COVID-19 vaccine uptake and effectiveness in adults aged 50 years and older in Wales UK: a 1.2m population data-linkage cohort approach

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RESEARCH PAPER

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ABSTRACT

Vaccination programs against COVID-19 vary globally with estimates of vaccine effectiveness (VE) affected by vaccine type, schedule, strain, outcome, and recipient characteristics. This study assessed VE of BNT162b2 and ChAdOx1 vaccines against PCR positive SARS-CoV-2 infection, hospital admission, and death among adults aged 50 years and older in Wales, UK during the period 7 December 2020 to 18 July 2021, when Alpha, followed by Delta, were the predominant variants. We used individual-level linked routinely collected data within the Secure Anonymized Information Linkage (SAIL) Databank. Data were available for 1,262,689 adults aged 50 years and over; coverage of one dose of any COVID-19 vaccine in this population was 92.6%, with coverage of two doses 90.4%. VE against PCR positive infection at 28-days or more post first dose of any COVID-19 vaccine was 16.0% (95%CI 9.6–22.0), and 42.0% (95%CI 36.5–47.1) seven or more days after a second dose. VE against hospital admission was higher at 72.9% (95%CI 63.6–79.8) 28 days or more post vaccination with one dose of any vaccine type, and 84.9% (95%CI 78.2–89.5) at 7 or more days post two doses. VE for one dose against death was estimated to be 80.9% (95%CI 72.1–86.9). VE against PCR positive infection and hospital admission was higher for BNT162b2 compared to ChAdOx1. In conclusion, vaccine uptake has been high among adults in Wales and VE estimates are encouraging, with two doses providing considerable protection against severe outcomes. Continued roll-out of the vaccination programme within Wales, and globally, is crucial in our fight against COVID-19.

Introduction

As of July 2021 almost every country has introduced a vaccination programme against COVID-19, with variations in coverage.[1] There are a number of authorized vaccines currently available with further candidates in development, with consideration for changing SARS-CoV-2 variants and potential booster doses required.[2] Early data suggest good effectiveness of the available vaccines against the current circulating variants.[3–11] The COVID-19 vaccination program in Wales began on 8 December 2020, at a time when the second wave of the pandemic was reaching its peak locally. Individuals were invited for vaccination, through the NHS Wales electronic vaccination register, in a phased approach according to the priorities advised by the UK Joint Committee on Vaccination and Immunization (JCVI).[12] The Pfizer-BioNTech (BNT162b2) vaccination was available first and was the sole vaccine used throughout December 2020, being mainly distributed through mass vaccination centers (MVCs), due to the cold-chain and handling requirements of the vaccine at the time, and the limitations these posed for remote vaccination. The Oxford-AstraZeneca (ChAdOx1) vaccine was used from 4 January 2021 in a variety of settings, including care homes, general practices and (later) community pharmacies, which contributed to rapid increases in coverage among the elderly population including care home residents. The Moderna mRNA-1273 vaccine has been used in a limited way, mainly in one of seven Health Board areas, since 7 April 2021. All three of these vaccinations follow a two dose schedule, which from January 2021 used a dose interval of 8–12 weeks.

The COVID-19 vaccination program has received high levels of acceptance in the Welsh population. As of 18 July 2021, routine surveillance reported that 85.6% of the population aged 18 years and older had received one dose of any COVID-19 vaccine and 72.8% had received two doses.[13] Coverage in those aged 50 years of age and older was 93.6% and 91.6% for one and two doses, respectively. As of 18 July 2021, there had been cumulatively 232,672 PCR confirmed episodes in Wales with 5,589 associated deaths.[13] The Alpha variant of SARS-CoV-2 was dominant in Wales from December 2020 to end of May 2021, accounting for over 98% of all genomically confirmed and probable cases (n = 12,848).[13] Onset of circulation of the Delta variant of SARS-CoV-2 in Wales was first detected in late April 2021 and became the dominant virus type by the beginning of June.

Independently reviewed estimates of vaccine effectiveness (VE) have been published from a relatively small number of large post-implementation studies in Israel, Qatar, Canada, England, and Scotland, assessing effectiveness of different vaccines against a range of outcomes and taking different approaches to analysis.[3,5–8] Large population based studies are important in strengthening the evidence for ongoing vaccination programmes and building capacity for ongoing monitoring of 'real-world' COVID-19 VE in different populations. The aim of this study was to provide estimates of VE of BNT162b2 and ChAdOx1 against PCR positive SARS-CoV-2 infection, hospital admission due to SARS-CoV-2 infection and death amongst adults aged 50 years and older in Wales.

Materials and methods

Analysis were carried out using individual-level linked routinely collected national-scale data available in the Secure Anonymized Information Linkage (SAIL) Databank, hosted by Swansea University.[14–16] The study population was all individuals aged 50 years and over, alive and resident in Wales as at 7 December 2020 and part of the SAIL Databank Con-COV e-cohort.[17] The population was identified on the basis of those registered for National Health Service (NHS) care in Wales on the Welsh Demographic Service Dataset (WDSD) within SAIL, which includes information on Lower-layer Super Output Area (LSOA) small geography of residence, date of birth, and sex. As care homes are prone to outbreaks and residents are subject to ongoing frequent virology testing in Wales, those identified as living at a residential care home address were excluded from this analysis to limit bias. Healthcare workers were included in the study population, but occupational status was controlled for. Although this population may be at increased risk of COVID-19 due to increased exposure, they are a fairly large cohort to exclude (n = 75,324) and level of risk may differ within this group and be challenging to define. Other occupational groups may be at comparable risk of infection to healthcare workers and may also be subject to increased testing.[18] Vaccination date and vaccine type were recorded in the COVID-19 Vaccination Data (CVVD) data, which originates from the all Wales Immunization System (WIS) population vaccination register for COVID-19. A second dose was considered valid when given at least 21 days after the first, doses with shorter time intervals were discarded and there was no upper exclusion limit to this interval.

The study population was described, and the odds of being vaccinated based on a number of characteristics, as at 18 July 2021 was calculated using univariate logistic regression.

Using a retrospective cohort study design, hazard ratios (HR) were calculated using an extended Cox regression model with vaccination status introduced as a time varying covariate. VE was calculated based on the HR, with VE = 1-HR. The baseline for all estimates is the unvaccinated population. Individuals entered the study at time zero (7 December 2020) and moved through categories based on the time since vaccination in 7-day intervals. In this design, individuals contribute unvaccinated time until the end of the observation period or point they are vaccinated. Individuals were censored if they moved out of Wales, died, reached the end of follow up (18th

July 2021) or had the outcome of interest. VE was assessed against three outcomes: i) PCR positive infection, defined as any PCR positive SARS-CoV-2 test recorded in the Pathology COVID-19 Daily data (PATD) allowing for 90 days between episodes for those with potential repeat infection ii) Hospital admission due to SARS-CoV-2 infection, defined as any hospital admission recorded in the Patient Episode Dataset for Wales (PEDW) where the individual had a PCR positive test in the 28-days prior to admission, on the day of admission or the day after admission and COVID-19 was listed as the primary cause for admission, and iii) Death with COVID-19 recorded as an underlying cause on the death certificate, where the individual had a PCR positive SARS-CoV-2 test in the 28-days prior.

The unadjusted Cox regression models included vaccination status and variables associated with priority status, and therefore when someone would have had the opportunity to be vaccinated: age as at 31st March 2021 as a restricted cubic spline, individual identified as clinically extremely vulnerable (CEV) based on shielding list status and health and care worker status.[19] In the fully adjusted model, a number of additional variables were included: any previous PCR positive SARS-CoV-2 test prior to the cohort start date, number of SARS-CoV-2 PCR tests prior to the cohort start, QCOVID score, Health Board of residence, sex, ethnic group, deprivation quintile (a measure for deprivation for small areas in Wales), and urban/rural location of residence.[20] Adjustment was also made for previous vaccination against shingles, previous vaccination against pneumococcal polysaccharide, vaccination against influenza between 1 October 2020 and 31 March 2021 and number of days with a General Practitioner (GP) consultation recorded in the year prior to 1 February 2020, prior to the pandemic reaching Wales. As part of a sensitivity analysis, VE calculations also including inverse propensity score weighting (IPW).[21] All variables included in the adjusted model were included in the calculation of propensity score to be vaccinated with at least one dose of COVID-19 vaccine.

Health Board of residence, identification of care home residents (based on address) and health and care worker status (based on provision of occupational records from employing organizations) were as recorded in the CVVD. Level of deprivation was assigned at ecological level by linking LSOA of residence to the Welsh Index of Multiple Deprivation (WIMD) 2019, LSOA's were then ranked according to overall WIMD score and divided into quintiles.[22] Urban/Rural location was assigned by linking LSOA of residence to the 2011 census rural urban classification data provided by the Office for National Statistics (ONS).[23] Shielding status for individuals was sourced from a central register of COVID-19 Shielding Persons (CVSP) who were advised to isolate due to high clinical risk, maintained by Digital Health and Care Wales (DHCW). Adjustment for important comorbidities was done using the QCOVID algorithm, which predicts the risk of being admitted to hospital or dying from COVID-19 in adults.[20,24] Ethnicity data were sourced from 20 electronic health record (EHR) and administrative data sources, including the ONS Census, and collated into the five minority ethnic categories (White, Asian, Black, Mixed, and Other)).[25]

Previous vaccination history, for pneumococcal, shingles, and influenza vaccination was assessed using Read coded primary care events data as part of the Wales Longitudinal General Practice (WLGP) data and included in the model as separate binary variables. WLGP includes data from ~80% of practices in Wales and was also used to determine the number of days with a GP consultation recorded in the year prior to the pandemic as a proxy for GP visits. These adjustments were made to account for differences in healthcare seeking behavior between the vaccinated and unvaccinated individuals. Where data were missing an unknown category was assigned.

SARS-CoV-2 PCR test data were taken from PATD which were obtained from Public Health Wales (PHW) Datastore and include all test data from NHS hospital laboratories (mainly hospital samples, with some community and other settings) and COVID-19 Lighthouse Laboratories (mainly community samples, with some other non-hospital setting). Hospital admissions were identified using PEDW where a primary cause for admission was recorded as COVID-19 (coded as ICD-10 U07.1 or U07.2) and linked to PATD to identify individuals who had a positive PCR test within the defined time period. The earliest of hospital admission date and positive PCR test sample date was used as the end point for follow up as this will be the closest to when the individual was first infected. COVID-19-related deaths were identified using the Consolidated Death Data Source (CDDS) held in SAIL (a consolidation of records from the Master Patient Index, the Office for National Statistics (ONS) Annual District Death Extract (ADDE) and the WDSD sources of all mortality records), linked to PATD.

Due to small numbers, estimates against death are presented for effectiveness of any COVID-19 vaccine type, whilst VE of one and two doses of vaccine against PCR confirmed infection and admission due to SARS-CoV-2 infection is additionally stratified by vaccine type.

All analysis were carried out using R version 4.0.4.

Results

There were 1,262,689 adults aged 50 years and over eligible for inclusion in the study, after excluding care home residents (n = 16,062) and individuals who had a vaccination other than BNT162b2 or ChAdOx1 (n = 5,406) or a mixed vaccine course (n = 551). As at 18 July 2021, coverage of one dose of any COVID-19 vaccine in this population was 92.6%, with coverage of two doses 90.4%. Over the course of the follow-up period 29.0% (n = 331,064) of those who received two doses, had received BNT162b2 and 71.0% (n = 810,771) had received ChAdOx1. In total, 36.8% (n = 464,455) were aged 70 years or over (Table 1). Over half (51.5%, n = 650,835) were female, with the odds of being vaccinated with a full two dose course 1.40 (95% CI 1.38–1.42) times higher compared to males (Table 1). Coverage varied by Health Board of residence, and coverage of a full two dose course was lowest in the most deprived areas (87.2%) compared to the least deprived areas (92.9%) and urban areas (92.4%) compared to rural

areas (93.0%) (Table 1). The odds of being vaccinated with a complete two dose course for a person in a Black ethnic group was 0.21 (95% CI 0.20–0.23) compared to those in a White ethnic group (Table 1).

Health and care workers (n = 75,324), and those on the list of individuals advised to shield due to increased clinical risk from COVID-19 (n = 94,531), were also more likely to be vaccinated (Table 1).

Additionally, those who had a record of receiving a herpes zoster, pneumococcal (PPV) or seasonal influenza vaccine in 2019/20 were more likely to be fully vaccinated as at 18 July 2021 than those who did not, as were those with a higher QCOVID score (Table 1). Overall, those who consulted their GP more frequently in the year prior to the pandemic were more likely to be vaccinated compared to those who did not. Fifteen percent (n = 193,039) of the study cohort had at least one SARS-CoV-2 PCR test prior to the cohort start date on 7th December 2020 and overall, the more SARS-CoV-2 PCR tests individuals had the more likely they were vaccinated with two doses of vaccine (Table 1). Of these, 26,778 (2.1%) individuals had a positive result prior to the cohort start date. Those with previous PCR confirmed infection, were more likely to be fully vaccinated (OR 1.18, 95% CI 1.13–1.23) (Table 1).

Over the course of follow up, 7 December 2020 to 18 July 2021, there were 38,163 individuals with SARS-CoV-2 PCR positive tests in the study population, 9,876 of which were in those aged 70 years and over (36.3 events per 1000 person years follow up) and 28,287 in those aged 50–69 years (60.8 events per 1000 person years follow-up) (Table 2, Supplementary Table S1). Adjusted estimates showed significant VE against SARS-CoV-2 PCR positive infection at 28-days or more post first dose of any COVID-19 vaccine to be 16.0% (95%CI 9.6–22.0) with effectiveness 7 or more days after a second dose 42.0% (95%CI 36.5–47.1) (Table 2). VE was higher in those aged 70 years and over (66.0%, 95%CI 57.8–72.6) compared to those aged 50 to 69 years (38.4%, 95%CI 31.8–44.4) (Figure 1, Supplementary Table S1). A difference was also seen by vaccine type with VE for those who received two doses of BNT162b2 higher than those who received ChAdOx1, 50.1% (95%CI 44.0–55.5) vs. 24.9% (95% CI 15.4–33.3) (Figure 1, Supplementary Table S1).

VE against hospital admission was higher at 72.9% (95%CI 63.6–79.8) 28 days post vaccination with one dose of any vaccine type and 84.9% (95%CI 78.2–89.5) at 7 or more days post two doses (Table 2). Estimates after two doses were lower in those aged 70 years and over (80.6% 95% CI 65.6–89.1) compared to those aged 50 to 69 years (88.4% 95% CI 80.9–93.0) (Figure 2, Supplementary Table S2). VE in those who received two doses of BNT162b2 (88.2% 95% CI 80.6–92.8) was higher compared to ChAdOx1 (81.4% 95% CI 71.5–87.9) (Figure 2, Supplementary Table S2). Neither differences were statistically significant.

Estimates from models including inverse propensity weighting were higher at all-time points post vaccination, although estimates for 7 or more days after dose two were similar.

Table 1. Summary of study the study population used in the estimation of BNT162b2 and ChAdOx1 vaccine effectiveness and odds of being vaccinated based on select characteristics, Wales UK.

			Dose 1			Dose 2		
		Population	Uptake	OR	95% CI	Uptake	OR	95% CI
Characteristic	Category	(n)	(%)			(%)		
Age group as at 31st March 2021	50–54	211,469	88.7			85.4		
	55–59	220,582	90.9	1.26	(1.24–1.29)	88.4	1.30	(1.28–1.32)
	60–64	194,705	92.5	1.58	(1.55–1.62)	90.6	1.64	(1.61–1.67)
	65–69	171,478	94.1	2.04	(1.99–2.09)	92.6	2.12	(2.08–2.17)
	70–74	175,223	95.3	2.60	(2.54–2.67)	94.1	2.73	(2.67–2.80)
	75–79	126,797	95.6	2.75	(2.67–2.83)	94.0	2.66	(2.59–2.73)
	80+	162,435	93.5	1.84	(1.80–1.89)	90.5	1.63	(1.60–1.67)
Gender	Male	611,854	91.2			88.9		
	Female	650,835	94.0	1.51	(1.49–1.53)	91.8	1.40	(1.38–1.42)
Ethnic group	White	1,139,248	94.5			92.3		
	Mixed	7,719	84.1	0.31	(0.29–0.33)	79.9	0.33	(0.31–0.35)
	Asian	14,253	87.3	0.40	(0.38–0.42)	83.4	0.42	(0.40–0.44)
	Black	4,027	76.8	0.19	(0.18–0.21)	72.1	0.21	(0.20–0.23)
	Other	2,893	77.4	0.20	(0.18–0.22)	73.3	0.23	(0.21–0.25)
	Unknown	94,549	73.2	0.16	(0.16–0.16)	70.5	0.20	(0.20–0.20)
Health Board of residence	HB 1	237,535	93.6			91.7		
	HB 2	293,949	92.4	0.83	(0.82–0.85)	90.0	0.82	(0.80–0.83)
	HB 3	172,261	91.3	0.72	(0.70–0.73)	89.2	0.75	(0.73–0.77)
	HB 4	178,376	93.8	1.05	(1.02–1.07)	91.4	0.97	(0.95–0.99)
	HB 5	164,316	92.7	0.88	(0.86–0.90)	90.4	0.85	(0.83–0.87)
	HB 6	60,640	90.1	0.63	(0.61–0.65)	88.5	0.70	(0.68–0.72)
	HB 7	155,612	92.8	0.88	(0.86–0.90)	90.4	0.85	(0.84–0.87)
Deprivation quintile	Most deprived	210,774	90.3			87.2		
	Quintile 2	240,295	92.3	1.28	(1.25–1.31)	89.7	1.28	(1.26–1.30)
	Quintile 3	258,405	92.5	1.33	(1.30–1.35)	90.4	1.38	(1.35–1.40)
	Quintile 4	274,767	93.0	1.43	(1.40–1.46)	91.1	1.51	(1.48–1.54)
	Least deprived	278,448	94.5	1.85	(1.81–1.89)	92.9	1.92	(1.89–1.96)
Location classification	Rural	436,106	93.0			91.0		
	Urban	826,583	92.4	0.91	(0.90–0.93)	90.1	0.90	(0.89–0.91)
Health or care worker	No	1,187,365	92.3			90.0		
	Yes	75,324	98.5	5.41	(5.11–5.74)	97.3	3.98	(3.81–4.16)
Advised to shield due to high clinical risk	No	1168158	92.4			90.2		
	Yes	94531	96.0	1.99	(1.93–2.06)	92.9	1.42	(1.39–1.46)
Q-COVID co-morbidity score	0	453,060	90.7			88.8		
	1	413,964	92.8	1.31	(1.29–1.33)	90.7	1.23	(1.21–1.25)
	2	205,667	94.7	1.82	(1.78–1.86)	92.2	1.50	(1.47–1.52)
	3	102,322	95.1	1.98	(1.92–2.04)	92.4	1.54	(1.50–1.58)
	4	48,780	95.0	1.96	(1.88–2.04)	92.1	1.46	(1.41–1.51)
	5+	38,896	94.1	1.63	(1.56–1.70)	90.0	1.13	(1.09–1.17)

(Continued)

Table 1. (Continued).

Characteristic	Category	Population (n)	Uptake (%)	Dose 1 OR	95% CI	Uptake (%)	Dose 2 OR	95% CI
Number of recorded days with a GP consultation 1st February 2019 to 31st January 2020	0	59,896	72.7			69.9		
	1	40,777	82.2	1.73	(1.68–1.79)	79.8	1.70	(1.65–1.75)
	2–4	83,928	89.2	3.10	(3.01–3.19)	86.9	2.87	(2.79–2.94)
	5–9	95,087	93.1	5.09	(4.93–5.25)	91.0	4.34	(4.22–4.47)
	10–19	228,908	95.2	7.39	(7.20–7.59)	93.2	5.91	(5.77–6.05)
	20–49	460,116	96.3	9.83	(9.60–10.06)	94.2	7.05	(6.90–7.20)
	50–99	72,583	94.9	6.95	(6.70–7.22)	91.4	4.56	(4.42–4.71)
	100–149	3,414	92.5	4.62	(4.06–5.26)	86.8	2.84	(2.57–3.15)
	150+	225	88.0	2.76	(1.84–4.13)	82.2	1.99	(1.41–2.81)
	Unknown	217,755	90.1	3.43	(3.35–3.51)	88.0	3.14	(3.08–3.21)
Record of herpes zoster vaccination	No	856,895	92.1			89.7		
	Yes	179,724	98.3	4.88	(4.70–5.06)	96.9	3.61	(3.51–3.71)
	Unknown	226,070	90.1	0.77	(0.76–0.79)	87.8	0.83	(0.81–0.84)
Record of pneumococcal (PPV) vaccination as an adult	No	641,351	90.7			88.3		
	Yes	402,221	97.2	3.52	(3.45–3.59)	95.3	2.72	(2.67–2.76)
	Unknown	219,117	90.0	0.92	(0.90–0.93)	87.8	0.95	(0.94–0.97)
Record of influenza vaccination during the 2019/20 season	No	576,854	89.4			86.8		
	Yes	460,341	98.0	5.67	(5.54–5.79)	96.3	3.95	(3.88–4.01)
	Unknown	225,494	90.1	1.07	(1.06–1.09)	87.8	1.10	(1.09–1.12)
Number of COVID-19 PCR tests prior to cohort start	0	1,069,650	92.3			90.2		
	1	129,927	95.7	1.86	(1.81–1.91)	93.2	1.49	(1.45–1.52)
	2–4	43,397	92.9	1.10	(1.06–1.15)	89.0	0.88	(0.85–0.91)
	5–9	7,608	87.7	0.60	(0.56–0.64)	81.4	0.47	(0.45–0.50)
	10–14	4,297	92.6	1.05	(0.94–1.18)	89.2	0.90	(0.82–0.99)
	15–19	4,894	96.0	2.03	(1.76–2.34)	93.8	1.64	(1.46–1.84)
	20+	2,916	96.4	2.22	(1.83–2.70)	94.3	1.80	(1.54–2.11)
Positive COVID-19 PCR test prior to cohort start	No	1,235,911	92.6			90.4		
	Yes	26,778	94.5	1.37	(1.30–1.45)	91.7	1.18	(1.13–1.23)

VE for one dose of any vaccine type against death with COVID-19, where COVID-19 was mentioned as a cause or contributing factor, was estimated to be 80.9% (95%CI 72.1–86.9).

Fewer than 10 individuals who had two doses of COVID-19 vaccine died between 7 December 2020 and 18 July 2021; therefore, VE estimates for two doses could not be produced due to potential disclosure of identity.

Discussion

The overall VE estimate 7 or more days post dose two of any vaccine type against SARS-CoV-2 PCR positive infection, in this large cohort study of the Welsh population was 42%. This estimate is lower compared to other published studies, which mainly include estimates for BNT162b2, whilst two thirds of this study population had received ChAdOx1.[3,4,11] Estimates against SARS-CoV-2 PCR positive infection were lower for ChAdOx1 compared to BNT162b2, as has been seen elsewhere.[9,10]

However, estimates of 85% against hospital admission due to SARS-CoV-2 PCR infection 7 or more days post dose two are encouraging, and in line with estimates from other studies. Haas EJ et al.[3] saw 97.2% (96.8–97.5) effectiveness of two doses of Pfizer-BioNTech BNT162b2 vaccine against COVID-19-related hospitalization 7 days after the second dose and data from Qatar 97.4% (92.2–99.5) for BNT162b2 against severe, critical or fatal disease 14-days after the second dose.[6] Interim data from a large population cohort in Scotland estimated 91% (95% CI 85–94)

Table 2. Cox-regression estimates of outcomes from COVID-19 infection following vaccination with BNT162b2 or ChAdOx1 in those aged 50 years and over, Wales UK.

Outcome	Category	Individuals	Person years	Events	Events per 1000 Person Years	Unadjusted model HR (95% CI)	Adjusted model Adjusted HR (95% CI)
PCR positive infection	Unvaccinated	1,253,665	284,477.9	32192	113.2	-	-
	0–6 days post dose 1	1,130,966	18,571.2	596	32.1	0.80 (0.74–0.87)	0.75 (0.69–0.81)
	7–13 days post dose 1	1,129,786	21,639.2	811	37.5	1.15 (1.07–1.24)	1.07 (0.99–1.15)
	14–20 days post dose 1	1,128,169	21,610.3	530	24.5	0.96 (0.88–1.06)	0.88 (0.81–0.97)
	21–27 days post dose 1	1,126,833	21,571.2	326	15.1	0.76 (0.67–0.85)	0.69 (0.61–0.77)
	>27 days post dose 1	1,123,892	128,657.6	1135	8.8	0.95 (0.88–1.02)	0.84 (0.78–0.90)
	0–6 days post dose 2	1,100,268	18,056.3	144	8.0	0.90 (0.76–1.07)	0.81 (0.68–0.96)
	>6 days post dose 2	1,097,663	222,928.2	2429	10.9	0.68 (0.62–0.75)	0.58 (0.53–0.64)
Hospital admission with PCR positive infection	Unvaccinated	1,253,665	289,509.2	5780	20.0	-	-
	0–6 days post dose 1	1,156,041	18,985.8	850	44.8	2.23 (2.05–2.42)	2.10 (1.94–2.28)
	7–13 days post dose 1	1,155,332	22,134.6	749	33.8	1.75 (1.60–1.91)	1.64 (1.50–1.80)
	14–20 days post dose 1	1,154,373	22,115.9	627	28.4	1.55 (1.41–1.71)	1.45 (1.31–1.60)
	21–27 days post dose 1	1,153,412	22,082.1	521	23.6	1.38 (1.24–1.54)	1.28 (1.15–1.43)
	>27 days post dose 1	1,150,614	131,872.1	465	3.5	0.30 (0.27–0.34)	0.26 (0.24–0.31)
	0–6 days post dose 2	1,126,920	18,493.9	197	10.7	1.14 (0.96–1.34)	1.00 (0.84–1.19)
	>6 days post dose 2	1,124,283	227,774.7	176	0.8	0.10 (0.08–0.12)	0.09 (0.07–0.10)
Deaths	Unvaccinated	1,253,438	290,130.7	1906	6.6	-	-
	0–6 days post dose 1	1,159,532	19,043.6	31	1.6	0.23 (0.16–0.33)	0.23 (0.16–0.33)
	7–13 days post dose 1	1,158,888	22,203.5	41	1.8	0.29 (0.21–0.40)	0.29 (0.21–0.40)
	14–20 days post dose 1	1,158,003	22,186.1	38	1.7	0.29 (0.20–0.41)	0.29 (0.20–0.41)
	21–27 days post dose 1	1,157,105	22,153.0	17	0.8	0.16 (0.10–0.26)	0.16 (0.09–0.26)
	>27 days post dose 1	1,154,321	132,371.1	48	0.4	0.21 (0.14–0.30)	0.19 (0.13–0.28)
	0–6 days post dose 2	1,130,563	18,553.5	<10	-	-	-
	>6 days post dose 2	1,127,897	228,453.3	<10	-	-	-

[1]Unadjusted model adjusted for age as at 31st March 2021, shielding list status and health and care worker status.
[2]Adjusted model adjusted for age as at 31st March 2021, shielding list status and health and care worker status, any previous PCR positive SARS-CoV-2 test, number of SARS-CoV-2 PCR tests prior to the cohort start, QCOVID score, Health Board of residence, sex, ethnic group, socio economic quintile of deprivation, Urban/Rural location of residence, previous vaccination against shingles or pneumococcal disease, vaccination against influenza between 1st October 2020 and 31st March 2021 and number of days with a GP consultation recorded in the year prior to 1st February 2020, prior to the pandemic reaching Wales.
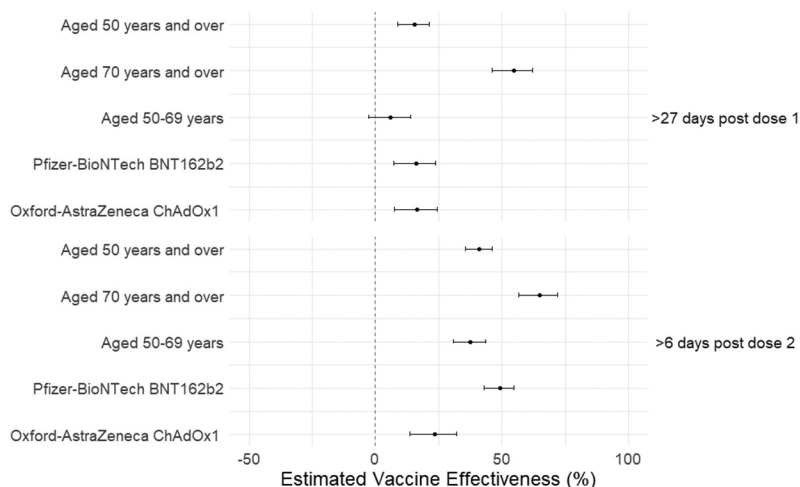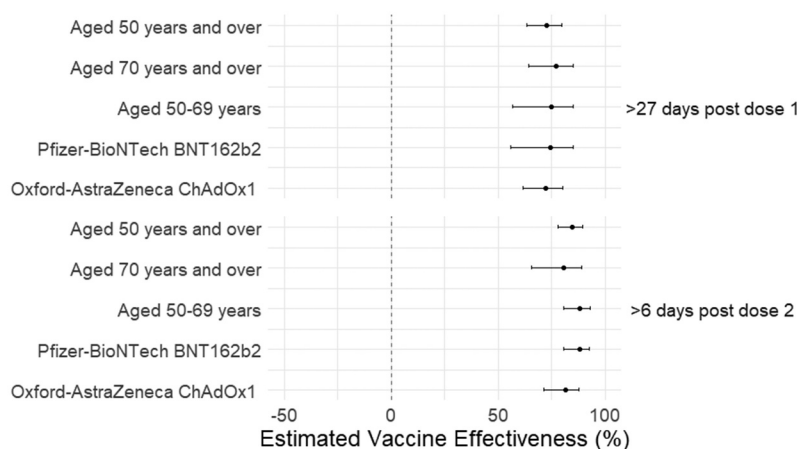

Figure 1. Vaccine effectiveness estimates of COVID-19 vaccination with BNT162b2 or ChAdOx1 against PCR positive SARS-CoV-2 infection in those aged 50 years and over, Wales UK.[1]. [1] Cox regression model adjusted for age as at 31st March 2021, shielding list status and health and care worker status, any previous PCR positive SARS-CoV-2 test, number of SARS-CoV-2 PCR tests prior to the cohort start, QCOVID score, Health Board of residence, sex, ethnic group, socio economic quintile of deprivation, Urban/Rural location of residence, previous vaccination against shingles or pneumococcal disease, vaccination against influenza between 1st October 2020 and 31st March 2021 and number of days with a GP consultation recorded in the year prior to 1st February 2020, prior to the pandemic reaching Wales.

Figure 2. Vaccine effectiveness estimates of COVID-19 vaccination with BNT162b2 or ChAdOx1 against hospitalization due to SARS-CoV-2 infection in those aged 50 years and over, Wales UK.[1]. [1] Cox regression model adjusted for age as at 31st March 2021, shielding list status and health and care worker status, any previous PCR positive SARS-CoV-2 test, number of SARS-CoV-2 PCR tests prior to the cohort start, QCOVID score, Health Board of residence, sex, ethnic group, socio economic quintile of deprivation, Urban/Rural location of residence, previous vaccination against shingles or pneumococcal disease, vaccination against influenza between 1st October 2020 and 31st March 2021 and number of days with a GP consultation recorded in the year prior to 1st February 2020, prior to the pandemic reaching Wales.

effectiveness of one dose BNT162b2 against hospitalization at 28 to 34 days post vaccination and 88% (95% CI 75–94) effectiveness of ChAdOx1 against the same outcome.[5]

Due to small numbers of COVID-19 related deaths in the study population, it was not possible to obtain estimates of VE against a complete two dose course at this time; however, one dose was estimated to reduce deaths by 81%.

Follow-up in this cohort started on 7 December 2020 when the vaccination program began in Wales. At this time Wales was reaching the peak in a second outbreak wave where the dominant variant was Alpha.[13] This adds complexities in interpreting the impact of the vaccine compared to other factors that changed over time, including changes in infection prevalence and restrictions that were implemented to control the second wave.[26] By the end of March 2021, cases returned to low levels and remained low until the beginning of June 2021 when cases started to increase and Delta was the dominant variant.

The estimates in this study can be considered to be mainly against the Alpha variant and provide a baseline for how the vaccination is working over time, and can be useful in comparing VE in the face of new variants of SARS-CoV-2 arising. A systematic long-term approach to surveillance of VE is important due to changing variants, the large number of vaccine candidates and proposed schedules and booster doses. Evidence is still emerging, but recent studies from England and Scotland suggest effectiveness against sequenced symptomatic cases is slightly reduced for Delta compared to Alpha after two doses of BNT162b2 or ChAdOx1.[9,10] Early data from Canada suggest similar VE following two doses of BNT162b2 when comparing Delta and Alpha, and similar VE for one dose against hospitalization or death.[8] It is too early to produce robust variant-specific estimates for Wales but the Delta dominant third wave does not appear to have resulted in a large increase in hospital admissions, as with waves 1 and 2 and mortality due to COVID-19 infection also appears lower than the previous two waves.[13] At time of writing, confirmed case incidence is consistently lower in the most highly vaccinated age-groups. Early evidence suggests VE against confirmed COVID-19 for BNT162b2 vaccination may decrease by more than ten percentage points 4 months post second dose.[27]

Comparing estimates from different studies using different definitions and statistical methods should be done with caution due to differences in surveillance systems and study populations, schedule, strain, outcome, and recipient characteristics. Whist direct comparison of our VE estimates against those reported from other studies is difficult due to differences in approach and the samples used, we found that in general our VE estimates against positive PCR were lower but our estimates against hospitalization were similar.

Vaccine effectiveness against hospital admission was seen 0–6 days post dose 1. This apparent immediate effectiveness post vaccination may be explained by bias in those who are unwell or having received a positive test, not being vaccinated in line with policy for attending appointments. These individuals would then be more likely to be admitted to hospital due to a COVID-19-related illness than people who were well enough to be vaccinated.

Symptom information was unavailable for this study, and when looking at the outcome of SARS-CoV-2 PCR positive infection, data may include those with asymptomatic infection identified through community screening activities, and enhanced case finding in other closed settings, outbreaks and incidents. This is likely to lead to under estimates of COVID-19 VE. In this study, estimates for hospital admission with COVID-19 may also be underestimated, given the age of the cohort, although COVD-19 may have been listed as the primary cause for admission, reasons for admission can be complex and co-morbidities are likely. The addition of misclassified outcomes (hospital admissions due to reasons other than testing positive for COVID-19) to both vaccinated and unvaccinated groups will tend to lead to an underestimation of vaccine effectiveness. Conversely, 47% of all admissions that could be linked to a SARS-CoV-2 PCR positive test were not included in this analysis, as COVID-19 was not listed as the primary reason for admission, these too could be miscoded.

Due to the rapid roll out of the vaccine program and high coverage, the individuals who remain unvaccinated are likely to have different characteristics or be less engaged with healthcare services compared to those who have received the vaccine, and if there is lower access to health care in the unvaccinated, case ascertainment is also likely to be lower, resulting in underestimation of VE. We have aimed to limit the impact of healthcare access bias by adjusting for number of GP consultations and previous vaccination history for this population. However, there is currently disruption in healthcare-seeking patterns, it is not known whether propensity to consult with a GP will be as good at predicting likelihood of accessing health care in the current context.

Propensity scores are commonly used in observational studies where 'gold standard' randomization of exposed and unexposed individuals is not possible.[28] Assigning propensity weights based on odds of being vaccinated with one dose as at 17 June 2021, when coverage was high produced large weights, which can cause estimation problems.[29] To account for this, weights can be trimmed to remove extreme values, however, this method lacks a clear framework and can be variably applied.[30] A sensitivity analysis in this study produced a range of estimates (data not shown), when applying different IPW trimming methods; therefore, these extreme estimates produced from the IPW model are potentially over adjusting and should be interpreted with caution, Acknowledging this, the adjusted model without propensity weighting is potentially underestimating VE.

The main limitation to this study was being unable to obtain further information on severity of illness. Having symptom information available to determine VE against asymptomatic and symptomatic infection would be beneficial. The proportion of missing data for the GP-derived variables used to control for propensity to consult (approximately 20%) may effect VE estimates, although sensitivity analysis shows this is minimal. Due to small population sizes, broad ethnic grouping was used in this analysis. As ethnicity is strongly associated with vaccination uptake, being able to use more refined categories to identify intra-group variation may have been beneficial.

These analyses included a diverse population and therefore further analysis for sub-groups, such as healthcare workers who have higher exposure or care home residents who may have higher transmission rates, is under way. In this study, the exclusion of care home residents may cause a bias to lower death rate in older age groups who are infected.

In conclusion, vaccine uptake has been high amongst adults in Wales and VE estimates are encouraging, with two doses providing considerable protection against severe infection. Continued roll-out of the vaccination program within Wales, and more globally, and ensuring people complete the two dose course, is crucial in our fight against COVID-19. Continued evaluation of effectiveness is important to assess issue such as waning and the impact of new variants.

Acknowledgments

Authors' contributions

MP led the conception and design of this work with input from LG, SC, MG, SB, CW and JS. MP performed the analysis, JL created the underlying QCOVID dataset and SB provided the code for the imputation, AA completed the linkage and analysis to create the ethnic group variable. MP drafted the first iteration of the manuscript. All authors critically reviewed the manuscript, provided important intellectual input, approved the final version and agreed to be accountable for their contributions.

Availability of data and materials

The data used in this study are available in the SAIL Databank at Swansea University, Swansea, UK, but as restrictions apply they are not publicly available. All proposals to use SAIL data are subject to review by an independent Information Governance Review Panel (IGRP). Before any data can be accessed, approval must be given by the IGRP. The IGRP gives careful consideration to each project to ensure proper and appropriate use of SAIL data. When access has been granted, it is gained through a privacy protecting safe haven and remote access system referred to as the SAIL Gateway. SAIL has established an application process to be followed by anyone who would like to access data via SAIL at https://www.saildatabank.com/application-process

Disclosure statement

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