Pfizer-BioNTech and Oxford AstraZeneca COVID-19 vaccine effectiveness and immune response among individuals in clinical risk groups

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Author contributions

HW, RT, JLB, SdeL, GA drafted the manuscript, with direction from MR. HW, NA, MS, SdeL, JLB designed the vaccine effectiveness study. HW carried out all statistical analyses. NA, JLB, SdeL FDRH, SA provided oversight of vaccine effectiveness. MZ, JE were responsible for overseeing testing of sentinel surveillance swabs. PSP, RB, JS for data management and linkage of swab data. JW, HC, EL, JH, JS for data management and linkage of serology data. EB GP for data quality and sampling from contributing GPs. AO oversaw testing of serology samples. GA, KB provided oversight of serology.

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Abstract

Background

Covid-19 vaccines have been found to be highly effective in general population cohorts, however, data on effectiveness among individuals with clinical conditions that place them at increased risk of severe disease is limited.

Methods

We use GP electronic health record data, sentinel virology swabbing and sentinel antibody testing within a cohort of over 700 general practices across England (representing 10% of the population) to estimate antibody response to vaccination and vaccine effectiveness against medically attended Covid-19 among individuals in clinical risk groups. Adjusted prevalence ratios of S-antibody positivity and titres after vaccination were estimated by clinical risk group. Adjusted vaccine effectiveness was estimated using a cohort analysis and a nested test negative case control analysis.

Findings

There was no notable reduction in S-antibody positivity or titres in most clinical risk groups. The only clinical risk group with significantly reduced S-antibody response after one and 2 doses was the immunocompromised group who had a 68% (95%CI: 43 to 82%) reduction in the geometric mean titre after 2 doses. Reduced vaccine effectiveness against clinical disease was also noted in the immunosuppressed group after one dose, however, after a second dose of either vaccine, high levels of effectiveness were seen (Pfizer: 73.0%, 95%CI 33.9 to 89.0%; AstraZeneca 74.6%, 95%CI 18.7 to 92.1%).

Interpretation

In most clinical risk groups, immune response to vaccination is maintained and high levels of VE are seen with both the Pfizer and AstraZeneca vaccines. Reduced antibody response and vaccine effectiveness were seen after one dose of vaccine among the immunosuppressed group, however, after a second dose there is only a small and non-significant reduction in vaccine effectiveness. These findings would support maximising coverage with two doses in immunosuppressed individuals.

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Introduction

A range of clinical comorbidities have been associated with more severe Covid-19 disease and poor outcomes.[1-3] COVID -19 vaccines have shown high levels of efficacy in older adults, healthcare workers and the general population both in clinical trials and real world effectiveness studies.[4-9] However, data on the effectiveness of these vaccines among individuals in clinical risk groups is limited.

The UK's Medicines and Healthcare Products Regulatory Agency (MHRA) gave emergency use authorisation to 3 vaccines against COVID-19 between December 2020 and January 2021, namely the Pfizer/BioNTech BNT162b2 mRNA, Oxford/AstraZeneca ChAdOx1 nCoV-19 adenoviral AZD1222; and Moderna mRNA-1273 vaccines. BNT162b2 and AZD1222 have been delivered through the national vaccination programme since 8 December 2020 and 4 January 2021, respectively. Rollout of the Moderna vaccine in England began 13 April 2021, though use of this vaccine has been more limited. Vaccination was initially prioritised for older people, health and social care workers and predefined clinical risk groups.[10] As of 4 July 2021, over 38 million individuals in England have received their first dose and 28 million have received two doses.[11]

The COVID-19 vaccine trials demonstrated high levels of efficacy.[4-6] This has been further supported by real world vaccine effectiveness studies which indicate 50 to 70% protection against infection or mild disease after a single dose of either BNT162b2 or AZD1222, 75 to 85% protection against hospitalisation or death. After two doses effectiveness reaches 65 to 90% against infection or mild disease, and 90 to 100% against severe disease.[7,9,12-17] These high levels of effectiveness are maintained in older adults, nevertheless, vaccine effectiveness estimates have not yet been reported for individuals in clinical risk groups.

Although age has been found to be the greatest risk factor for adverse outcomes following COVID-19 infection, clinical comorbidities may also increase the risk of severe disease. Diabetes, severe asthma, chronic heart disease, chronic kidney disease, chronic liver disease, neurological disease, and disease or therapy associated with immunosuppression have all been linked to an increased risk of hospitalisation or death with COVID-19.[1-3] Individuals with these conditions have been prioritised for vaccination in many national programmes. In the UK, those at highest risk of severe disease have been advised to 'shield' by remaining isolated at home for long periods of the pandemic.[18] This group were offered vaccination from January 2021 along with older adults. Individuals aged under 65 in other clinical risk groups were offered vaccination from February 2021.[19]

A number of studies have monitored antibody responses to vaccination in individuals with clinical comorbidities. Reduced seroconversion rates have been seen in transplant recipients, haematological malignancy, solid organ cancer patients and patients on some immunosuppressive therapies after one dose of vaccine. [20-25] Reduced antibody responses have also been seen after 2 doses among patients with haematological malignancy and transplant recipients.[23,26,27] Conversely other studies have found similar seroconversion rates among patients on immunosuppressive therapy, patients with end stage renal disease and solid organ cancer patients, in particular after 2

doses.[22,23,25,28-31] However, it is not yet clear how differences in antibody responses translate into changes in vaccine effectiveness.

In this study we use electronic health record (EHR) data from a cohort of general practice patients and sentinel antibody testing within the same cohort to estimate antibody responses and vaccine effectiveness against symptomatic medically attended COVID-19 among patients in different clinical risk groups.

Methods

Summary:

We conducted cohort and nested test-negative case-control (TNCC) VE analyses. Our population of interest were individuals in risk groups and those advised to shield. Our outcome was medically attended COVID-19, with the diagnosis confirmed by PCR test.

Data sources

We used pseudonymised data extracted from computerised medical record (CMR) data collected by the in the Oxford-Royal College of General Practitioners Research and Surveillance Centre (RSC),[32] one of Europe's oldest primary care sentinel systems.[33] A cohort was created to support the Public Health England (PHE) COVID-19 VE studies comprising the registered patients from 718 English general practices (N=7,217,929), 11% of general practices and 10% of the population. These practices used the systematised nomenclature of medicine (SNOMED) clinical terms (CT) to record key data. Data were held in in a trusted research environment (TRE), the Oxford-RCGP Clinical Informatics Digital Hub (ORCHID).[34]

National COVID-19 testing results through community testing, hospital laboratories and public health laboratories are posted electronically into the general practice EHR. UK general practice has had a system of electronic laboratory links since 2004, allowing pathology results including COVID-19 test results to be sent through direct to that individual's record.

For a subset of sentinel surveillance practices, swabs were collected from individuals presenting with flu or COVID-like symptoms and sent to the Virus Reference Laboratory at PHE for SARS-CoV-2, influenza and RSV PCR testing.

A further subset of practices collected additional sera from patients presenting at their GP for a routine blood test as part of SARS-CoV-2 serological surveillance. Patients in older age groups and in clinical risk groups were oversampled to match the rollout of the vaccination programme. Samples were tested at Public Health England Porton using two assays from Roche diagnostics (Basel, Switzerland): the Elecsys Anti-SARS-CoV-2 spike (S) and neucleoprotein (N) assays. The N assay detects only antibodies acquired following natural infection, while the S assay detects both post-infection and vaccine-induced antibodies.

Antibody response to vaccination

Prevalence ratios of N-assay seropositivity from December 2020 to May 2021 were calculated using multivariable log-Binomial regression, with age and region poststratification. Terms for each of the specific risk groups, NHS region, 10-year age group, sex and month sample taken were included. Marginal predictions of N seropositivity by risk group are presented to give a picture of prior infection rates (and likely susceptibility in the absence of vaccination) for each risk group. The analysis was repeated without specific risk groups, but with a term for non-risk, risk (non-shielding), and shielding included.

Post vaccination spike (S) antibody response was assessed in N-assay negative individuals that is in those who had no evidence of antibodies from prior infection, and who had received dose 1 vaccination at least 28 days prior. % positive with binomial exact confidence interval was calculated. Approximate adjusted prevalence ratios were calculated using multivariable Poisson regression with robust error variance and including terms for each specific risk group, age group, sex, vaccine manufacturer and time since dose (28 to 41 days, 42+ days). Again, the analysis was repeated without specific risk groups, but including a term for non-risk / risk (non-shielding) / shielding. Similar analyses were carried out on antibody concentrations that are described and presented in supplementary material S4.

VE outcomes and exposures

Our outcome was a case of acute symptomatic COVID-19, defined as symptoms or clinical illness consistent with COVID-19 within 10 days before or after a positive PCR test for COVID-19 (Box 1) recorded in the practice CMR entry. The CMR entry was usually an encounter (phone or face-to-face) with the GP, though may have been an entry from a hospital, emergency or out of hours encounter. The PCR test was conducted ether as part of sentinel surveillance or through the national testing process.

Symptomatic COVID-19

- Diagnosis of COVID-19 infection confirmed by positive virology test

  AND

- Symptoms of COVID 19 in the 10 days before/after the virology test
  - Cough
  - Fatigue
  - Fever
  - Diarrhoea
  - Headache
  - Anosmia
  - Loss of taste
  - Sore Throat
  - Shortness of Breath
  - Nausea
  - Myalgia

  OR

  Acute clinical illnesses associated with COVID-19 and in the 10 days before/after the virology test
  - Influenza-like-illness
  - Acute bronchitis
  - Pneumonia or pneumonitis
  - Lower respiratory infection
  - Upper respiratory infection

Box 1: symptomatic COVID-19 outcome definition

Symptom onset dates were not available, so we used whichever came first of test or consultation date.

Test-negative study controls met the same case-definition and symptoms within 10 days of a negative test. We excluded negative tests with symptoms if within 21 days before or 90 days after any positive test, and we allowed a maximum of one negative test within a 21 day period because these could represent a single illness episode.

The exposure of interest was COVID-19 vaccination. Our dataset included available information in GP records on the date and dose of vaccine given, manufacturer and batch number. Where

manufacturer was unavailable, we inferred vaccine brand from the batch number or vaccination date (Pfizer if before 4 Jan 2021). Dose 1 vaccine effectiveness was considered as 28 to 90 days after the first dose and dose 2 as 14+ days after the second dose.

VE statistical analyses

The study start date was 7 December 2021 and the study end date was 13 June 2021; individuals were censored at death, deregistration or at the last recorded vaccination date within a patient's registered GP practice.

Cohort analyses were conducted using acute symptomatic COVID-19 as outcomes (Box 1). We used Poisson regression on outcomes, including vaccination status as a time-varying covariate and further adjusting for time and region by fitting an interaction between NHS region and cubic splines over weeks, and demographic and clinical variables. Time after first event was retained in analyses and probable re-infections were included.

TNCC analyses also included people with acute symptomatic COVID-19. Logistic regression was used for analysis, including vaccination status at the event time and further adjusting for time-region interaction, demographic and clinical variables as for the cohort study.

Adjusted analyses for demographic and clinical variables included only those with complete data. Adjustments were made for: age group (in 5-year bands, then 90+), sex, ethnicity, index of multiple deprivation (IMD) quintile, GP record indicating prior COVID-19, large household (<10, divided into those with a median age <70 and ≥70 years old), GP consultation rate quartile, comorbidity, shielding recommendation, and latest smoking status.

The first set of analyses presented are for the population aged 16 to 64, and aged 65 and above. These comprise: all individuals, those not in risk groups, those in predefined risk groups,[10] and people who had a shielding recommendation. We checked two-way interactions with vaccination status (any manufacturer, for simplicity) for all covariates. Since health and social care workers are not flagged in GP records, the analysis for 16 to 64 year olds was initiated from 1 February 2021 and excluded those who were vaccinated before or experienced an event between 7 December and this date. Results are presented 28 to 90 days post first dose and 14+ days post second dose both separately for Astra Zeneca and Pfizer and combined for all manufacturers. The second set of analyses focused on people in predefined risk groups, and results are presented for VE within each risk group. Results are presented 28 to 90 days post first dose and 14+ days post second dose combined for all manufacturers.

All statistical analyses were carried out using STATA version 14.2.

Ethical considerations

Surveillance and COVID-19 VE studies were approved by the PHE Caldicott Guardian as Health Protection permitted under Regulation 3 of the Health Service (Control of Patient Information) Regulations 2002.

Role of the funding source

The funder of the study had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Results

The full vaccine effectiveness cohort included 7,217,929 individuals. After exclusions, which are listed in Supplementary material S1, the cohort included 5,642,687 individuals, of which 1,276,517 were aged 65 years and above and 1,054,510 belonged to a risk group.

Descriptive characteristics and case fatality rates are shown in Supplementary material S2 and vaccine coverage in Supplementary material S3. Chronic heart disease and vascular disease (CHD), chronic kidney disease, chronic respiratory and neurological risk groups saw a higher proportion of individuals vaccinated during December to January, the earliest phase of vaccine rollout. Ages 65+ were largely vaccinated during January and February, with a fairly even split between AstraZeneca and Pfizer vaccines. Vaccination rollout is ongoing in the healthy 16 to 64 cohort; more have received AstraZeneca.

Since the cohort start date up to 21 May 2021, 11,812 serology samples were collected, of which we were able to link 9,071 to GP records; all were members of the vaccine effectiveness cohort. 7,992 serology samples were taken since January 2021 and contributed to analyses of seropositivity. 3,905 linked serology samples were taken post vaccination, of which 3,592 were N antibody negative (indicating no evidence of past infection): 1,539 fell within in the period 28 to 90 days after dose 1 and 532 were taken 10+ days after dose 2.

Seropositivity

Modelled and adjusted N-assay based seropositivity is given in Supplementary Figure S4.1. For individuals not belonging to a risk group seropositivity was 9.0% (95% CI 8.1 to 9.9%). Seropositivity was lower for individuals in risk groups and shielding, though not significantly. For the specific risk groups seropositivity was only significantly lower for the immune-compromised group, although the chronic respiratory and chronic liver disease groups also showed relatively low seropositivity of around 6%.

Vaccine-induced antibodies

Spike (S) serology outcomes were available for 1539 adults with no evidence of naturally-acquired N antibodies who had received dose 1 vaccination at least 28 days prior; we assume S positive outcomes in N negative individuals indicate vaccine-induced antibodies. Table 1 gives full estimates from a multivariable regression model of S seropositivity including all specific risk groups, and Table 1 also includes estimates for no risk group / risk (non-shielding) / shielding (fitted separately). The prevalence ratio of seropositivity is significantly lower for ages 80+. Within the specific risk groups, seropositivity is significantly lower for the diabetes and immunocompromised groups, and the immunocompromised group especially stands out as having a less vaccine-induced antibodies - 70% as compared with 95% in non-immunocompromised individuals. Seropositivity also appears a little lower in the CHD group. Individuals who were shielding or belonging to a risk group had significantly lower seropositivity than those not in a risk group. Reduced S-antibody titres after dose 1 were seen in the immunosuppressed, morbid obesity, diabetes and CHD risk groups (Supplementary material, Table S1.1). After 2 doses, there were only 5 individuals in the whole cohort who were not S-antibody positive (Table 2). Reduced titres were seen in the immunocompromised (68% reduction; 95%CI 43 to 82%) and chronic respiratory disease groups (65% reduction; 95%CI 42 to 80%).

Table 1. presence of spike (S) antibodies 28+ days after dose 1 COVID-19 vaccination in N-negative individuals: % positive and approximate adjusted prevalence ratios. Risk group status (none / risk (non-shielding) / shielding) was fitted in a separate model with the same adjustments.

	n pos / N	% pos (95% CI)	prevalence ratio (95% CI)	p-value
age group				
18-49	159 / 166	96 (92 - 98)	1 (ref)	
50-59	179 / 189	95 (90 - 97)	0.99 (0.95 - 1.04)	0.712
60-69	313 / 330	95 (92 - 97)	0.99 (0.95 - 1.03)	0.58
70-74	277 / 293	95 (91 - 97)	0.99 (0.95 - 1.03)	0.668
75-79	230 / 252	91 (87 - 94)	0.96 (0.91 - 1.01)	0.08
80-84	163 / 184	89 (83 - 93)	0.92 (0.86 - 0.98)	**0.007**
85+	112 / 125	90 (83 - 94)	0.92 (0.86 - 0.99)	**0.027**
sex				
F	778 / 829	94 (92 - 95)	1 (ref)	
M	655 / 710	92 (90 - 94)	0.99 (0.96 - 1.01)	0.354
days after dose				
28-41	473 / 532	89 (86 - 91)	1 (ref)	
42-90	960 / 1007	95 (94 - 97)	1.06 (1.03 - 1.1)	**<0.001**
vaccine manufacturer				
Astra Zeneca	448 / 477	94 (91 - 96)	0.99 (0.95 - 1.02)	0.472
Pfizer BioNTech	447 / 482	93 (90 - 95)	1 (ref)	
unknown	538 / 580	93 (90 - 95)	0.99 (0.96 - 1.02)	0.589
risk group status				
no risk group	675 / 699	97 (95 - 98)	1 (ref)	
any risk group	709 / 780	91 (89 - 93)	0.95 (0.92 - 0.98)	**<0.001**
shielding	49 / 60	82 (70 - 90)	0.86 (0.76 - 0.97)	**0.013**
Specific risk groups				
CHD: no	1129 / 1201	94 (93 - 95)	1 (ref)	
CHD: yes	304 / 338	90 (86 - 93)	0.96 (0.93 - 1)	0.054
diabetes: no	1210 / 1286	94 (93 - 95)	1 (ref)	
diabetes: yes	223 / 253	88 (84 - 92)	0.95 (0.9 - 0.99)	**0.019**
neurological: no	1290 / 1386	93 (92 - 94)	1 (ref)	
neurological: yes	143 / 153	93 (88 - 97)	1.03 (0.98 - 1.08)	0.257
chronic kidney: no	1233 / 1317	94 (92 - 95)	1 (ref)	
chronic kidney: yes	200 / 222	90 (85 - 94)	0.99 (0.95 - 1.04)	0.83
morbid obesity: no	1350 / 1450	93 (92 - 94)	1 (ref)	
morbid obesity: yes	83 / 89	93 (86 - 97)	0.97 (0.91 - 1.02)	0.259
chronic respiratory: no	1313 / 1413	93 (91 - 94)	1 (ref)	
chronic respiratory: yes	120 / 126	95 (90 - 98)	1.04 (1 - 1.08)	0.067
immuno: no	1340 / 1407	95 (94 - 96)	1 (ref)	
immuno: yes	93 / 132	70 (62 - 78)	0.75 (0.67 - 0.83)	**<0.001**
chronic liver: no	1366 / 1465	93 (92 - 94)	1 (ref)	
chronic liver: yes	67 / 74	91 (81 - 96)	0.98 (0.91 - 1.05)	0.594

Table 2: Median responses, and geometric mean ratios given by multivariable regression of (log) Roche S antibody concentrations, 10+ days post dose 2

	N	n pos (%)	median (IQR)	geometric mean ratio (95% CI)	p-value
age group					
18-49	39	38 (97%)	>2500 (1047 - 11567)	1 (ref)	
50-59	31	31 (100%)	3761 (788 - 8462)	0.9 (0.4 - 2.01)	0.799
60-69	85	84 (99%)	1157 (551 - 4025)	0.54 (0.28 - 1.04)	0.064
70-74	83	83 (100%)	1567 (709 - 2552)	0.58 (0.3 - 1.14)	0.113
75-79	76	75 (99%)	>2500 (1305 - 5223.5)	0.54 (0.27 - 1.07)	0.079
80-84	126	125 (99%)	1306.5 (366 - >2500)	0.6 (0.31 - 1.14)	0.117
85+	92	91 (99%)	1138 (317.5 - >2500)	0.69 (0.35 - 1.37)	0.292
sex					
F	282	282 (100%)	1966 (658 - 3918)	1 (ref)	
M	250	245 (98%)	1488 (428 - >2500)	0.61 (0.45 - 0.83)	**0.002**
days after dose					
10-41	392	388 (99%)	2455.5 (747.5 - 3971.5)	1 (ref)	
42+	140	139 (99%)	729 (240 - 2033)	0.56 (0.37 - 0.86)	**0.008**
vaccine manufacturer					
Astra Zeneca	101	100 (99%)	1040 (555 - 1879)	1 (ref)	
Pfizer BioN-Tech	232	228 (98%)	>2500 (608.5 - 4705.5)	3.78 (2.39 - 5.99)	**<0.001**
unknown	199	199 (100%)	1273 (460 - 3441)	1.97 (1.28 - 3.04)	**0.002**
schedule / weeks between doses					
standard 2-5 weeks	115	113 (98%)	426 (176 - 987)	0.12 (0.07 - 0.19)	**<0.001**
extended 6-9 weeks	95	93 (98%)	969 (488 - >2500)	0.33 (0.22 - 0.5)	**<0.001**
extended 10+ weeks	322	321 (100%)	>2500 (1326 - 6178)	1 (ref)	
risk group status					
CHD: no	413	410 (99%)	1560 (570 - 2933)	1 (ref)	
CHD: yes	119	117 (98%)	2316 (426 - 3189)	1.35 (0.91 - 2)	0.13
diabetes: no	441	437 (99%)	1616 (540 - 3079)	1 (ref)	
diabetes: yes	91	90 (99%)	1756 (548 - >2500)	0.89 (0.59 - 1.32)	0.553
neurological: no	478	474 (99%)	1636 (551 - 2856)	1 (ref)	
neurological: yes	54	53 (98%)	1628 (338 - 6019)	0.85 (0.52 - 1.41)	0.539
chronic kidney: no	441	436 (99%)	1863 (570 - 3522)	1 (ref)	
chronic kidney: yes	91	91 (100%)	1096 (362 - >2500)	0.73 (0.49 - 1.1)	0.135
morbid obesity: no	514	509 (99%)	1611 (538 - 2810)	1 (ref)	
morbid obesity: yes	18	18 (100%)	2759.5 (581 - 13282)	1.22 (0.53 - 2.83)	0.643
chronic respiratory: no	484	481 (99%)	1871 (571 - 3510.5)	1 (ref)	
chronic respiratory: yes	48	46 (96%)	776.5 (157 - 2258)	0.35 (0.2 - 0.58)	**<0.001**
immuno: no	493	489 (99%)	1778 (552 - 3189)	1 (ref)	
immuno: yes	39	38 (97%)	832 (85.6 - >2500)	0.32 (0.18 - 0.57)	**<0.001**
chronic liver: no	518	513 (99%)	1624 (540 - 2949)	1 (ref)	
chronic liver: yes	14	14 (100%)	1885 (570 - 2870)	1.36 (0.53 - 3.47)	0.522

Vaccine effectiveness

Table 4 and Figure 2 show vaccine effectiveness estimates by age group or risk group using the cohort analysis. Overall VE after one dose was approximately 60% after one dose, with little variation by age group. VE was similar for AstraZeneca and Pfizer after one dose, though confidence intervals overlapped. After 2 doses, there were more notable differences by vaccine type in both age cohorts though confidence intervals generally continued to overlap. In the 16 to 64 years cohort VE with Pfizer was 93.3% (85.8% to 96.8%) and with AstraZeneca 78.0% (69.7% to 84.0%). In the 65 years and older cohort VE with Pfizer was 86.7% (80.1% to 91.1%) and with AstraZeneca 76.4% (58.8% to 86.5%). The TNCC, generally gave slightly higher estimates (Supplementary Table S5.1 and Supplementary Figures S5.1a, S5.1b).

When considering all risk groups together or when focussing on the shielding group, there was generally no reduction in VE compared to those not in risk groups. In some cases, VE was higher in the shielding group after 2 doses, though confidence intervals were very wide. When stratifying into groups of specific conditions the only group where VE was notably diminished was the immunocompromised group. In the cohort analysis, VE after one dose of any vaccine was just 4.0% (95% CI -31.5% to 29.9%). However, this increased to 74.1% (95% CI 48.8% to 87.0%) after 2 doses. In the TNCC, dose 2 effects were similar but dose 1 VE was 18.3% (95% CI -18.4% to 43.7%). Dose 2 effects were similar for the Pfizer and AstraZeneca vaccines. Among other risk groups, VE estimates do not differ significantly from those in non-risk groups.

Table 4: Vaccine effectiveness 28 to 90 days post dose one and 14+ days post dose 2, for any vaccine, Pfizer and AstraZeneca (cohort analysis)

		Unvaccinated		Dose 1			Dose 2		
Vaccine	group	cases	person years	cases	person years	aVE	cases	person years	aVE
Any vaccine									
	all, ages 16-64	4228	1460811.4	245	182926.8	54.2% (46.5% - 60.7%)	56	43065.6	84.3% (78.9% - 88.3%)
	non-risk, ages 16-64	3563	1336831.5	175	140371.9	51.5% (42.1% - 59.4%)	35	26108.1	79.9% (71.1% - 86.0%)
	risk group, ages 16-64	570	107574.3	58	37293.1	62.5% (49.4% - 72.3%)	18	14582.3	89.1% (82.0% - 93.5%)
	shielding, ages 16-64	237	39600.9	38	14641	50.6% (28.5% - 65.8%)	7	7088	92.3% (82.5% - 96.6%)
	all, ages 65+	4895	207391.2	344	139033.5	60.4% (53.1% - 66.5%)	67	130839.9	84.9% (78.6% - 89.3%)
	non-risk, ages 65+	1413	113371.9	60	69913.2	64.6% (51.7% - 74.1%)	19	59697.8	78.7% (63.2% - 87.6%)
	risk group, ages 65+	3220	87109.2	264	64187	58.7% (50.5% - 65.5%)	44	65606	86.8% (80.4% - 91.1%)
	shielding, ages 65+	1511	29831.8	175	22809.9	52.4% (41.5% - 61.3%)	28	25590.9	84.3% (75.4% - 90.0%)
	CHD	2452	63661.8	153	39009.2	51.9% (41.5% - 60.5%)	27	36024.5	87.8% (80.8% - 92.2%)
	diabetes	2523	63282.7	119	34748	44.2% (30.9% - 55.0%)	28	26941.8	81.8% (71.7% - 88.3%)
	neurological	1810	38859	148	22722.5	47.4% (35.3% - 57.2%)	13	20628	91.6% (84.4% - 95.5%)
	chronic kidney	1276	28936.1	105	20851.1	48.6% (35.4% - 59.2%)	23	21920.7	83.0% (72.8% - 89.3%)
	morbid obesity	1555	41487.3	54	16345.9	41.8% (20.6% - 57.3%)	7	9231.8	86.3% (70.4% - 93.7%)
	chronic respiratory	1122	27317.4	59	16675.4	50.1% (33.8% - 62.4%)	11	14939.3	87.6% (76.4% - 93.5%)
	immuno-compromised	601	16695.3	50	9707.6	4.0% (-31.5% - 29.9%)	9	8219.4	74.1% (48.8% - 87.0%)
	chronic liver	725	20729.8	27	8662.8	31.1% (-3.2% - 54.0%)	5	5436.5	84.7% (58.4% - 94.4%)
Pfizer									
	all, ages 16-64	4228	1460811.4	41	24781.7	48.6% (27.9% - 63.3%)	8	12273.3	93.3% (85.8% - 96.8%)
	non-risk, ages 16-64	3563	1336831.5	20	13937.8	50.2% (19.4% - 69.2%)	7	6828.3	84.0% (66.2% - 92.4%)
	risk group, ages 16-64	570	107574.3	19	9858	49.3% (17.2% - 69.0%)	1	4879.7	
	shielding, ages 16-64	237	39600.9	7	3199.8	55.2% (4.5% - 79.0%)	1	1789.6	
	all, ages 65+	4895	207391.2	198	47362.7	56.6% (47.6% - 64.1%)	33	62686.1	86.7% (80.1% - 91.1%)
	non-risk, ages 65+	1413	113371.9	41	21027.3	50.7% (29.4% - 65.6%)	11	25376	75.0% (53.0% - 86.7%)
	risk group, ages 65+	3220	87109.2	148	24474.9	56.4% (46.2% - 64.6%)	22	34364.1	88.5% (81.5% - 92.9%)
	shielding, ages 65+	1511	29831.8	101	9343	46.5% (31.7% - 58.0%)	16	14280.1	83.7% (72.4% - 90.3%)
	CHD	2452	63661.8	80	14856.7	52.6% (39.1% - 63.2%)	15	19426.7	87.9% (78.8% - 93.1%)
	diabetes	2523	63282.7	56	12163	45.1% (26.8% - 58.8%)	12	13287.6	86.0% (73.5% - 92.6%)
	neurological	1810	38859	76	8176.3	46.3% (29.7% - 59.1%)	7	10517.5	89.6% (77.8% - 95.1%)
	chronic kidney	1276	28936.1	58	8746.4	51.5% (34.7% - 63.9%)	10	12640.7	87.7% (76.0% - 93.7%)
	morbid obesity	1555	41487.3	24	4470.6	33.9% (-2.5% - 57.4%)	2	3954.9	91.4% (65.1% - 97.9%)
	chronic respiratory	1122	27317.4	30	5926.8	51.6% (29.1% - 67.0%)	5	7406.9	89.1% (73.4% - 95.5%)
	immuno-compromised	601	16695.3	22	3248.3	15.9% (-32.3% - 46.5%)	5	3800.7	73.0% (33.9% - 89.0%)
	chronic liver	725	20729.8	14	2618.7	18.1% (-42.7% - 53.0%)	1	2416.1	91.8% (41.5% - 98.9%)
AZ									
	all, ages 16-64	4228	1460811.4	184	115517.4	50.2% (40.8% - 58.2%)	47	22157.2	78.0% (69.7% - 84.0%)
	non-risk, ages 16-64	3563	1336831.5	140	92374.7	46.9% (35.4% - 56.4%)	27	13738	76.2% (63.9% - 84.3%)
	risk group, ages 16-64	570	107574.3	37	20250.4	59.4% (41.5% - 71.8%)	17	7207.9	80.6% (67.7% - 88.3%)
	shielding, ages 16-64	237	39600.9	26	8339.9	44.6% (14.4% - 64.2%)	6	3898.7	87.4% (71.5% - 94.4%)
	all, ages 65+	4895	207391.2	99	56672.1	60.9% (49.0% - 70.0%)	30	43298.9	76.4% (58.8% - 86.5%)
	non-risk, ages 65+	1413	113371.9	15	28547.6	65.6% (40.0% - 80.3%)	8	20681.3	72.1% (31.3% - 88.7%)
	risk group, ages 65+	3220	87109.2	78	26294.1	60.0% (46.5% - 70.1%)	19	21009	79.7% (61.6% - 89.3%)
	shielding, ages 65+	1511	29831.8	55	9585.6	58.0% (41.3% - 69.9%)	10	8236.7	82.7% (61.9% - 92.2%)
	CHD	2452	63661.8	54	16416	48.5% (29.1% - 62.6%)	10	11290.7	86.8% (71.1% - 93.9%)
	diabetes	2523	63282.7	47	15634.2	40.5% (17.0% - 57.4%)	15	9395.3	70.2% (45.7% - 83.6%)
	neurological	1810	38859	51	10258.1	50.4% (30.8% - 64.4%)	5	7146.8	93.5% (79.4% - 98.0%)
	chronic kidney	1276	28936.1	34	8347.3	42.5% (16.6% - 60.3%)	11	6412.7	72.8% (45.2% - 86.5%)
	morbid obesity	1555	41487.3	24	8345.8	39.1% (3.5% - 61.6%)	5	3543.8	75.0% (37.5% - 90.0%)
	chronic respiratory	1122	27317.4	16	7429.5	57.8% (29.9% - 74.5%)	5	5235.8	84.0% (56.0% - 94.2%)
	immuno-compromised	601	16695.3	26	4381.1	-43.9% (-120.4% - 6.0%)	3	2993	74.6% (18.7% - 92.1%)
	chronic liver	725	20729.8	10	4343.2	36.2% (-20.7% - 66.3%)	4	2151	70.2% (4.8% - 90.7%)

*adjusted for week-NHS region interaction, 5-yr age group, sex, ethnicity, IMD quintile, GP record of prior COVID-19, large household, GP consultation quartile, chapter count, shielding recommendation, overall PRIMIS risk group status (overall only) and latest smoking status

Figure 2a: cohort vaccine effectiveness 28 to 90 days after dose one of vaccination

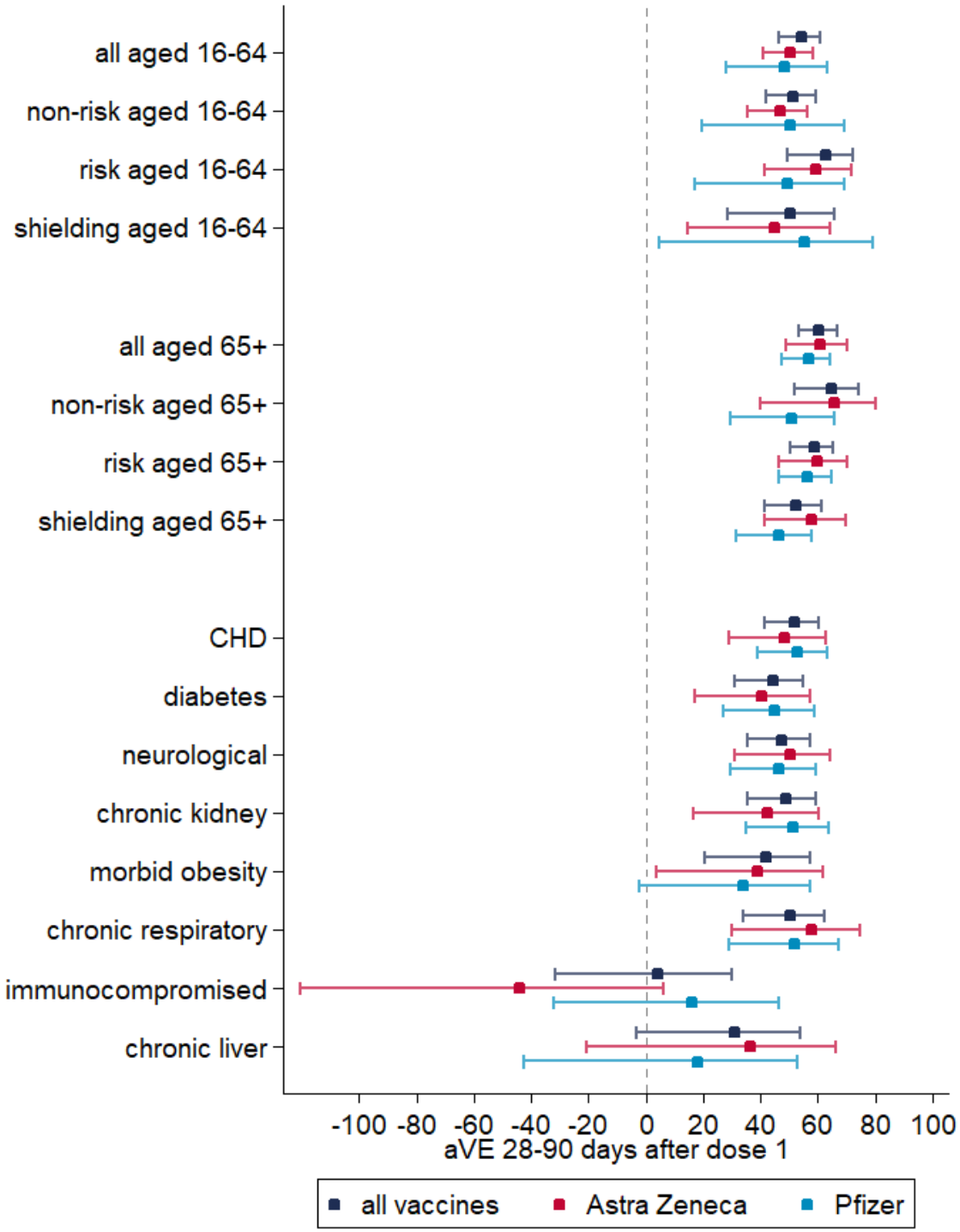
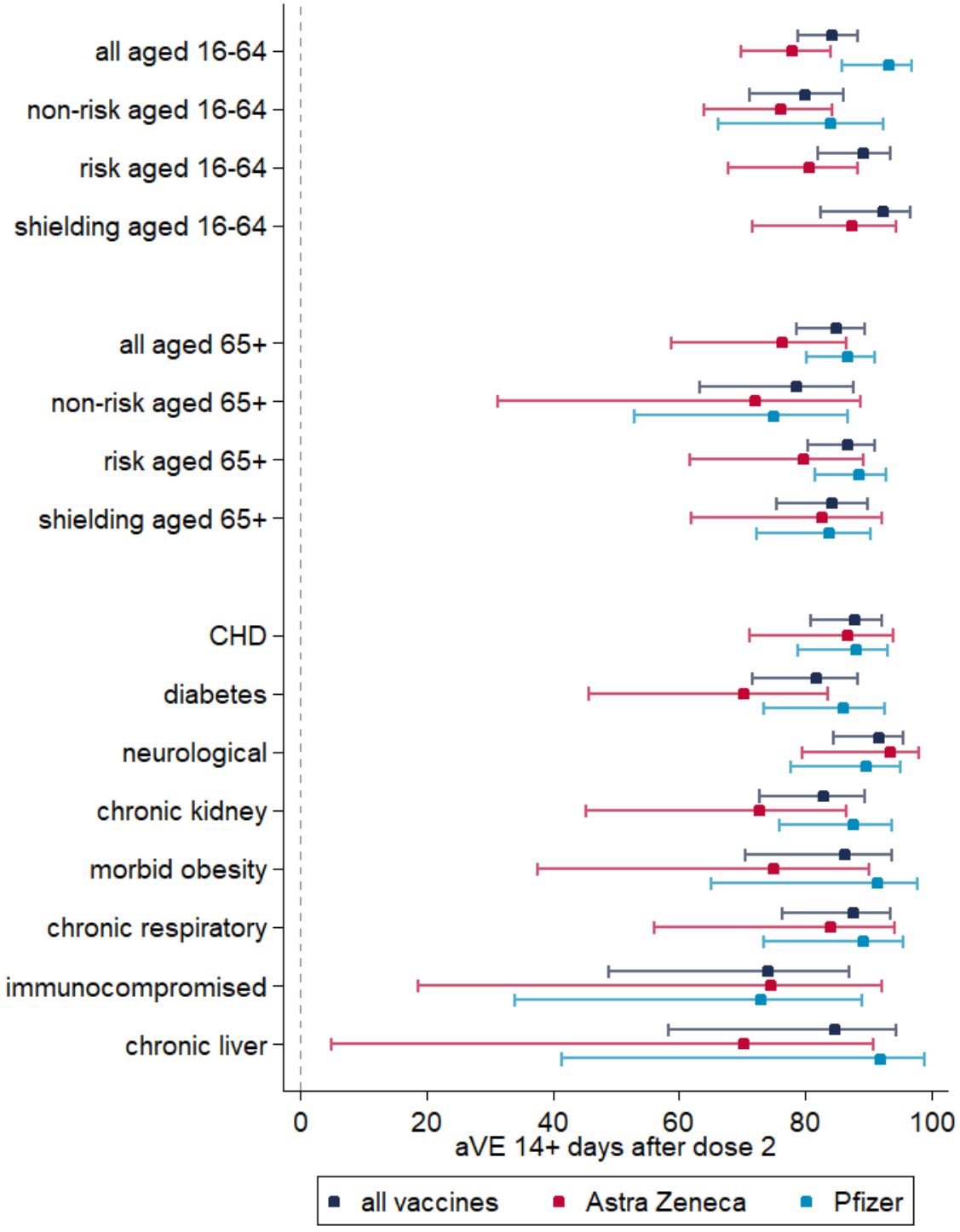


Figure 2b: cohort vaccine effectiveness 14+ days after dose 2 of vaccination



Discussion

This study provides evidence of a strong S-antibody response and high levels of effectiveness of COVID-19 vaccines against symptomatic medically attended disease in most clinical risk groups. We see reduced S-antibody response and reduced VE among the immunocompromised group, though VE in this group is much higher after the second dose and confidence intervals overlap with those in non-risk groups.

The overall immunogenicity and VE findings are similar to those reported previously. Like other studies we found that that the proportion of individuals who are S-antibody positive is initially higher with the Pfizer vaccine but from 4 weeks after the first dose onwards, the proportion positive is similar for both vaccines.[24] The levels of VE in our study after one and 2 doses are similar to those previously reported in other real world studies.[7,9,12-16]

Our finding of reduced S-antibody positivity and antibody titres in immunocompromised individuals is in line with that seen in other immunogenicity studies of specific immunosuppressed groups.[20-25] One other study found reduced S antibody titres among individuals with cardiovascular disease, in particular among those on statin therapy.[24] Mechanisms for any reduction in vaccine response in this group are unclear though the association between statins and lipid nanoparticle vaccines merits further investigation. VE against clinical outcomes has not previously been reported. Our findings suggest that the reduced S-antibody response after one dose translate into reduced VE in immunocompromised individuals, but after a second dose VE is much higher. After 2 doses of mRNA vaccine previous studies have suggested that individuals on immunosuppressive therapy maintain an immune response,[30,31] however other studies have reported reduced immune response among individuals with haematological malignancy.[23,26] Considering a broad immunosuppressed group we found only a modest and non-significant reduction in VE after 2 doses of either vaccine. There were 9 cases after 2 doses among immunosuppressed individuals, the majority of whom were over 70 years of age. Cases under 70 years had autoimmune conditions (Crohn's disease; type 1 diabetes and multiple sclerosis; psoriatic arthritis) and were on immune modulating therapy.

Our findings would support maximising coverage with 2 doses of vaccine among immunocompromised groups. In the context of high rates of COVID-19 in the population, there may be a case for reducing the interval between doses in order to maximise coverage. However, other studies have suggested that longer dosing intervals result in improved immune response, therefore such a move may be counterproductive, in particular in the context of low COVID-19 activity, a finding that we also see in our serology data (Table 2).[35] These findings are based on medically attended symptomatic disease, protection against severe disease after one dose, including hospitalisation and death, may be greater.

This study has a number of strengths: we rely on cases attending general practice and having relevant symptoms recorded by a medical practitioner, which is likely to be more reliable than self-reporting. We also have a large amount of data on previous medical history and demographic characteristics from the full clinical record which allows us to adjust for a large number of possible confounders. Furthermore, we have both immunogenicity data and vaccine effectiveness data (with

2 distinct methods to estimate VE) and in general the findings from these different analyses are concordant.

As with any observational study, there are also limitations. Disease epidemiology and testing policies have changed over the period of study. For example, with increased use of lateral flow devices in the community, PCR testing may have shifted toward more confirmatory testing of lateral flow outcomes, which could introduce temporal bias, especially in the TNCC design. We adjust for week which should help to control for such temporal changes. Risk of COVID-19 is likely be greater in health and social care workers (HSCW) who are at high risk of transmission and were among the first to be vaccinated. Care home residents were almost all offered vaccination before the end of January 2021, and since severity increases with age, GP consultation with symptoms may be more likely among the oldest age group. While it was possible to control for age effects, HSCW status is not known and our large household variable is a limited proxy for care home resident status. Imperfect control of these important variables will introduce bias, including temporal biases given the timing of vaccination in these groups, especially affecting the cohort study.

Unvaccinated individuals are likely to differ from vaccinated individuals in an important way. Vaccination coverage shows that individuals aged 90+, aged 65 to 69 and belonging to black, Asian and minority ethnic (BAME) groups, especially black ethnicities, are less likely to be vaccinated. Disparities in transmission rates are understood to exist by these sociodemographic characteristics. Those close to the end of life may be less likely to vaccinate. Those who have had recent infection are expected to wait 28 days from resolution of symptoms before vaccinating. We control for many of these factors, but some residual confounding is likely. While the cohort under study is large, once stratifying by clinical risk groups, numbers in some groups remain small and we were unable to further stratify, for example by specific cause of immunosuppression. It is likely that there are differences in immune response and VE according to the severity of immunosuppression.

In most clinical risk groups, immune response to vaccination is maintained and high levels of VE are seen with both the Pfizer and AstraZeneca vaccines. The immunosuppressed group stands out as having reduced response to vaccination after one and 2 doses. However, after second dose this only translated into a minor reduction in vaccine effectiveness against clinical disease. These findings would support maximising coverage with 2 doses in this group. Further research is needed to understand vaccine effectiveness against severe disease among immunosuppressed groups.

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