveness against covid-19 hospital admissions or death after full vaccination, defined as admission or death occurring seven or 14 days after the second dose of the mRNA vaccines (BNT162b2 and mRNA-1273), was estimated at 80% or more.[7 9 23 25–27 30 31 34 44–48 50–54] However, reports on the effectiveness of two doses of ChAdOx1-S have been less frequent so far,[42 43 46 48 50 52 55–58] mainly because of differences in the interval between the first and second doses (that is, about 12 weeks for ChAdOx1-S *v* four weeks for mRNA vaccines in France); a two dose vaccination schedule requires a much longer interval for ChAdOx1-S than for the mRNA vaccines. Additionally, availability and use of the ChAdOx1-S vaccine were relatively limited worldwide. We found 10 published studies examining its two dose vaccine effectiveness in vaccinated and unvaccinated individuals living in the following regions or countries: Scotland,[42 57] England,[46] Sweden,[48] Hungary,[43] Ontario (Canada),[50] Colombia,[52] Sao Paulo (Brazil),[55] Argentina,[58] and India.[56] Among these studies, only two were conducted that included more than 300 000 individuals vaccinated with ChAdOx1-S and that were adequately adjusted for comorbidities; both were set up in the UK.[46 57] Large observational studies from other countries are needed to back up the evidence.

In this cohort study, we estimated the effectiveness of the BNT162b2, mRNA-1273, and ChAdOx1-S vaccines against covid-19 related hospital admission or covid-19 related death in hospital by assessing results from different follow-up time intervals after receipt of the first and second doses. We assessed data for individuals aged ≥50 years from the French nationwide database.

Methods

Data source

This cohort study used data from the French National Health Data System (Système National des Données de Santé (SNDS), formerly known as SNIIRAM)).[59] SNDS covers the entire population of France (67 million residents). Each person is identified anonymously by a unique, lifelong number. Since 2006, SNDS has recorded all reimbursement data for outpatient care including drugs, imaging, and laboratory tests; inpatient care (including diagnoses and procedures performed) from the national hospital discharge database (Programme de Médicalisation des Systèmes d'Information (PMSI)); and health expenditure for patients with long term diseases, such as cancer and diabetes, which is fully reimbursed in France. The SNDS has been extensively used to conduct real life pharmacoepidemiological studies, including those on the covid-19 pandemic.[60–72] The SNDS also contains sociodemographic data and, when applicable, the date of death.

Information on hospital stays is routinely collected monthly in the PMSI. In April 2020, the French government encouraged hospitals to report all hospital stays related to covid-19 once a week or once a fortnight until July 2020 and then monthly through a fast track procedure (fast track PMSI). Our study was based on the fast track PMSI database available as of 12 October 2021. A cut-off discharge date of 20 August 2021 was chosen to ensure completeness of data over the study period.

Definitions of all variables used in this study were based on the International Classification of Diseases, 10th revision (ICD-10) codes for primary and secondary diagnosis; Common Classification of Medical Procedures codes for procedures; and Anatomical Therapeutic Chemical, French medication ID (code identifiant de presentation, or common unit of dispensation unité commune de dispensation) codes for drugs. We used algorithms developed by national health insurance employees in the Diseases and Healthcare Expenditure Mapping.[71 73] These algorithms are detailed in online supplemental table 1.

Information on covid-19 vaccination status (ie, vaccine products and dates of first and second injections) was derived from the national information

system on covid-19 vaccines VAC-SI (Système d'Information Vaccin covid-19) database. Information on SARS-CoV-2 test results (by reverse transcription polymerase chain reaction, antigen, or antibody) was derived from the national information system on SARS-CoV-2 tests (the Système d'Informations de DEPistage database). We linked all the extracted data required for this study to the SNDS using individuals' unique and anonymous identifiers.

Study design and population

We conducted a matched cohort study. Participants were eligible if they received at least one healthcare reimbursement between 2018 and 2020 (reflecting recent healthcare use before the vaccine rollout) and were aged ≥50 years. All newly vaccinated people were matched on a 1:1 ratio to randomly selected unvaccinated controls. Matching criteria included age, sex, and region of residence, and residency in a nursing home for those individuals aged ≥75 years (three categories: no, yes without inpatient pharmacy, and yes with inpatient pharmacy). Newly vaccinated people were eligible for inclusion, even if they had previously been selected as a control. All included individuals were followed up from the date of their inclusion (as defined by the vaccination date of the vaccinated individual, both for the vaccinated and their matched counterpart in each pair) until the end of follow-up. Follow-up of the pair ended at the earliest instance of the following events: occurrence of an outcome of interest, death, vaccination of the unvaccinated control, or the end of the study period (20 August 2021). From this cohort, we separately examined the three subcohorts, BNT162b2 mRNA, mRNA-1273, and ChAdOx1-S vaccine groups, and their respective control group. Individuals who received two doses of vaccine within an interval of <15 days were excluded along with their matched controls.

Outcomes of interest

The primary outcome was covid-19 related hospital admission, defined on the basis of one of the following principal or secondary diagnosis discharge codes derived from the ICD-10 codes: U07.10 (covid-19, respiratory form, virus identified), U07.11 (covid-19, respiratory form, virus not identified), U07.14 (covid-19, other clinical forms, virus identified), U07.15 (covid-19, other clinical forms, virus not identified), U04.9 (severe acute respiratory syndrome, unspecified). The secondary outcome was death in hospital from covid-19.

Covariables

In addition to variables used for matching (ie, age, sex, region of residence, and nursing home status), information was made available on the following characteristics:

- Social deprivation index categorised by quintiles as a marker of socioeconomic status based on the residence area's median household income, percentage of high school graduates in the population aged ≥15 years, percentage of manual workers in the labour force, and unemployment in the individual's city of residence
- History of positive covid-19 status based on history of covid-19 related hospitalisation or positive SARS-CoV-2 infection test before inclusion date
- History of influenza vaccination in 2018 or 2019
- Presence of health conditions that were previously shown to be associated with severe covid-19 outcomes.[71]

These considered health conditions were: frailty, alcohol related conditions, cardiovascular risk factors (that is, smoking related conditions, hypertension, diabetes mellitus, dyslipidaemia, and obesity related conditions), cardiovascular diseases (that is, coronary heart disease, heart failure, cardiac rhythm disorder, valvular heart disease, occlusive peripheral arterial disease, stroke, and pulmonary embolism), chronic respiratory conditions, dialysis, having a transplanted kidney, liver failure, active cancer, depression, psychosis, dementia, epilepsy, Parkinson's disease, inflammatory bowel disease, rheumatoid arthritis, and ankylosing spondylitis.

Statistical analysis

The categorical variables are reported as frequencies with percentages and the continuous variables reported as means with standard deviations. To report the balance in each individual covariable between vaccine and control groups, the difference in proportions for categorical variables and means for continuous variables is standardised (standardised means difference).[74] The imbalance between the groups is defined as an absolute value greater than 0.10.[74]

We conducted Cox proportional hazards models that were systematically adjusted for matching variables to compare the incidence of outcomes of interest between the vaccinated and control groups. We ran two types of models: the first model adjusted for matching variables, and the second was model 1 but with further adjustment for all the baseline characteristics described in the Covariables section above. For all models, vaccine effectiveness was calculated as 1−hazard ratio (HR)×100; with the lower and upper limits of the confidence interval calculated as $(1-HR_{Upper})\times100$ and $(1-HR_{Lower})\times100$, respectively.[75]

We considered seven follow-up time intervals to estimate the risk reduction over time: four after the receipt of the first dose (≥0, 0-6, 7-13, and 14-28 days for the BNT162b2 and mRNA-1273 vaccines or 14-84 days for the ChAdOx1-S vaccine) and three after the receipt of the second dose (≥0, ≥7, and ≥14 days). The

primary outcome measure was vaccine effectiveness estimated ≥14 days after the second dose.

We conducted two sets of complementary analyses. Firstly, to study the duration of vaccine protection against the studied outcomes, we estimated vaccine effectiveness by monthly intervals starting 14 days after the second dose. Secondly, to examine vaccine protection at the time of the circulation of the delta variant (B.1.617.2) of SARS-CoV-2, we estimated vaccine effectiveness between 1 July and 20 August 2021. In France, the proportion of the delta variant increased from 55.4% on 1 July 2021 to 80.5% 10 days later; on 20 August, delta represented 95.2% of all monitored variants (online supplemental figure 1).

Subgroup analyses were undertaken by sex and age groups (age 50-64, 65-74, 75-84, ≥85 years) among vaccinated individuals (≥14 days after the second dose) and their unvaccinated controls. We used SAS Enterprise Guide version 4.3 software (SAS Institute, Cary, NC) for all our analyses.

Patient and public involvement

Patients and the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Results

From 27 December 2020 to 30 April 2021, 28 611 967 individuals aged ≥50 years were eligible to be enrolled into our study; the 1:1 matching procedure identified 11 256 832 people in the vaccinated group (7 161 658 (63.6%) individuals in the BNT162b2 group, 856 599 (7.6%) in the mRNA-1273 group, and 3 238 575 (28.8%) in the ChAdOx1-S group) and 11 256 832 in the unvaccinated group (table 1). Overall, 4 406 052 (39.1%) of unvaccinated controls were vaccinated during the inclusion period (figure 1). The median follow-up time from the first dose was 49 days (interquartile range 19-116) in the BNT162b2 vaccine group, 48 days (20-117) in the mRNA-1273 vaccine group, and 51 days (22-116) in the ChAdOx1-S vaccine group (table 2).

Regardless of vaccine product, vaccinated individuals versus unvaccinated individuals were less likely to be socially disadvantaged (proportions in the first group (least deprived) of the social deprivation index: 20.8% *v* 17.6% in the BNT162b2 cohort, 22.2% *v* 18.7% in the mRNA-1273 cohort, and 21.2% *v* 17.7% in the ChAdOx1-S cohort), less likely to be infected by SARS-CoV-2 before covid-19 vaccination (2.7% *v* 5.1% in the BNT162b2 cohort, 2.6% *v* 4.9% in the mRNA-1273 cohort, and 2.1% *v* 4.8% in the ChAdOx1-S cohort), and more likely to be vaccinated against influenza (42.6% *v* 29.5% in the BNT162b2 cohort, 40.6% *v* 27.2% in the mRNA-1273 cohort, and 28.0% *v* 15.5% in the ChAdOx1-S cohort; table 1; online supplemental tables 2–4). Differences in comorbidities between the vaccinated group and unvaccinated group were small in the mRNA vaccine cohorts (absolute standardised difference <0.10). In the ChAdOx1-S cohort, vaccinated individuals were more likely than unvaccinated individuals to have hypertension (47.2% *v* 36.1%), diabetes (17.8% *v* 11.4%), dyslipidaemia (31.4% *v* 21.7%), and coronary heart disease (8.2% *v* 5.6%; online supplemental table 4). Furthermore, among vaccinated individuals, people given ChAdOx1-S differed from those who received the mRNA vaccines. They were younger (mean age of 65 years *v* ≥71), less likely to be women (49% *v*>57%), and less likely to live in a nursing home (0% *v* 2.2%); and more likely to have received influenza vaccines in the preceding years (28% *v* ≥40%), be frail (4% *v* ≥8%), and have a cardiac comorbidity (heart failure 1.5% *v*≥2.8%; cardiac rhythm disorder 4.3% *v* ≥7.2%; valvular heart disease 1.7% *v* ≥2.9%), or dementia 0.5% *v* ≥1.5%; table 1).

In the mRNA vaccine groups, 96% of individuals who initially received either BNT162b2 or mRNA-1273 vaccines received the same product for the second dose. Of those who initially had the ChAdOx1-S vaccine, 87% received the same vaccine (online supplemental table 5). The median interval between two doses was 28 days (interquartile range 27-29) for the BNT162b2 vaccine group, 28 days (28-29) for the mRNA-1273 vaccine group, and 77 days (69-84) for the ChAdOx1-S vaccine group. Among those who did not receive a second dose (n=413 402 (3.7%)), about half had a history of covid-19 infection (47% (123 552/264 414) in the BNT162b2 vaccine group, 50% (16 801/33 463) in the mRNA-1273 vaccine group, and 43% (49 583/115 153) in the ChAdOx1-S vaccine group).

During follow-up, when the alpha variant was dominant from January to June 2021 and by the delta variant from July to August 2021, 43 158 (33 209 in the unvaccinated group, 9949 in the vaccinated group) covid-19 related admissions to hospital and 7957 (6171 unvaccinated, 1786 vaccinated) covid-19 related deaths in hospital were recorded. Table 2 presents the effectiveness of the three study vaccines against covid-19 related hospital admission according to follow-up time intervals. Compared with unvaccinated groups, all vaccines reduced the risk of admission by ≥90% after receiving the second dose. From ≥14 days after the second dose, effectiveness reached 91% (95% confidence interval 91% to 92%) for the BNT162b2 vaccine, 95% (93% to 96%) for the mRNA-1273 vaccine, and 91% (89% to 94%) for the ChAdOx1-S vaccine. Similar results were observed in a sensitivity analysis performed after excluding individuals

Table 1 | Baseline characteristics of vaccinated individuals and matched unvaccinated controls, by covid-19 vaccine

	BNT162b2		mRNA-1273		ChAdOx1-S	
	Unvaccinated (n=7 161 658)	Vaccinated (n=7 161 658)	Unvaccinated (n=856 599)	Vaccinated (n=856 599)	Unvaccinated (n=3 238 575)	Vaccinated (n=3 238 575)
Matching variables						
Mean (SD) age (years)	72.7 (11.0)	72.7 (11.0)	71.4 (10.8)	71.4 (10.8)	65.1 (7.6)	65.1 (7.6)
Age categories (years):						
50-54	377 325 (5.3)	377 325 (5.3)	55 167 (6.4)	55 167 (6.4)	171 769 (5.3)	171 769 (5.3)
55-59	537 178 (7.5)	537 178 (7.5)	75 542 (8.8)	75 542 (8.8)	643 022 (19.9)	643 022 (19.9)
60-64	846 820 (11.8)	846 820 (11.8)	107 143 (12.5)	107 143 (12.5)	769 338 (23.8)	769 338 (23.8)
65-69	1 049 776 (14.7)	1 049 776 (14.7)	132 543 (15.5)	132 543 (15.5)	774 172 (23.9)	774 172 (23.9)
70-74	1 347 207 (18.8)	1 347 207 (18.8)	183 281 (21.4)	183 281 (21.4)	684 629 (21.1)	684 629 (21.1)
75-79	978 840 (13.7)	978 840 (13.7)	99 719 (11.6)	99 719 (11.6)	74 189 (2.3)	74 189 (2.3)
80-84	856 384 (12.0)	856 384 (12.0)	88 274 (10.3)	88 274 (10.3)	47 256 (1.5)	47 256 (1.5)
85-89	669 000 (9.3)	669 000 (9.3)	69 720 (8.1)	69 720 (8.1)	40 975 (1.3)	40 975 (1.3)
≥90	499 128 (7.0)	499 128 (7.0)	45 210 (5.3)	45 210 (5.3)	33 225 (1.0)	33 225 (1.0)
Sex:						
Men	3 046 267 (42.5)	3 046 267 (42.5)	370 469 (43.2)	370 469 (43.2)	1 659 165 (51.2)	1 659 165 (51.2)
Women	4 115 391 (57.5)	4 115 391 (57.5)	486 130 (56.8)	486 130 (56.8)	1 579 410 (48.8)	1 579 410 (48.8)
Region of residence:						
Auvergne-Rhône-Alpes	841 801 (11.8)	841 801 (11.8)	107 028 (12.5)	107 028 (12.5)	384 565 (11.9)	384 565 (11.9)
Bourgogne-Franche-Comté	281 988 (3.9)	281 988 (3.9)	67 089 (7.8)	67 089 (7.8)	139 519 (4.3)	139 519 (4.3)
Bretagne	391 114 (5.5)	391 114 (5.5)	34 373 (4.0)	34 373 (4.0)	203 205 (6.3)	203 205 (6.3)
Centre-Val de Loire	296 583 (4.1)	296 583 (4.1)	34 651 (4.0)	34 651 (4.0)	133 607 (4.1)	133 607 (4.1)
Corse	54 351 (0.8)	54 351 (0.8)	5480 (0.6)	5480 (0.6)	7438 (0.2)	7438 (0.2)
Grand Est	589 212 (8.2)	589 212 (8.2)	85 690 (10.0)	85 690 (10.0)	286 427 (8.8)	286 427 (8.8)
Hauts-de-France	577 660 (8.1)	577 660 (8.1)	53 838 (6.3)	53 838 (6.3)	353 666 (10.9)	353 666 (10.9)
Ile-de-France	1 082 060 (15.1)	1 082 060 (15.1)	149 954 (17.5)	149 954 (17.5)	483 113 (14.9)	483 113 (14.9)
Normandie	367 197 (5.1)	367 197 (5.1)	45 665 (5.3)	45 665 (5.3)	184 751 (5.7)	184 751 (5.7)
Nouvelle-Aquitaine	738 685 (10.3)	738 685 (10.3)	92 921 (10.8)	92 921 (10.8)	346 196 (10.7)	346 196 (10.7)
Occitanie	745 627 (10.4)	745 627 (10.4)	64 099 (7.5)	64 099 (7.5)	296 694 (9.2)	296 694 (9.2)
Pays de la Loire	418 607 (5.8)	418 607 (5.8)	31 969 (3.7)	31 969 (3.7)	205 586 (6.3)	205 586 (6.3)
Provence-Alpes-Côte d'Azur	669 461 (9.3)	669 461 (9.3)	83 690 (9.8)	83 690 (9.8)	209 865 (6.5)	209 865 (6.5)
Overseas departments	107 312 (1.5)	107 312 (1.5)	152 (0.0)	152 (0.0)	3943 (0.1)	3943 (0.1)
Resident of nursing home:						
No	6 973 945 (97.4)	6 973 945 (97.4)	856 426 (100)	856 426 (100)	3 238 572 (100)	3 238 572 (100)
Yes, with inpatient pharmacy	30 819 (0.4)	30 819 (0.4)	29 (0.0)	29 (0.0)	—	—
Yes, without inpatient pharmacy	156 894 (2.2)	156 894 (2.2)	144 (0.0)	144 (0.0)	3 (0.0)	3 (0.0)
Baseline characteristics						
Social deprivation index (in groups separated by quintiles):						
Group 1 (least deprived)	1 257 486 (17.6)	1 489 831 (20.8)	160 171 (18.7)	189 927 (22.2)	572 837 (17.7)	686 070 (21.2)
Group 2	1 321 002 (18.4)	1 375 859 (19.2)	159 929 (18.7)	176 113 (20.6)	618 182 (19.1)	663 072 (20.5)
Group 3	1 449 205 (20.2)	1 428 226 (19.9)	173 172 (20.2)	175 924 (20.5)	651 040 (20.1)	654 273 (20.2)
Group 4	1 500 897 (21.0)	1 409 661 (19.7)	177 979 (20.8)	164 960 (19.3)	693 554 (21.4)	641 172 (19.8)
Group 5 (most deprived)	1 460 106 (20.4)	1 281 541 (17.9)	178 409 (20.8)	142 471 (16.6)	685 683 (21.2)	576 992 (17.8)
Unknown	172 962 (2.4)	176 540 (2.4)	6939 (0.8)	7204 (0.8)	17 279 (0.5)	16 996 (0.5)
History of covid-19 status (hospital admission, screening tests)	367 168 (5.1)	194 256 (2.7)	41 859 (4.9)	22 462 (2.6)	154 234 (4.8)	66 938 (2.1)
Influenza vaccines	2 111 818 (29.5)	3 052 557 (42.6)	232 594 (27.2)	347 543 (40.6)	501 684 (15.5)	905 508 (28.0)
Frailty	672 566 (9.4)	577 506 (8.1)	70 535 (8.2)	64 188 (7.5)	133 980 (4.1)	129 275 (4.0)
Alcohol related conditions	91 486 (1.3)	68 337 (1.0)	11 129 (1.3)	8699 (1.0)	59 293 (1.8)	69 197 (2.1)
Cardiovascular risk factors						
Smoking related conditions	276 474 (3.9)	288 017 (4.0)	35 196 (4.1)	37 227 (4.3)	179 206 (5.5)	232 873 (7.2)
Hypertension	3 408 862 (47.6)	3 672 637 (51.3)	392 734 (45.8)	430 155 (50.2)	1 168 717 (36.1)	1 528 465 (47.2)
Diabetes mellitus	1 035 574 (14.5)	1 017 204 (14.2)	120 098 (14.0)	120 385 (14.1)	370 656 (11.4)	577 780 (17.8)
Dyslipidaemia	1 900 814 (26.5)	2 214 303 (30.9)	223 015 (26.0)	263 299 (30.7)	701 455 (21.7)	1 017 307 (31.4)
Obesity related conditions	89 311 (1.2)	107 924 (1.5)	11 109 (1.3)	13 949 (1.6)	48 789 (1.5)	80 385 (2.5)
Cardiovascular diseases						
Coronary heart disease	573 867 (8.0)	666 022 (9.3)	65 033 (7.6)	76 724 (9.0)	179 765 (5.6)	264 501 (8.2)
Heart failure	253 722 (3.5)	226 907 (3.2)	26 180 (3.1)	23 642 (2.8)	44 316 (1.4)	50 024 (1.5)

Continued

Table 1 Continued

	BNT162b2		mRNA-1273		ChAdOx1-S	
	Unvaccinated (n=7 161 658)	Vaccinated (n=7 161 658)	Unvaccinated (n=856 599)	Vaccinated (n=856 599)	Unvaccinated (n=3 238 575)	Vaccinated (n=3 238 575)
Cardiac rhythm disorder	535 751 (7.5)	572 562 (8.0)	57 104 (6.7)	61 887 (7.2)	108 641 (3.4)	139 738 (4.3)
Valvular heart disease	208 467 (2.9)	229 270 (3.2)	21 985 (2.6)	24 464 (2.9)	42 090 (1.3)	55 039 (1.7)
Occlusive peripheral arterial disease	198 548 (2.8)	196 846 (2.7)	22 069 (2.6)	22 513 (2.6)	61 873 (1.9)	78 521 (2.4)
Stroke	265 417 (3.7)	259 026 (3.6)	27 546 (3.2)	27 051 (3.2)	66 318 (2.0)	80 531 (2.5)
Pulmonary embolism	41 277 (0.6)	46 055 (0.6)	4533 (0.5)	5095 (0.6)	11 171 (0.3)	11 373 (0.4)
Other comorbidities						
Chronic respiratory conditions	616 243 (8.6)	670 036 (9.4)	71 564 (8.4)	78 654 (9.2)	230 761 (7.1)	314 488 (9.7)
Dialysis	7389 (0.1)	20 654 (0.3)	724 (0.1)	3079 (0.4)	1648 (0.1)	305 (0.0)
Having a transplanted kidney	4337 (0.1)	14 041 (0.2)	508 (0.1)	2025 (0.2)	2249 (0.1)	1161 (0.0)
Liver failure	71 757 (1.0)	76 187 (1.1)	8567 (1.0)	9308 (1.1)	34 532 (1.1)	40 949 (1.3)
Active cancer	316 750 (4.4)	423 905 (5.9)	35 917 (4.2)	50 219 (5.9)	103 965 (3.2)	124 921 (3.9)
Depression	862 045 (12.0)	925 978 (12.9)	95 802 (11.2)	104 511 (12.2)	315 949 (9.8)	409 417 (12.6)
Psychosis	126 159 (1.8)	108 782 (1.5)	12 416 (1.4)	10 560 (1.2)	46 500 (1.4)	55 545 (1.7)
Dementia	242 006 (3.4)	216 286 (3.0)	17 687 (2.1)	12 775 (1.5)	19 352 (0.6)	16 183 (0.5)
Epilepsy	45 478 (0.6)	42 848 (0.6)	4950 (0.6)	4879 (0.6)	17 354 (0.5)	20 389 (0.6)
Parkinson's disease	88 159 (1.2)	90 242 (1.3)	8824 (1.0)	9199 (1.1)	17 923 (0.6)	23 155 (0.7)
Inflammatory bowel disease	29 909 (0.4)	41 857 (0.6)	3766 (0.4)	5182 (0.6)	15 906 (0.5)	20 347 (0.6)
Rheumatoid arthritis	70 356 (1.0)	85 965 (1.2)	8114 (0.9)	9967 (1.2)	23 986 (0.7)	28 644 (0.9)
Ankylosing spondylitis	30 143 (0.4)	43 555 (0.6)	3751 (0.4)	5229 (0.6)	15 697 (0.5)	21 419 (0.7)

Data are number (%) of individuals, unless otherwise specified. SD=standard deviation.

who received different vaccine products between the first and second doses and their matched controls (online supplemental table 6). Vaccine effectiveness against covid-19 related death in hospital (table 3) was 91% (90% to 93%) for the BNT162b2 vaccine, 96% (92% to 98%) for the mRNA-1273 vaccine, and 88% (68% to 95%) for the ChAdOx1-S vaccine.

At 5-6 months following at least 14 days after the second dose, BNT162b2 and mRNA-1273 vaccines were still effective with risk reductions of 94% (92% to 95%) and of 98% (93% to 100%; table 4). Vaccine effectiveness of the ChAdOx1-S vaccine was measurable only at 3-4 months following at least 14 days after the second dose and reached 90% (63% to 97%).

Vaccine effectiveness at the time of the delta variant circulation is presented in table 5. All three vaccines remained highly effective during this period with risk reductions of 89% (87% to 90%) for BNT162b2, 95% (90% to 98%) for mRNA-1273, and of 91% (88% to 94%) for ChAdOx1-S.

Subgroup analyses show that mRNA vaccines were effective across all studied age categories with vaccine effectiveness of 90% or higher regardless of age (online supplemental table 7). By contrast, vaccine effectiveness of the ChAdOx1-Svaccine tended to decrease with age: 96% (93% to 98%) in individuals aged 50-64 years, 89% (83% to 92%) in those aged 65-74 years, and 80% (52% to 91%) in those aged 75-84 years. Vaccine effectiveness of the three vaccines was consistent in both sexes (online supplemental table 8).

Discussion

Principal findings

We did a cohort study in a nationwide mass vaccination setting of more than 11 million vaccinated people aged ≥50 years, matched with their unvaccinated controls. We found that all three vaccines (BNT162b2, mRNA-1273, and ChAdOx1 nCoV-19) decreased the risk of covid-19 related hospital admission by ≥90% after individuals received the two doses (estimated vaccine effectiveness 91% for BNT162b2, 95% for mRNA-1273, 91% for ChAdOx1 nCoV-19). We observed similar results when effectiveness was examined against covid-19 related death in hospital. Our results also suggest that the level of vaccine effectiveness remained higher than 90% at 5-6 months following at least 14 days after the receipt of the second dose for the mRNA vaccines (BNT162b2, mRNA-1273) and at 3-4 months for the ChAdOx1-S vaccine. Additionally, the effectiveness of the three vaccines appeared to be maintained against the delta variant. Furthermore, while mRNA vaccines appeared consistently effective across all age subgroups, ChAdOx1-S vaccine effectiveness tended to decrease in people aged ≥65 years compared with those aged 50-64 years.

Comparison with other studies

Our estimates of the two dose vaccine effectiveness of the mRNA vaccines against covid-19 related hospital

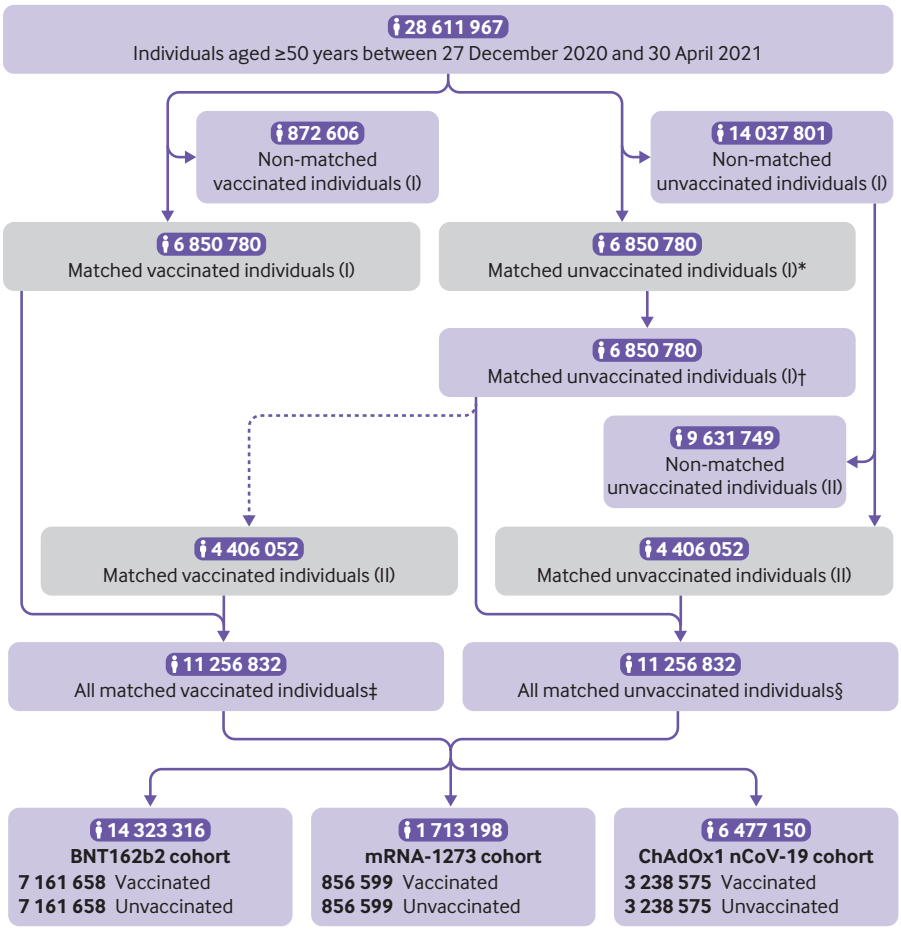

Figure 1 | Flowchart of participant inclusion. Matching criteria included age, sex, and region of residence, plus residency in a nursing home for those individuals aged ≥75 years. Date of inclusion was defined by the vaccination date of the first dose of the vaccinated individual, both for the vaccinated and matched controls in each pair. Matching procedure was performed on a daily basis. Individuals who were initially (matching procedure I) in the control group were eligible for inclusion in the exposure group when vaccinated during the inclusion period (matching procedure II). Follow-up of pairs ended at the earliest instance of the following events: occurrence of an outcome of interest, death, vaccination of unvaccinated controls, or the end of the study period (20 August 2021). *During matching procedure I, all individuals of the control group were unvaccinated (n=6 850 780). †In the matched unvaccinated group from matching procedure I (n=6 850 780), some individuals were vaccinated afterwards during the inclusion period (matching procedure II, n=4 406 052); they were eligible for inclusion in the vaccinated group. ‡All matched vaccinated individuals included those who were matched during matching procedure I (n=6 850 780) and those who were in the unvaccinated group from matching procedure I (n=6 850 780) who were vaccinated during matching procedure II (n=4 406 052; they were included twice in the study). §All matched unvaccinated individuals included those who were matched during matching procedure I (n=6 850 780) and those who were not matched during matching procedure I but were during matching procedure II (n=4 406 052)

admission or covid-19 related death in hospital are consistent with the 81.0% to 97.4% estimates reported in previously published studies based on different designs (test negative, case-control studies and cohort studies).[7 9 22 25–27 29 31 34 35 42 44–54] Although estimates of the two dose vaccine effectiveness of ChAdOx1-S are less abundant, they were also similar to our results, ranging from 81.5% to 97.5%.[42 43 46 48 50 52 55–58] Two reasons might explain the lack or delayed publication of results on the two dose vaccine effectiveness of the ChAdOx1-S vaccine. It had less worldwide use than the other vaccines and its interdose interval was long (≥12 weeks in the UK, where ChAdOx1-S was mainly used) compared with that of the mRNA vaccines (four weeks). These reasons might be due to restrictions in the ChAdOx1-S vaccine supply and the temporary loss of trust in this vaccine following reports of blood clots and one death after its use in March 2021.[76] We found that the effectiveness of two doses of the ChAdOx1-S vaccine was similar to that of the mRNA vaccines. This finding, based on more than 3 million people vaccinated with the ChAdOx1 nCoV-19 vaccine, is reassuring.

Several studies have shown that the effectiveness of mRNA vaccines to protect against SARS-CoV-2 infection waned with time[77] (eg, effectiveness fell from 88% (within the first month after full

Table 2 | Vaccine effectiveness against covid-19 related hospital admission by follow-up time intervals and vaccine group

Follow-up time intervals and vaccination status	No of individuals in hospital/Total No in group (%)	Median follow-up (IQR)	Model 1 (HR, 95% CI)*	Model 2 (adjusted HR, 95% CI)†	Vaccine effectiveness (%, 95% CI)
After the first dose					
≥0 days:					
BNT162b2—No	23 781/7 161 658 (0.33)	49 (19-115)	1	1	—
BNT162b2—Yes	7115/7161 658 (0.1)	49 (19-116)	0.30 (0.29 to 0.30)	0.30 (0.29 to 0.30)	70 (70 to 71)
mRNA-1273—No	2616/856 599 (0.31)	47 (20-115)	1	1	—
mRNA-1273—Yes	643/856 599 (0.08)	48 (20-117)	0.24 (0.22 to 0.27)	0.25 (0.23 to 0.27)	75 (73 to 77)
ChAdOx1-S—No	6812/323 8575 (0.21)	51 (22-115)	1	1	—
ChAdOx1-S—Yes	2191/3 238 575 (0.07)	51 (22-116)	0.32 (0.31 to 0.34)	0.30 (0.28 to 0.31)	70 (69 to 72)
0-6 days:					
BNT162b2—No	3513/7 161 658 (0.05)	6 (6-6)	1	1	—
BNT162b2—Yes	815/7 161 658 (0.01)	6 (6-6)	0.23 (0.21 to 0.25)	0.29 (0.27 to 0.31)	71 (69 to 73)
mRNA-1273—No	407/856 599 (0.05)	6 (6-6)	1	1	—
mRNA-1273—Yes	75/856 599 (0.01)	6 (6-6)	0.18 (0.14 to 0.24)	0.23 (0.18 to 0.30)	77 (70 to 82)
ChAdOx1-S—No	1083/3 238 575 (0.03)	6 (6-6)	1	1	—
ChAdOx1-S—Yes	165/3 238 575 (0.01)	6 (6-6)	0.15 (0.13 to 0.18)	0.20 (0.17 to 0.24)	80 (76 to 83)
7-13 days:					
BNT162b2—No	3131/6 518 914 (0.05)	6 (6-6)	1	1	—
BNT162b2—Yes	2025/6 518 914 (0.03)	6 (6-6)	0.65 (0.61 to 0.68)	0.67 (0.64 to 0.71)	33 (29 to 36)
mRNA-1273—No	344/783 793 (0.04)	6 (6-6)	1	1	—
mRNA-1273—Yes	241/783 793 (0.03)	6 (6-6)	0.70 (0.59 to 0.83)	0.76 (0.64 to 0.90)	24 (10 to 36)
ChAdOx1-S—No	949/3 023 849 (0.03)	6 (6-6)	1	1	—
ChAdOx1-S—Yes	582/3 023 849 (0.02)	6 (6-6)	0.61 (0.55 to 0.68)	0.59 (0.53 to 0.65)	41 (35 to 47)
14-28 days:					
BNT162b2—No	5288/5 828 107 (0.09)	14 (14-14)	1	1	—
BNT162b2—Yes	2472/5 828 107 (0.04)	14 (14-14)	0.47 (0.45 to 0.49)	0.45 (0.42 to 0.47)	55 (53 to 58)
mRNA-1273—No	585/704 523 (0.08)	14 (14-14)	1	1	—
mRNA-1273—Yes	214/704 523 (0.03)	14 (14-14)	0.37 (0.31 to 0.43)	0.35 (0.30 to 0.41)	65 (59 to 70)
14-84 days:					
ChAdOx1-S—No	4074/2 765 229 (0.15)	49 (19-70)	1	1	—
ChAdOx1-S—Yes	1364/2 765 229 (0.05)	49 (20-70)	0.33 (0.31 to 0.36)	0.29 (0.27 to 0.31)	71 (69 to 73)
After the second dose					
≥0 days:					
BNT162b2—No	11 973/4 510 470 (0.27)	61 (22-103)	1	1	—
BNT162b2—Yes	1362/4 510 470 (0.03)	62 (22-105)	0.11 (0.11 to 0.12)	0.10 (0.10 to 0.11)	90 (89 to 90)
mRNA-1273—No	1260/531 145 (0.24)	59 (20-105)	1	1	—
mRNA-1273—Yes	71/531 145 (0.01)	61 (20-106)	0.06 (0.04 to 0.07)	0.05 (0.04 to 0.06)	95 (94 to 96)
ChAdOx1-S—No	794/1 161 249 (0.07)	52 (29-72)	1	1	—
ChAdOx1-S—Yes	83/1 161 249 (0.01)	52 (29-72)	0.10 (0.08 to 0.13)	0.09 (0.07 to 0.11)	91 (89 to 93)
≥7 days:					
BNT162b2—No	10 026/4 109 949 (0.24)	63 (22-100)	1	1	—
BNT162b2—Yes	1103/4 109 949 (0.03)	64 (23-101)	0.11 (0.10 to 0.12)	0.10 (0.09 to 0.10)	90 (90 to 91)
mRNA-1273—No	1047/479 662 (0.22)	64 (21-101)	1	1	—
mRNA-1273—Yes	62/479 662 (0.01)	64 (21-101)	0.06 (0.05 to 0.08)	0.05 (0.04 to 0.07)	95 (93 to 96)
ChAdOx1-S—No	703/1 082 665 (0.06)	49 (28-67)	1	1	—
ChAdOx1-S—Yes	73/1 082 665 (0.01)	49 (28-67)	0.10 (0.08 to 0.13)	0.09 (0.07 to 0.11)	91 (89 to 93)
≥14 days:					
BNT162b2—No	8250/3 702 098 (0.22)	62 (25-98)	1	1	—
BNT162b2—Yes	810/3 702 098 (0.02%)	62 (25-98)	0.10 (0.09 to 0.10)	0.09 (0.08 to 0.09)	91 (91 to 92)
mRNA-1273—No	831/426 617 (0.19)	63 (25-98)	1	1	—
mRNA-1273—Yes	48/426 617 (0.01)	64 (25-98)	0.06 (0.04 to 0.08)	0.05 (0.04 to 0.07)	95 (93 to 96)
ChAdOx1-S—No	617/1 001 776 (0.06)	43 (27-62)	1	1	—
ChAdOx1-S—Yes	62/1 001 776 (0.01)	43 (27-62)	0.10 (0.08 to 0.13)	0.09 (0.06 to 0.11)	91 (89 to 94)

IQR=interquartile range; HR=hazard ratio; CI=confidence interval; Yes=vaccinated; No=unvaccinated.

*Model 1: adjusted for matching variables (age, sex, region of residence, nursing home status).

†Model 2: model 1 with further adjustment for social deprivation index, history of positive covid-19 status, history of influenza vaccination, frailty, alcohol related conditions, smoking related conditions, hypertension, diabetes mellitus, dyslipidaemia, obesity related conditions, coronary heart disease, heart failure, cardiac rhythm disorder, valvular heart disease, occlusive peripheral arterial disease, stroke, pulmonary embolism, chronic respiratory conditions, dialysis, having a transplanted kidney, liver failure, active cancer, depression, psychosis, dementia, epilepsy, Parkinson's disease, inflammatory bowel disease, rheumatoid arthritis, and ankylosing spondylitis.

Table 3 | Vaccine effectiveness against covid-19 related death in hospital by follow-up time intervals and vaccine group

Follow-up time intervals and vaccination status	No of individuals who died/Total No in group (%)	Median follow-up (IQR)	Model 1 (HR, 95% CI)*	Model 2 (adjusted HR, 95% CI)†	Vaccine effectiveness (%, 95% CI)
After the first dose					
≥0 day:					
BNT162b2—No	5024/7 161 658 (0.07)	49 (19 to 115)	1	1	—
BNT162b2—Yes	1481/7 161 658 (0.02)	49 (19 to 116)	0.29 (0.27 to 0.31)	0.28 (0.26 to 0.29)	72 (71 to 74)
mRNA-1273—No	499/856 599 (0.06)	47 (20 to 115)	1	1	—
mRNA-1273—Yes	126/856 599 (0.01)	48 (20 to 117)	0.25 (0.21 to 0.30)	0.24 (0.19 to 0.29)	76 (71 to 81)
ChAdOx1 nCoV-19—No	648/3 238 575 (0.02)	51 (22 to 115)	1	1	—
ChAdOx1-S—Yes	179/3 238 575 (0.01)	51 (22 to 116)	0.27 (0.23 to 0.32)	0.27 (0.23 to 0.32)	73 (68 to 77)
0–6 days:					
BNT162b2—No	689/7 161 658 (0.01)	6 (6 to 6)	1	1	—
BNT162b2—Yes	198/7 161 658 (0)	6 (6 to 6)	0.29 (0.25 to 0.34)	0.32 (0.28 to 0.38)	68 (62 to 72)
mRNA-1273—No	70/856 599 (0.01)	6 (6 to 6)	1	1	—
mRNA-1273—Yes	19/856 599 (0)	6 (6 to 6)	0.27 (0.16 to 0.45)	0.28 (0.17 to 0.47)	72 (53 to 83)
ChAdOx1-S—No	126/3 238 575 (0)	6 (6 to 6)	1	1	—
ChAdOx1-S—Yes	25/3 238 575 (0)	6 (6 to 6)	0.20 (0.13 to 0.30)	0.27 (0.17 to 0.41)	73 (59 to 83)
7–13 days:					
BNT162b2—No	657/6 518 914 (0.01)	6 (6 to 6)	1	1	—
BNT162b2—Yes	373/6 518 914 (0.01)	6 (6 to 6)	0.57 (0.50 to 0.64)	0.57 (0.50 to 0.65)	43 (35 to 50)
mRNA-1273—No	51/783 793 (0.01)	6 (6 to 6)	1	1	—
mRNA-1273—Yes	49/783 793 (0.01)	6 (6 to 6)	0.96 (0.65 to 1.42)	1.04 (0.69 to 1.57)	−4 (−57 to 31)
ChAdOx1-S—No	96/3 023 849 (0)	6 (6 to 6)	1	1	—
ChAdOx1-S—Yes	49/3 023 849 (0)	6 (6 to 6)	0.51 (0.36 to 0.72)	0.48 (0.33 to 0.68)	52 (32 to 67)
14–28 days:					
BNT162b2—No	1132/5 828 107 (0.02%)	14 (14 to 14)	1	1	—
BNT162b2—Yes	513/5 828 107 (0.01%)	14 (14 to 14)	0.45 (0.41 to 0.50)	0.42 (0.38 to 0.47)	58 (53 to 62)
mRNA-1273—No	118/704 523 (0.02%)	14 (14 to 14)	1	1	—
mRNA-1273—Yes	39/704 523 (0.01%)	14 (14 to 14)	0.33 (0.23 to 0.47)	0.31 (0.21 to 0.45)	69 (55 to 79)
14–84 days:					
ChAdOx1-S—No	377/2 765 229 (0.01)	49 (19 to 70)	1	1	—
ChAdOx1-S—Yes	100/2 765 229 (0)	49 (20 to 70)	0.26 (0.21 to 0.33)	0.24 (0.19 to 0.30)	76 (70 to 81)
After the second dose					
≥0 days:					
BNT162b2—No	2619/4 510 470 (0.06)	61 (22 to 103)	1	1	—
BNT162b2—Yes	300/4 510 470 (0.01)	62 (22 to 105)	0.11 (0.10 to 0.13)	0.10 (0.09 to 0.11)	90 (89 to 91)
mRNA-1273—No	263/531 145 (0.05)	59 (20 to 105)	1	1	—
mRNA-1273—Yes	11/531 145 (0)	61 (20 to 106)	0.04 (0.02 to 0.08)	0.04 (0.02 to 0.07)	96 (93 to 98)
ChAdOx1-S—No	56/1161249 (0%)	52 (29 to 72)	1	1	—
ChAdOx1-S—Yes	6/1 161 249 (0)	52 (29 to 72)	0.11 (0.05 to 0.25)	0.12 (0.05 to 0.29)	88 (71 to 95)
≥7 days:					
BNT162b2—No	2162/4 109 949 (0.05%)	63 (22 to 100)	1	1	—
BNT162b2—Yes	247/4 109 949 (0.01%)	64 (23 to 101)	0.11 (0.10 to 0.13)	0.10 (0.09 to 0.11)	90 (89 to 91)
mRNA-1273—No	210/479 662 (0.04%)	64 (21 to 101)	1	1	—
mRNA-1273—Yes	10/479 662 (0%)	64 (21 to 101)	0.05 (0.02 to 0.09)	0.04 (0.02 to 0.08)	96 (92 to 98)
ChAdOx1-S—No	48/1 082 665 (0)	49 (28 to 67)	1	1	—
ChAdOx1-S—Yes	5/1 082 665 (0)	49 (28 to 67)	0.10 (0.04 to 0.26)	0.12 (0.05 to 0.31)	88 (69 to 95)
≥14 days:					
BNT162b2—No	1778/3 702 098 (0.05)	62 (25 to 98)	1	1	—
BNT162b2—Yes	183/3 702 098 (0)	62 (25 to 98)	0.10 (0.09 to 0.12)	0.09 (0.07 to 0.10)	91 (90 to 93)
mRNA-1273—No	163/426 617 (0.04)	63 (25 to 98)	1	1	—
mRNA-1273—Yes	7/426 617 (0)	64 (25 to 98)	0.04 (0.02 to 0.09)	0.04 (0.02 to 0.08)	96 (92 to 98)
ChAdOx1-S—No	45/1 001 776 (0)	43 (27 to 62)	1	1	—
ChAdOx1-S—Yes	5/1 001 776 (0%)	43 (27 to 62)	0.11 (0.04 to 0.28)	0.12 (0.05 to 0.32)	88 (68 to 95)

IQR=interquartile range; HR=hazard ratio; CI=confidence interval; Yes=vaccinated; No=unvaccinated.

*Model 1: adjusted for matching variables (age, sex, region of residence, nursing home status).

†Model 2: model 1 with further adjustment for social deprivation index, history of positive covid-19 status, history of influenza vaccination, frailty, alcohol related conditions, smoking related conditions, hypertension, diabetes mellitus, dyslipidaemia, obesity related conditions, coronary heart disease, heart failure, cardiac rhythm disorder, valvular heart disease, occlusive peripheral arterial disease, stroke, pulmonary embolism, chronic respiratory conditions, dialysis, having a transplanted kidney, liver failure, active cancer, depression, psychosis, dementia, epilepsy, Parkinson's disease, inflammatory bowel disease, rheumatoid arthritis, and ankylosing spondylitis.

Table 4 | Vaccine effectiveness against covid-19 related hospital admission by follow-up duration starting 14 days after the second dose and vaccine group

Follow-up from 14 days after second dose	No of individuals in hospital/Total No in group (%)	Median (IQR) follow-up (days)	Model 1 (HR, 95% CI)*	Model 2 (adjusted HR, 95% CI)†	Vaccine effectiveness (%, 95% CI)
≤1 months					
BNT162b2—No	1700/1 299 510 (0.13)	16 (8-27)	1	1	—
BNT162b2—Yes	236/1 299 510 (0.02)	16 (8-27)	0.13 (0.11 to 0.15)	0.10 (0.09 to 0.12)	90 (88 to 91)
mRNA-1273—No	155/148 183 (0.1)	15 (7-26)	1	1	—
mRNA-1273—Yes	16/148 183 (0.01)	16 (7-27)	0.10 (0.06 to 0.16)	0.08 (0.05 to 0.15)	92 (85 to 95)
ChAdOx1-S—No	146/401 700 (0.04)	22 (12-30)	1	1	—
ChAdOx1-S—Yes	11/401 700 (0)	22 (12-30)	0.07 (0.04 to 0.14)	0.06 (0.03 to 0.12)	94 (88 to 97)
>1–2 months					
BNT162b2—No	1405/812 094 (0.17)	50 (40-59)	1	1	—
BNT162b2—Yes	185/812 094 (0.02)	51 (40-59)	0.13 (0.11 to 0.15)	0.11 (0.09 to 0.12)	89 (88 to 91)
mRNA-1273—No	136/86 852 (0.16)	50 (40-59)	1	1	—
mRNA-1273—Yes	12/86 852 (0.01)	51 (40-59)	0.08 (0.05 to 0.15)	0.07 (0.04 to 0.12)	93 (88 to 96)
ChAdOx1-S—No	277/417 902 (0.07)	45 (38-53)	1	1	—
ChAdOx1-S—Yes	35/417 902 (0.01)	45 (38-53)	0.13 (0.09 to 0.18)	0.11 (0.08 to 0.16)	89 (84 to 92)
>2–3 months					
BNT162b2—No	1474/789 263 (0.19)	77 (67-86)	1	1	—
BNT162b2—Yes	108/789 263 (0.01)	77 (67-86)	0.07 (0.06 to 0.09)	0.06 (0.05 to 0.07)	94 (93 to 95)
mRNA-1273—No	143/89 122 (0.16)	76 (66-86)	1	1	—
mRNA-1273—Yes	7/89 122 (0.01)	76 (66-86)	0.05 (0.02 to 0.10)	0.04 (0.02 to 0.09)	96 (91 to 98)
ChAdOx1-S—No	174/171 401 (0.1)	70 (65-77)	1	1	—
ChAdOx1-S—Yes	13/171 401 (0.01)	70 (65-77)	0.07 (0.04 to 0.13)	0.06 (0.03 to 0.11)	94 (89 to 97)
>3–4 months					
BNT162b2—No	1709/558 114 (0.31)	105 (96-113)	1	1	—
BNT162b2—Yes	142/558 114 (0.03)	105 (96-113)	0.08 (0.07 to 0.10)	0.06 (0.05 to 0.08)	94 (92 to 95)
mRNA-1273—No	220/80 794 (0.27)	103 (95-111)	1	1	—
mRNA-1273—Yes	8/80 794 (0.01)	103 (95-111)	0.04 (0.02 to 0.07)	0.03 (0.01 to 0.06)	97 (94 to 99)
ChAdOx1-S—No	20/10 701 (0.19)	93 (91-98)	1	1	—
ChAdOx1-S—Yes	3/10 701 (0.03)	93 (91-98)	0.15 (0.04 to 0.50)	0.10 (0.03 to 0.37)	90 (63 to 97)
>4–5 months					
BNT162b2—No	1080/146 765 (0.74)	130 (126-142)	1	1	—
BNT162b2—Yes	70/146 765 (0.05)	130(126-142)	0.06 (0.05 to 0.08)	0.04 (0.03 to 0.05)	96 (95 to 97)
mRNA-1273—No	107/16 036 (0.67)	136 (127-147)	1	1	—
mRNA-1273—Yes	3/16 036 (0.02)	136 (127-147)	0.03 (0.01 to 0.09)	0.02 (0.01 to 0.06)	98 (94 to 99)
>5–6 months					
BNT162b2—No	871/95 266 (0.91)	163 (157-169)	1	1	—
BNT162b2—Yes	69/95 266 (0.07)	163 (157-169)	0.08 (0.06 to 0.10)	0.06 (0.05 to 0.08)	94 (92 to 95)
mRNA-1273—No	70/5630 (1.24)	157 (154-164)	1	1	—
mRNA-1273—Yes	2/5630 (0.04)	157 (154-164)	0.03 (0.01 to 0.12)	0.02 (0.00 to 0.07)	98 (93 to 100)
>6 months					
BNT162b2—No	11/1086 (1.01)	183 (182-185)	1	1	—
BNT162b2—Yes	0/1086 (0.00)	183 (182-185)	—	—	—

IQR=interquartile range; HR=hazard ratio; CI=confidence interval; Yes=vaccinated; No=unvaccinated.

*Model 1: adjusted for matching variables (age, sex, region of residence, nursing home status).

†Model 2: Model 1 with further adjustment for social deprivation index, history of positive covid-19 status, history of influenza vaccination, frailty, alcohol related conditions, smoking related conditions, hypertension, diabetes mellitus, dyslipidaemia, obesity related conditions, coronary heart disease, heart failure, cardiac rhythm disorder, valvular heart disease, occlusive peripheral arterial disease, stroke, pulmonary embolism, chronic respiratory conditions, dialysis, having a transplanted kidney, liver failure, active cancer, depression, psychosis, dementia, epilepsy, Parkinson's disease, inflammatory bowel disease, rheumatoid arthritis, and ankylosing spondylitis.

vaccination) to 47% (after about five months),[25] 78% to 17%,[28] 82% to 33%,[45] 84% to 69%,[46] 92% to 47%,[48] 88% to 68%,[49] 90% to 70%,[51] and 94% to 80%[53]). However, these vaccines maintained better effectiveness against severe covid-19 than against SARS-CoV-2 infection. Two dose vaccine effectiveness varied from 87% (within the first month after full vaccination) to 88% (after five months),[25] 96.0% to 88.9%,[28] 96% to 80%,[45] 98.6% to 93.8%,[46] 89% to 64%,[48] 94% to 92%,[49] 92% to 81%,[51] and 98% to 80%.[53] We also found that the effectiveness of two doses of mRNA vaccines against

Table 5 | Vaccine effectiveness of two doses against covid-19 related hospital admission at the time of delta variant circulation in France between 1 July and 20 August 2021

Vaccine product and vaccination status	No of individuals in hospital/ Total No in group (%)	Median (IQR) follow-up (days)	Model 1 (HR, 95% CI)*	Model 2 (adjusted HR, 95% CI)†	Vaccine effectiveness (%, 95% CI)
BNT162b2—No	1658/1 984 730 (0.08)	87 (63 to 109)	1	1	—
BNT162b2—Yes	202/1 984 730 (0.01)	87 (63 to 109)	0.12 (0.11 to 0.14)	0.11 (0.10 to 0.13)	89 (87 to 90)
mRNA-1273—No	175/239 651 (0.07%)	89 (64 to 107)	1	1	—
mRNA-1273—Yes	9/239 651 (0%)	89 (64 to 107)	0.05 (0.03 to 0.10)	0.05 (0.02 to 0.10)	95 (90 to 98)
ChAdOx1-S—No	430/763 455 (0.06%)	43 (28 to 58)	1	1	—
ChAdOx1-S—Yes	44/763 455 (0.01%)	43 (28 to 58)	0.10 (0.07 to 0.14)	0.09 (0.06 to 0.12)	91 (88 to 94)

IQR=interquartile range; HR=hazard ratio; CI=confidence interval; Yes=vaccinated; No=unvaccinated.

*Model 1: adjusted for matching variables (age, sex, region of residence, nursing home status).

†Model 2: model 1 with further adjustment for social deprivation index, history of positive covid-19 status, history of influenza vaccination, frailty, alcohol related conditions, smoking related conditions, hypertension, diabetes mellitus, dyslipidaemia, obesity related conditions, coronary heart disease, heart failure, cardiac rhythm disorder, valvular heart disease, occlusive peripheral arterial disease, stroke, pulmonary embolism, chronic respiratory conditions, dialysis, having a transplanted kidney, liver failure, active cancer, depression, psychosis, dementia, epilepsy, Parkinson's disease, inflammatory bowel disease, rheumatoid arthritis, and ankylosing spondylitis.

severe covid-19 remained at a high level, from 90% for BNT162b2 and 92% for mRNA-1273 within the first month after the receipt of two doses to 94% for BNT162b2 and 98% for mRNA-1273 at 5-6 months after the receipt of two doses.

Owing to a long interdose interval for the ChAdOx1-S vaccine and its delayed use from February 2021 in France, we could not estimate its effectiveness at 5-6 months after the receipt of two doses. However, its effectiveness was estimated at 90% after 3-4 months versus 94% during the first month after full vaccination. In a study from England, researchers found a similar result to ours: from 96% effectiveness within the first month after the receipt of two doses to 90% after four months[46]; in two studies conducted in Sweden and Scotland, researchers found a larger decrease in vaccine effectiveness: 89% to 64%,[48] and 84% to 64%,[57] respectively. Effectiveness of all vaccine products with a longer follow-up still needs to be studied.

For some of the results, the confidence intervals for the ChAdOx1-S vaccine are much wider than for the mRNA vaccines it is being compared to. These wider confidence intervals could be explained by a systematically shorter follow-up time after the second dose, leaving less time to develop outcomes of interest. This shorter follow-up time was caused by a longer interdose interval for the ChAdOx1-S vaccine than for the mRNA vaccines.

Two dose vaccine effectiveness during the time of the circulation of the delta variant of SARS-CoV-2 was 89% for the BNT162b2 vaccine, 95% for the mRNA-1273 vaccine, and 91% for the ChAdOx1-S vaccine. A similar result was reported in published studies on these vaccines from different countries.[25 45 46 50 51 53]

We also observed that mRNA vaccines were highly effective (≥90%) across all studied age categories. However, the ChAdOx1-S vaccine's effectiveness tended to decrease with age. Lower effectiveness (80%) among adults aged ≥75 years than among those aged ≤74 years might be due partly to a selection bias, because this vaccine was not formally recommended for this older portion of the population. Decreased vaccine effectiveness of ChAdOx1 nCoV-19[58] and mRNA vaccines[44 45 52] among older participants has also been observed elsewhere.

Strengths and limitations

This study had some limitations. Firstly, given the observational nature of the data, our study could have been affected by residual confounding owing to differences between vaccinated individuals and unvaccinated controls, especially in terms of healthcare seeking behaviour or risk of infection, which could have been affected by changes in public health policy or transmission dynamics during the study.[78] To take into account these differences, each newly vaccinated person was matched on the day of the vaccination to an unvaccinated control of the same age, sex, region of residence, and nursing home status for individuals aged ≥75 years. Subsequently, we adjusted all analyses on history of influenza vaccine received during the previous two years before the covid-19 outbreak and for a varied range of comorbidities that were shown to be associated with covid-19 related hospital admission.[71]

Secondly, during the first week after the receipt of the first dose, a risk reduction was observed among vaccinated individuals, although such an early reduction could not be due to the effect of the vaccine. This effect might be explained by healthier or more health conscious people being more likely to be included in the vaccinated group, and by the temporary exclusion of the vaccination of individuals having symptoms suggestive of covid-19 in the unvaccinated group. Owing to the matching procedure, vaccinated and unvaccinated groups had a similar proportion of comorbidities except that vaccinated individuals were less likely to be socially disadvantaged, less likely to be infected by SARS-CoV-2

before vaccination, and more likely to be vaccinated against influenza than unvaccinated controls (online supplemental tables 2–4). We took into account observed differences by adjusting for these covariables and using specific outcomes related to covid-19 vaccines.[79] However, residual healthy vaccinee bias could have overestimated vaccine effectiveness against severe covid-19.

Thirdly, our results could have been overestimated because vaccinated individuals were more likely to live in an environment surrounded by vaccinated individuals. Two studies have shown that individuals without SARS-CoV-2 immunity had at least 39% lower risk of infection as the number of immune family members increased.[80 81] Finally, our study did not look at covid-19 vaccine effectiveness against non-severe covid-19 outcomes, such as asymptomatic or mild SARS-CoV-19 infections that did not lead to hospital admission.

SNDS, a claims database comprising of the population of France, has allowed us to comprehensively examine the effectiveness of three covid-19 vaccines in adults aged ≥50 years. This study also provides estimates of the effectiveness of two doses of the ChAdOx1-S vaccine at a national level in France, among the 3 million individuals who have received this vaccine. Our study population, derived from the general population, should limit the risk of selection bias.

Conclusions

This nationwide cohort study of more than 11 million vaccinated people matched with unvaccinated controls showed that the BNT162b2, mRNA-1273, and ChAdOx1-S vaccines were highly and equally effective against severe covid-19 outcomes after completing a two dose vaccination schedule. The level of effectiveness persisted at 5-6 months after the receipt of the second dose for mRNA vaccines, at 3-4 months after the second dose of the ChAdOx1-S vaccine, and at the time of the delta variant of SARS-CoV-2 circulation. These results from the study conducted between 27 December 2020 and 20 August 2021 cannot be assumed to be entirely transferable to the current or future dominant variants. The effectiveness of covid-19 vaccines should be carefully examined over a longer period and with regard to possible surges of new SARS-CoV-2 variants of concern.

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Contributors MZ, AW, and RD-S had the idea for the study. MZ, AW, RD-S, and JB conceived and planned the study. KB drafted the manuscript. BB and JD performed data management. BB and KB performed statistical analyses. MZ, AW, and RD-S ensured project and study management. All authors contributed to interpretation of the data and revised the manuscript. All authors approved the final manuscript. The corresponding author (MZ) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. MZ is the guarantor.Transparency: The lead author (the guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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