Effectiveness of first dose of COVID-19 vaccines against hospital admissions in Scotland: national prospective cohort study of 5.4 million people

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Summary

Background: The BNT162b2 mRNA (Pfizer-BioNTech) and ChAdOx1 (Oxford-AstraZeneca) COVID-19 vaccines have demonstrated high efficacy against infection in phase 3 clinical trials and are now being used in national vaccination programmes in the UK and several other countries. There is an urgent need to study the 'real-world' effects of these vaccines. The aim of our study was to estimate the effectiveness of the first dose of these COVID-19 vaccines in preventing hospital admissions.

Methods: We conducted a prospective cohort study using the Early Pandemic Evaluation and Enhanced Surveillance of COVID-19 (EAVE II) database comprising of linked vaccination, primary care, Real-Time Polymerase Chain Reaction (RT-PCR) testing, hospitalisation and mortality records for 5.4 million people in Scotland (covering ~99% of population). A time-dependent Cox model and Poisson regression models were fitted to estimate effectiveness against COVID-19 related hospitalisation (defined as 1- Adjusted Hazard Ratio) following the first dose of vaccine.

Findings: The first dose of the BNT162b2 vaccine was associated with a vaccine effect of 85% (95% confidence interval [CI] 76 to 91) for COVID-19 related hospitalisation at 28-34 days post-vaccination. Vaccine effect at the same time interval for the ChAdOx1 vaccine was 94% (95% CI 73 to 99). Results of combined vaccine effect for prevention of COVID-19 related hospitalisation were comparable when restricting the analysis to those aged ≥80 years (81%; 95% CI 65 to 90 at 28-34 days post-vaccination).

Interpretation: A single dose of the BNT162b2 mRNA and ChAdOx1 vaccines resulted in substantial reductions in the risk of COVID-19 related hospitalisation in Scotland.

Funding: UK Research and Innovation (Medical Research Council); Research and Innovation Industrial Strategy Challenge Fund; Health Data Research UK.

Research in context

Evidence before this study

We searched PubMed and medRxiv for observational studies using the terms "COVID-19 vaccine effect". We found one preprint that reported a 51% relative risk reduction against SARS-CoV-2 infection 13-24 days after the first dose of the BNT162b2 mRNA (Pfizer-BioNTech) vaccine. This study used data from a state-mandated health provider in Israel covering 503,875 individuals. We also found a correspondence article that reported adjusted rate reductions for SARS-CoV-2 infections of 30% and 75%, respectively for the periods 1–14 and 15–28 days after the first dose of the BNT162b2 vaccine in a cohort of 9,109 healthcare workers in Israel's largest hospital.

Added value of this study

UK policy for use of vaccines against COVID-19 involves an offer of a first dose followed by a second dose 12 weeks later. To our knowledge, this is the first study of COVID-19 vaccine effect against hospitalisation for an entire nation after a single dose of vaccine. We found that a single dose of BNT162b2 COVID-19 vaccine was associated with a vaccine effect (VE) of 85% (95% CI 76 to 91) for COVID-19 hospitalisation 28-34 days post-vaccination. A single dose of ChAdOx1 vaccine was associated with a vaccine effect 94% (95% CI 73 to 99) at 28-34 days post-vaccination. VEs increased over time with a peak at 28-34 days post-vaccination for both vaccines. Comparable VEs were seen in those aged ≥80 years for prevention of COVID-19 hospitalisation with a high combined VE of 81% (95% CI 65 to 90) at 28-34 days post-vaccination.

Implications of all the available evidence

We provide compelling evidence that the two COVID-19 vaccines currently being used in the UK vaccination programme substantially reduce the risk of COVID-19 related hospital admissions in the population who are at highest risk for severe COVID-19 outcomes.

Introduction

In December 2019, there was an outbreak of a novel Severe Acute Respiratory Coronavirus (SARS-CoV-2) in Wuhan, China, which was later declared as a Coronavirus disease (COVID-19) pandemic by the World Health Organization (WHO).[1] As of 14 February 2021, more than 108 million cases and 2.3 million deaths have been reported in over 223 countries and territories.[1] The UK has among the highest morbidity and mortality rates worldwide. Scotland has reported more than 21,000 hospitalisations and 6,700 deaths due to COVID-19.[2]

There has been an unprecedented investment in vaccine technology, evaluation, and production in response to the pandemic. Authorisation of the first COVID-19 vaccines occurred soon after publication of the initial phase 3 safety and efficacy studies.[3] The UK was one of the first countries to license these vaccines.[2] As of 18 February 2021, first dose vaccine coverage of over 22% has been reported in Scotland with over 1.3 million vaccines administered across the Scottish population, and delivery targeting specified priority groups of those most at risk of harm (including the elderly and healthcare workers).[2,4]

Clinical trials of all three currently UK authorised vaccines (i.e., Pfizer-BioNTech, Oxford-AstraZeneca and Moderna) have reported high vaccine efficacy. For the Pfizer-BioNTech vaccine (BNT162b2 mRNA COVID-19 Vaccine), 95% efficacy was reported against laboratory confirmed COVID-19.[5] The Oxford-AstraZeneca vaccine was found to have 70% efficacy against symptomatic COVID-19 amongst seronegative participants.[6] The Moderna vaccine (mRNA-1273) was reported to have 95% efficacy against confirmed COVID-19, but it will not be administered in the UK until Spring 2021 at the earliest, and is therefore not included in this analysis.[7]

Large post-licensure epidemiological studies are needed to complement the findings of pre-licensure trials and assess the effectiveness of these vaccines at the population level in 'real-world' settings.[8] The COVID-19 vaccination policy of the UK is at odds with the manufacturer guidance on timing between the first and second dose. Reflecting the need to gather evidence on this policy, we sought to assess the effectiveness of the first doses of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines against COVID-19 related hospital admissions amongst adults in Scotland.

Methods

Study design and population

We constructed an open, real-time prospective observational cohort with national level coverage in Scotland using a unique dataset consisting of linked vaccination, primary care, laboratory testing, hospitalisation, and mortality data (see Figure 1 in Supplementary Material). Data were available for 5.4 million people in Scotland.[9] Primary care data derived from 940 general practices across Scotland were linked to the laboratory data from the Electronic Communication of Surveillance in Scotland (ECOSS),[9] the hospital admission data available from the Scottish Morbidity Record (SMR) 01 database and Rapid Preliminary Inpatient Data (RAPID),[10] and mortality data available from the death registry within National Records of Scotland (NRS).[9] Vaccination data were available from general practices and the Turas Vaccination Management Tool (TVMT),[11] which is a web-based tool to capture vaccinations in the community and create real-time vaccination records. Laboratory data from ECOSS included all Real-Time Polymerase Chain Reaction (RT-PCR) test results from both NHS laboratories (Pillar 1) and Lighthouse Government laboratories (Pillar 2).[12]

Exposure definition

We studied the first doses of the BNT162b2 mRNA COVID-19 (also known as the Pfizer-BioNTech) vaccine [5] and ChAdOx1 nCoV-19 (AZD1222; also known as the Oxford-AstraZeneca) vaccine.[6] An individual was defined as exposed if they received a single dose of vaccine between 8th December 2020 and 15th February 2021, with maximum follow-up time censored at 15th February 2021 - the latest event date. Vaccinated groups were stratified by time intervals including 7-13, 14-20, 21-27, 28-34, 35-41 and $\geq$42 days post-vaccination, and by the type of vaccine received. Vaccinations information was extracted from the GP records and included individuals vaccinated in community hubs and in general practice.

Definition of outcomes

We assessed VE against hospital admissions with COVID-19 as the main cause of admission, or hospital admission within 28 days of a positive RT-PCR test for SARS-CoV-2 infection from 8 December 2020 to 13 February 2021. See Table 1 in Supplementary Material for ICD-10 codes used for COVID-19 illness.

Patient characteristics and confounders

At the baseline of our cohort (8th December 2020), a number of population characteristics that could potentially confound the association between COVID-19 vaccination and the outcomes of interest were determined. These included age, sex, socio-economic status (SES) measured by quintiles of the Scottish Index of Multiple Deprivation (SIMD) (1 refers to most deprived and 5 refers to least deprived),[9] residential settlement measured by the urban/rural 6 fold classification (1 refers to large urban areas and 6 refers to small remote rural areas),[9] and the number and types of comorbidities commonly associated with COVID-19 illness.[9]

Statistical analysis

The primary analyses included VE estimates for vaccination status overall and for each vaccine type. The secondary analysis included VE estimates for vaccine status overall stratified by age groups (18-64, 65-79 and ≥80 years old).

Baseline characteristics in the vaccinated and unvaccinated groups were described using proportions and risk ratios (RRs). We assessed the effect of one dose of either vaccine against hospital admissions related to laboratory confirmed SARS-CoV-2 infection, or clinical diagnosis of COVID-19 on admission. Poisson regression adjusting for an offset representing the time at risk and time-dependent Cox models (taking into account the time at risk) were used to derive the RRs and hazard ratios (HR) and 95% confidence intervals (CIs) for the prevention of COVID-19 hospitalisation, where the HR was derived from the coefficient of vaccine status in the model.

Cox models included spline terms for age and number of RT-PCR tests prior to vaccination (a marker for healthcare workers, social care workers and care home residents who had repeated tests). Additional adjustments were made for sex, SES and underlying medical conditions at-risk of COVID-19 illness with vaccination groups representing a time-dependent covariate. Calendar time intervals by week were included as stratification variables. Poisson regression was used for the full adjustment and propensity weighting. This used age groups in 5 year intervals and adjustment for the following clinical conditions, all of which are associated with an increased risk of hospitalisation: Type 1 and type 2 diabetes, high and low blood pressure, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), dementia, stroke, learning disorders, fractures, neurological conditions, chronic cardiac failure, asthma,

epilepsy, blood cancer, liver cirrhosis, venous thromboembolism (VTE), peripheral vascular disease, atrial fibrillation, pulmonary hypertension, Parkinson's disease, rare pulmonary disorders, rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).

The analysis was repeated using Poisson regression, with age groups and test groups. The Poisson regression results are presented. The statistical model results are derived from a subset of the data by selecting those without the event for each event and performing a weighted regression. The weights reflected two aspects. First, the sample weights were used to correct for the size of the registered GP population being bigger than the population in Scotland. These weights were derived by matching the age and sex numbers in the GP data to the Scottish population data. Second, the weights reflected the sampling frequency of controls.

The models were fit to a dataset with all events and a random sample, without replacement, of 100 individuals per event with sample weights calculated to represent the sampling fraction. A combined weight was used in the statistical modelling. A propensity model for vaccination was developed using a logistic regression model including terms for age group, SES, sex, number of previous PCR tests and number of clinical risk groups. A final adjustment included using inverse propensity weighting.

Individuals who had previously tested positive (by RT-PCR) for SARS-CoV-2 infection prior to 8th December 2020 were excluded from this analysis. All statistical tests were two-tailed with a 5% significance level.

The statistical software R (Version 3.6.1) was used to carry out all statistical analysis.[13]

Ethics and permissions

Approvals were obtained from the National Research Ethics Service Committee, Southeast Scotland 02 (reference number: 12/SS/0201) and Public Benefit and Privacy Panel for Health and Social Care (reference number: 1920-0279).

Reporting

We produced a detailed analysis protocol prior to undertaking the analysis. We followed the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) [14] and

Reporting of studies Conducted using Observational Routinely-collected Data (RECORD) [15] checklists to guide transparent reporting of this cohort study (see Tables 2 and 3 in Supplementary Material). We will make our analysis code available on GitHub at the time of publication.

Role of the funding source

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

Results

Vaccine uptake by baseline characteristics

Between 8 December 2020 to 15 February 2021, 1,137,775 (35%) patients were vaccinated in our study. Rapid uptake of BNT162b2 mRNA and ChAdOx1 vaccines was observed over the study period (Figure 1 and Table 1), with the largest increase amongst the first priority target group aged ≥ 80 years. For the BNT162b2 mRNA vaccine, high uptake rate was found in patients <65 years old while for the ChAdOx1 vaccine, higher vaccine uptake was found in patients >80 years old (Figure 2). The subgroups with highest vaccine uptake for both vaccine combined were females (30.6%), the second least deprived quintile of SIMD (27.5%), those living in remote rural areas (33.2%), those with five or more comorbidities (72.2%), ex-smokers (42.3%) and those with very raised blood pressure (39.1%) (Table 1).

Vaccine effect against hospital admissions

During all time periods after vaccination, a statistically significant adjusted VE was found against COVID-19 related hospital admissions among those who received the first dose of either BNT162b2 or ChAdOx1 vaccines (Table 2).

We found that VEs increased over time until a peak at day 28-34 days post-vaccination for both vaccines. The highest VE against COVID-19 hospitalisation amongst those receiving the first dose of the vaccine BNT162b2 was 85%, (95% CI 76 to 91) and for ChAdOx1 it was 94% (95% CI 73 to 99) (Table 2).

Similar findings were observed in a pooled analysis for both vaccines of VE against COVID-19 hospitalisation stratified by age group (Table 3). High VEs were found amongst all age

groups. VE estimates for 18-64, 65-79 and ≥80 year olds were highest at 28-34 days after the first dose of vaccine (85%, 95% CI 68 to 93; 79%, 95% CI 17 to 95; 81%, 95% CI 65 to 90, respectively).

Discussion

This national prospective cohort study comprising almost the entire Scottish population demonstrated that a single dose of either the BNT162b2 mRNA or ChAdOx1 vaccines was associated with substantial protection against COVID-19 hospitalisation. Peak VEs of 85% for the BNT162b2 vaccine and 94% for the ChAdOx1 vaccine were found against COVID-19 related hospitalisations. In the oldest age group (≥80 years), based on a pooled analysis for both vaccines, we observed peak VE of 81% against COVID-19 related hospitalisations. VE tended to increase over time after the first dose for this age group, with the optimal time being >28 days.

Two studies from Israel have reported on the vaccine effect of BNT162b2 mRNA. Using data on over 500,000 individuals, an effect of 51% was demonstrated for the first dose against SARS-CoV-2 infection 13-24 days after immunisation.[16] A cohort study of 9,109 healthcare workers in Israel's largest hospital reported adjusted rate reductions for SARS-CoV-2 infections of 30% and 75% for the periods 1–14 and 15–28 days after the first dose of the BNT162b2 vaccine.[17] There have also been recent news reports of a study using a dataset consisting of 1.2 million people from the Clalit Institute in Israel finding 94% VE against symptomatic infection for those having received two doses of the Pfizer-BioNTech vaccine.[18] Complementary to these three studies, we have found high VE against COVID-19 hospitalisation for the BNT162b2 mRNA and ChAdOx1 vaccines after a single dose.

This is, to our knowledge, the first national population level study assessing the effect of currently licensed COVID-19 vaccines on a serious COVID-19 outcome. Our study has several strengths. We developed a national linked dataset and have created a platform which allowed rapid access to and analysis of data on vaccination status and medical condition status from routinely collected electronic health records (EHR) data and national databases.[9,19] This study is therefore less susceptible to recall or misclassification bias than studies of sub-samples of the population. The inclusion of large population samples increased the study power, facilitating estimation of VE in multiple age groups and time intervals after the first dose of the

vaccination. We are likely to have excellent generalisability across the UK and potentially other countries with national programmes using these same vaccines.

Our study also had several limitations. First, we estimated vaccine effects against COVID-19 related hospital admission. However, there are other outcomes of interest, including GP and accident & emergency (A&E) department consultations, ICU admission, death, rate of secondary SARS-CoV-2 infection within households as well as maternal and neonatal outcomes. We did not estimate VE against these outcomes. Second, although our VE estimates were adjusted for potential confounders, unmeasured confounders could still have influenced our estimates. In addition, the effect of confounding likely differed between age groups. Individuals aged ≥80 years have been universally offered vaccination, whereas only those designated as clinically extremely vulnerable or at high occupation risk have been targeted for the receipt of a vaccine amongst the 18-65 year age group.[4] Also the ChAdOx1 vaccine has predominantly been used in the elderly and was only available from 4th January 2021, giving less time for follow-up. Finally, although we have large population samples, there was an insufficient number of people who had received the second dose of the vaccines to reliably study VE after receiving a full course of vaccination. However, the VE of a single dose is of policy interest given the ongoing debate over whether to defer a second dose to allow more rapid population coverage.

Monitoring the effect of currently licensed vaccines in the general population needs to be continued in Scotland and the other UK nations, especially in high-risk subgroups such as those in care homes where more data will be needed to produce reliable VE estimates. Similarly, further monitoring to assess the effect of receiving two doses, rather than just one, is needed. Robust observational epidemiological studies should be carried out to measure the coverage of these newly introduced vaccines in relation to demographic and other population characteristics and to detect adverse events. These post-marketing observational studies will add value to the pre-licensure clinical trials as they can assess 'real-life' effects of the COVID-19 vaccines and the impact of the vaccination programme at a population level. We plan in due course to report on the effectiveness of the second dose and the effects on mortality.

In summary, we provide compelling national evidence that the first doses of the BNT162b2 mRNA and ChAdOx1 vaccines protect against COVID-19 hospitalisations in adults.

Data sharing: A data dictionary covering the datasets used in this study can be found at https://github.com/EAVE-II/EAVE-II-data-dictionary. All code used in this study will be made publicly available at https://github.com/EAVE-II/Covid-VE upon publication. The data used in this study are sensitive and will not be made publicly available.

Contributors: AS conceived this study, commented on the draft protocol, oversaw the analysis and edited the final manuscript. EV, CRS, TS and SK wrote the first draft of the protocol. CR cleaned and analysed the data. All authors contributed to the study design. All authors contributed to drafting the protocol and revised the manuscript for important intellectual content. All authors gave final approval of the version to be published.

Declaration of interests: AS is a member of the Scottish Government Chief Medical Officer's COVID-19 Advisory Group and the New and Emerging Respiratory Virus Threats (NERVTAG) Risk Stratification Subgroup. CRS declares funding from the MRC, NIHR, CSO and New Zealand Ministry for Business, Innovation and Employment and Health Research Council during the conduct of this study. SVK is co-chair of the Scottish Government's Expert Reference Group on COVID-19 and ethnicity, is a member of the Scientific Advisory Group on Emergencies (SAGE) subgroup on ethnicity and acknowledges funding from a NRS Senior Clinical Fellowship, MRC and CSO. All other authors report no conflicts of interest.

Acknowledgments: EAVE II is funded by the Medical Research Council (MR/R008345/1) with the support of BREATHE - The Health Data Research Hub for Respiratory Health [MC_PC_19004], which is funded through the UK Research and Innovation Industrial Strategy Challenge Fund and delivered through Health Data Research UK. Additional support has been provided through Public Health Scotland and Scottish Government DG Health and Social Care. FDRH acknowledges part support from the NIHR School for Primary Care Research (SPCR), the NIHR Collaboration for Leadership in Applied Health Research and Care (CLAHRC) Oxford, and the NIHR Oxford BRC. We thank Dave Kelly from Albasoft Ltd for his support with making primary care data available and James Pickett, Wendy Inglis-Humphrey, Vicky Hammersley, Maria Georgiou and Laura Gonzalez Rienda for their support with project management and administration.

References

1. World Health Organization. Coronavirus disease (COVID-19) pandemic. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019 (accessed 14 February 2021).
2. UK Government. Coronavirus in the UK. Available at: https://coronavirus.data.gov.uk/ (accessed 14 February 2021).
3. Ramasamy MN, Minassian AM, Ewer KJ, et al. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. Lancet 2020;396(10267):P1979-1993.

4. UK Government. Joint Committee on Vaccination and Immunisation: advice on priority groups for COVID-19 vaccination, 30 December 2020. Available at: https://www.gov.uk/government/publications/priority-groups-for-coronavirus-covid-19-vaccination-advice-from-the-jcvi-30-december-2020/joint-committee-on-vaccination-and-immunisation-advice-on-priority-groups-for-covid-19-vaccination-30-december-2020 (accessed 18 February 2021).
5. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. New England Journal of Medicine 2020;383(27): 2603-15.
6. Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. The Lancet 2021; 397(10269): 99-111.
7. Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med 2021;384(5):403-416.
8. Lopalco PL, DeStefano F. The complementary roles of Phase 3 trials and post-licensure surveillance in the evaluation of new vaccines. Vaccine 2015;33(13):1541-1548.
9. Simpson CR, Robertson C, Vasileiou E, et al. Early Pandemic Evaluation and Enhanced Surveillance of COVID-19 (EAVE II): protocol for an observational study using linked Scottish national data. BMJ Open 2020;10:e039097.
10. National Services Scotland. National Data Catalogue. Rapid Preliminary Inpatient Data (RAPID). Available at: https://www.ndc.scot.nhs.uk/National-Datasets/data.asp?SubID=37 (accessed 15 February 2021).
11. Turas Vaccination Management Tool. Available at: https://learn.nes.nhs.scot/42708/turas-vaccination-management-tool (accessed 14 February 2021).
12. UK Government. COVID-19 testing data: methodology note. Available at: https://www.gov.uk/government/publications/coronavirus-covid-19-testing-data-methodology/covid-19-testing-data-methodology-note (accessed 15 February 2021).
13. R Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.r-project.org/
14. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in

Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007 Oct 20;370(9596):1453-7.

15. Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM; RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. PLoS Med. 2015 Oct 6;12(10):e1001885.
16. The effectiveness of the first dose of BNT162b2 vaccine in reducing SARS-CoV-2 infection 13-24 days after immunization: real-world evidence. Gabriel Chodick, Lilac Tene, Tal Patalon, Sivan Gazit, Amir Ben Tov, Dani Cohen, Khitam Muhsen. medRxiv 2021.01.27.21250612; doi: https://doi.org/10.1101/2021.01.27.21250612
17. Sharon Amit, Gili Regev-Yochay, Arnon Afek, Yithsak Kreiss. Early rate reduction of SARS-CoV2 infection in BNT162b2 vaccine recipients. *Lancet correspondence* Feb 18 2021 doi:https://doi.org/10.1016/S0140-6736(21)00448-7
18. Major Israeli study finds Pfizer jab 94 percent effective in 'real world' use, Paul Nuki, The Telegraph newspaper, 14/02/21.
19. Simpson CR, Beever D, Challen K, *et al.* The UK's pandemic influenza research portfolio: a model for future research on emerging infections. *Lancet Infect Dis* 2019;19:e295–300.

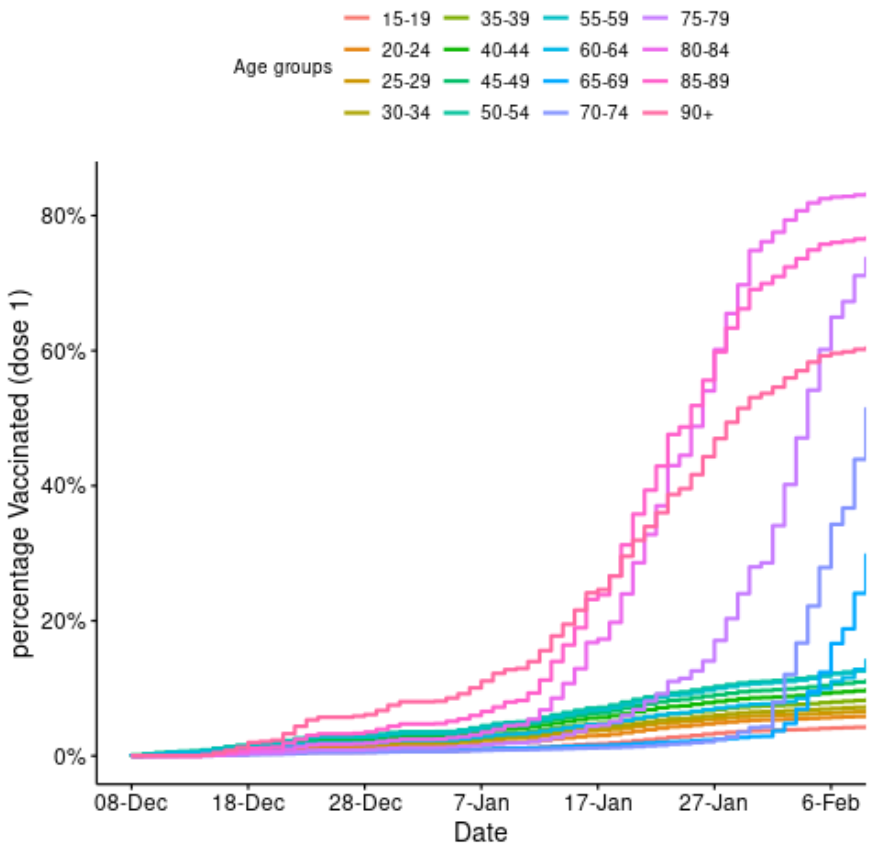

Figure 1: COVID-19 vaccine uptake by age over time

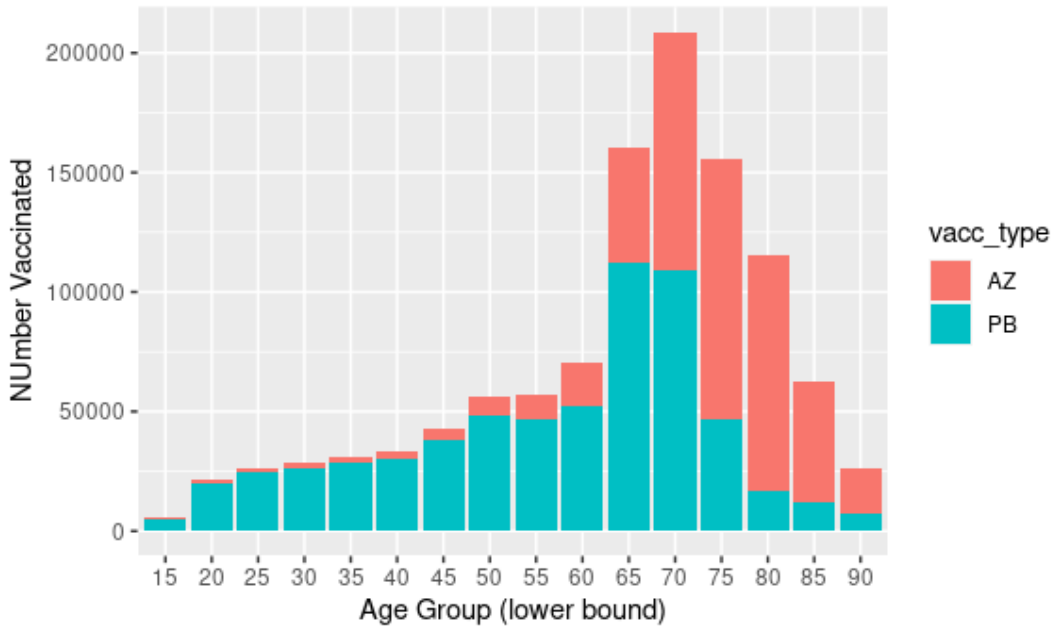

Figure 2: Vaccine uptake by age and vaccine type (AZ: Oxford-AstraZeneca. PB: Pfizer-BioNTech).

Table 1. Baseline characteristics by vaccine status (BNT162b2 and ChAdOx1nCoV-19)

Characteristic	Vaccinated (% of total)	Unvaccinated (% of total)	Uptake (% of total)	Uptake RR (95% CI)
Sex				
Female	697,506 (61.3)	1,583,408 (48.4)	30.6	1
Male	440,269 (38.7)	1,688,428 (51.6)	20.7	0.68
Age group (years)				
18-64	395,439 (34.8)	2,989,015 (91.4)	11.7	1
65-79	535,607 (47.1)	223,349 (6.8)	70.6	6.04
≥80	206,729 (18.2)	59,473 (1.8)	77.7	6.65
Socio-economic Status				
1 – Most deprived	191,510 (16.8)	674,542 (20.6)	22.1	1
2	220,609 (19.4)	645,735 (19.7)	25.5	1.15
3	238,986 (21.0)	634,121 (19.4)	27.4	1.24
4	240,467 (21.1)	635,293 (19.4)	27.5	1.24
5 – Least deprived	240,370 (21.1)	646,240 (19.8)	27.1	1.23
Unknown	5,833 (0.5)	35,905 (1.1)	14.0	0.63
Urban/rural score				
1 – Large urban area	353,190 (31.0)	1,237,574 (37.8)	22.2	1
2	415,063 (36.5)	1,137,322 (34.8)	26.7	1.2
3	115,015 (10.1)	288,174 (8.8)	28.5	1.28
4	66,692 (5.9)	144,696 (4.4)	31.6	1.42
5	109,712 (9.6)	282,899 (8.6)	27.9	1.26
6 – Remote rural area	72,270 (6.4)	145,699 (4.5)	33.2	1.49
Unknown	5,833 (0.5)	35,910 (1.1)	14.0	0.63
Number of comorbidities				
0	479,656 (42.2)	2,167,916 (66.3)	18.1	1
1	320,130 (28.1)	782,067 (23.9)	29.0	1.6
2	174,284 (15.3)	223,653 (6.8)	43.8	2.42

3	88,995 (7.8)	64,847 (2.0)	57.8	3.19
4	43,659 (3.8)	21,393 (0.7)	67.1	3.7
≥5	31,051 (2.7)	11,960 (0.4)	72.2	3.98
Asthma	147,942 (13.0)	411328 (12.6)	26.5	1.03
Chronic Kidney condition (Level 3)	121,584 (10.7)	39,951 (1.2)	75.3	3.15
Liver cirrhosis	9,595 (0.8)	13,744 (0.4)	41.1	1.60
Chronic neurological condition	6,395 (0.6)	11,719 (0.4)	35.3	1.37
Heart Failure	32,059 (2.8)	16,044 (0.5)	66.6	2.63
Diabetes (type 1)	5,229 (0.5)	16,193 (0.5)	24.4	0.95
Diabetes (type 2)	130,674 (11.5)	127,870 (3.9)	50.5	2.08
Dementia	30,742 (2.7)	7,069 (0.2)	81.3	3.21
Coronary Heart Disease	128,040 (11.3)	74,070 (2.3)	63.4	2.64
Smoking Status				
Ex-smoker	240,969 (21.2)	328,066 (10.0)	42.3	1.61
Smoker	259,727 (22.8)	648,129 (19.8)	28.6	1.09
Non-smoker	439,324 (38.6)	1,238,432 (37.9)	26.2	1
Unknown	133,650 (11.7)	697,620 (21.3)	16.1	0.51
Blood pressure level (systolic/diastolic)				
Very high (>160/100mmHg)	32,924 (2.9)	51,200 (1.6)	39.1	1.25
High (141-160/91-100 mmHg)	151,030 (13.3)	247,750 (7.6)	37.9	1.21
Normal (110-140/65-90 mmHg)	735,389 (64.6)	1,616,986 (49.4)	31.3	1
Low (<110/65 mmHg)	11,142 (1.0)	42,537 (1.3)	20.8	0.66
Unknown	133,650 (11.7)	697,620 (21.3)	16.1	0.51

Table 2. COVID-19 hospitalisation and days post-vaccination for both BNT162b2 and ChAdOx1nCoV-19 and by vaccine type

Vaccination status	Person years	Number of events	Age-adjusted Hazard Ratios (95% CI)*	Full-adjusted Hazard Ratios (95% CI)**	Full and inverse propensity adjusted Hazard Ratios (95% CI)***	Vaccine effect (95% CI)
Vaccinated overall						
Unvaccinated	787518	7472	1	1	1	NA
Vaccine dose 1 (7-13 days)	13487	212	0.73 (0.64 to 0.84)	0.74 (0.64 to 0.86)	0.53 (0.47 to 0.61)	47% (39 to 53)
Vaccine dose 1 (14-20 days)	9191	120	0.61 (0.5 to 0.73)	0.63 (0.52 to 0.76)	0.4 (0.34 to 0.48)	60% (52 to 66)
Vaccine dose 1 (21-27 days)	6343	52	0.43 (0.33 to 0.56)	0.44 (0.33 to 0.58)	0.3 (0.23 to 0.38)	70% (62 to 77)
Vaccine dose 1 (28-34 days)	3867	20	0.34 (0.22 to 0.52)	0.31 (0.2 to 0.48)	0.16 (0.1 to 0.26)	84% (74 to 90)
Vaccine dose 1 (35-41 days)	2326	17	0.6 (0.38 to 0.97)	0.46 (0.28 to 0.76)	0.39 (0.26 to 0.58)	61% (42 to 74)
Vaccine dose 1 (42+ days)	3843	21	0.52 (0.34 to 0.81)	0.51 (0.33 to 0.79)	0.42 (0.3 to 0.61)	58% (39 to 70)
BNT162b2 or Pfizer-BioNTech						
Unvaccinated	708129	6690	1	1	1	NA
Vaccine dose 1 (7-13 days)	7766	104	0.71 (0.58 to 0.86)	0.56 (0.46 to 0.68)	0.62 (0.53 to 0.72)	38% (28 to 47)
Vaccine dose 1 (14-20 days)	5758	60	0.61 (0.47 to 0.78)	0.42 (0.32 to 0.55)	0.4 (0.32 to 0.5)	60% (50 to 68)
Vaccine dose 1 (21-27 days)	4688	34	0.43 (0.31 to 0.6)	0.29 (0.21 to 0.41)	0.28 (0.21 to 0.38)	72% (62 to 79)
Vaccine dose 1 (28-34 days)	3346	18	0.33 (0.21 to 0.53)	0.22 (0.14 to 0.35)	0.15 (0.09 to 0.24)	85% (76 to 91)
Vaccine dose 1 (35-41 days)	2275	17	0.46 (0.28 to 0.73)	0.29 (0.18 to 0.48)	0.32 (0.21 to 0.47)	68% (53 to 79)
Vaccine dose 1 (42+ days)	3842	21	0.38 (0.25 to 0.58)	0.32 (0.21 to 0.51)	0.36 (0.25 to 0.51)	64% (49 to 75)
ChAdOx1nCoV-19 or Oxford-AstraZeneca						
Unvaccinated	700859	7090	1	1	1	NA
Vaccine dose 1 (7-13 days)	5721	108	0.49 (0.41 to 0.6)	0.51 (0.42 to 0.62)	0.3 (0.24 to 0.37)	70% (63 to 76)
Vaccine dose 1 (14-20 days)	3433	60	0.4 (0.31 to 0.52)	0.46 (0.35 to 0.6)	0.26 (0.19 to 0.34)	74% (66 to 81)

Vaccine dose 1 (21-27 days)	1655	18	0.24 (0.15 to 0.38)	0.29 (0.18 to 0.47)	0.16 (0.1 to 0.28)	84% (72 to 90)
Vaccine dose 1 (28-34 days)	521	2	0.08 (0.02 to 0.33)	0.1 (0.03 to 0.41)	0.06 (0.01 to 0.27)	94% (73 to 99)
Vaccine dose 1 (35-41 days)	51	0	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	NA
Vaccine dose 1 (42+ days)	1	0	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	NA

NA=not applicable
*Adjusted for: age
**Adjusted for: time (in weeks), age, sex, SIMD, number of RT-PCR tests prior to vaccination and number of underlying medical conditions.
***Adjusted for: time (in weeks), age, sex, SIMD, number of RT-PCR tests prior to vaccination and number of underlying medical conditions and inverse propensity of being vaccinated
Omitting individuals who had previously tested positive

Table 3. COVID-19 hospitalisation by age group and days post-vaccination (BNT162b2 and ChAdOx1nCoV-19

Age group	**Vaccination status**	**Person years**	**Number of events**	**Age-adjusted Hazard Ratios (95% CI)***	**Full-adjusted Hazard Ratios (95% CI)****	**Full and inverse propensity adjusted Hazard Ratios (95% CI)*****	**Vaccine effect (95% CI)**
18-64 years	Unvaccinated	609892	3202	1	1	1	NA
	Vaccine dose 1 (7-13 days)	5467	46	1.4 (1.04 to 1.87)	1.27 (0.94 to 1.71)	1.36 (1.14 to 1.63)	-36% (-63 to -14)
	Vaccine dose 1 (14-20 days)	4805	21	0.74 (0.48 to 1.14)	0.7 (0.45 to 1.08)	0.67 (0.51 to 0.88)	33% (12 to 49)
	Vaccine dose 1 (21-27 days)	3933	9	0.39 (0.2 to 0.74)	0.36 (0.18 to 0.71)	0.44 (0.31 to 0.64)	56% (36 to 69)
	Vaccine dose 1 (28-34 days)	2824	3	0.18 (0.06 to 0.56)	0.17 (0.05 to 0.54)	0.15 (0.07 to 0.32)	85% (68 to 93)
	Vaccine dose 1 (35-41 days)	1894	6	0.53 (0.24 to 1.19)	0.48 (0.21 to 1.11)	0.57 (0.35 to 0.93)	43% (7 to 65)
	Vaccine dose 1 (42+ days)	3291	8	0.41 (0.21 to 0.83)	0.45 (0.22 to 0.94)	0.49 (0.31 to 0.77)	51% (23 to 69)
65-79 years	Unvaccinated	137190	2409	1	1	1	NA
	Vaccine dose 1 (7-13 days)	4230	51	0.59 (0.44 to 0.77)	0.84 (0.63 to 1.13)	0.38 (0.28 to 0.53)	62% (47 to 72)
	Vaccine dose 1 (14-20 days)	1199	20	0.74 (0.48 to 1.16)	0.86 (0.55 to 1.35)	0.41 (0.24 to 0.68)	59% (32 to 76)
	Vaccine dose 1 (21-27 days)	504	7	0.65 (0.31 to 1.36)	0.56 (0.26 to 1.21)	0.29 (0.12 to 0.69)	71% (31 to 88)
	Vaccine dose 1 (28-34 days)	248	3	0.61 (0.2 to 1.9)	0.44 (0.14 to 1.36)	0.21 (0.05 to 0.83)	79% (17 to 95)
	Vaccine dose 1 (35-41	145	4	1.5 (0.56 to 4.01)	0.82 (0.29 to 2.31)	0.44 (0.14 to 1.46)	56% (-46 to 86)

	days)						
	Vaccine dose 1 (42+ days)	213	7	1.82 (0.87 to 3.82)	1.44 (0.67 to 3.07)	0.92 (0.41 to 2.05)	8% (-105 to 59)
>80 years	Unvaccinated	40436	1861	1	1	1	NA
	Vaccine dose 1 (7-13 days)	3789	115	0.67 (0.56 to 0.81)	0.68 (0.55 to 0.83)	0.33 (0.26 to 0.41)	67% (59 to 74)
	Vaccine dose 1 (14-20 days)	3188	79	0.55 (0.44 to 0.69)	0.65 (0.51 to 0.84)	0.33 (0.25 to 0.43)	67% (57 to 75)
	Vaccine dose 1 (21-27 days)	1906	36	0.41 (0.29 to 0.57)	0.5 (0.35 to 0.72)	0.25 (0.17 to 0.37)	75% (63 to 83)
	Vaccine dose 1 (28-34 days)	795	14	0.37 (0.22 to 0.62)	0.39 (0.23 to 0.68)	0.19 (0.1 to 0.35)	81% (65 to 90)
	Vaccine dose 1 (35-41 days)	288	7	0.49 (0.23 to 1.03)	0.41 (0.19 to 0.87)	0.23 (0.1 to 0.52)	77% (48 to 90)
	Vaccine dose 1 (42+ days)	339	6	0.36 (0.16 to 0.79)	0.37 (0.16 to 0.85)	0.2 (0.08 to 0.51)	80% (49 to 92)

NA=not applicable
*Adjusted for: age
**Adjusted for: time (in weeks), age, sex, SIMD, number of RT-PCR tests prior to vaccination and number of underlying medical conditions.
***Adjusted for: time (in weeks), age, sex, SIMD, number of RT-PCR tests prior to vaccination and number of underlying medical conditions and inverse propensity of being vaccinated
Omitting individuals who had previously tested positive