

Supplementary appendix

Methods

Study design

A test negative case control design was used to estimate vaccine effectiveness against hospitalisation with Omicron sub-lineages BA.2, BA.4 and BA.5 in individuals aged 18 years and older. The odds of vaccination in Pillar 1 PCR positive cases were compared to the odds of vaccination in individuals who tested negative in England.

Data sources

COVID-19 testing data

Prior to 1 April 2022, PCR testing for SARS CoV-2 in England was undertaken by hospital and public health laboratories (Pillar 1), as well as by community testing (Pillar 2). Pillar 1 testing is PCR testing in public health laboratories and NHS hospitals and was available for inpatients and others presenting to secondary care as well as health and care workers. Pillar 2 testing included lateral flow tests (LFTs) and PCR tests. In Pillar 2, LFTs were available to everyone, and PCR testing was available to anyone with symptoms consistent with COVID-19 (high temperature, new continuous cough, or loss or change in sense of smell or taste), anyone who was a contact of a confirmed case, care home staff and residents, and to those who self-tested as positive using an LFT. Since 1 April 2022, community testing has been scaled down and PCR tests are no longer freely available for most people. LFT tests are available for people with certain health conditions, for those going into hospital and for those who work in the NHS or in adult social care. Since 1 April 2022, PCR testing is still being undertaken via Pillar 1.

Individuals who were PCR tested in Pillar 1 between 18 April 2022 and 17 July 2022 (a period of co-circulation of BA.2, BA.4, and BA.5) were included in the final analysis. Any negative tests taken within 7 days of a previous negative test were excluded as these likely represent the same episode. Negative tests taken within 21 days of any subsequent positive test (LFT or PCR, Pillar 1 or Pillar 2) were also excluded as chances are high that these are false negatives. Positive and negative tests within 90 days of any previous positive test (LFT or PCR, Pillar 1 or Pillar 2) were also excluded. After linkage to the admission hospital data negatives tests within 21 days of a previous negative were also excluded, and, for individuals who had more than one linked negative test, one was selected at random in the study period. The test date of the most recent previous positive test (Pillar 1 or Pillar 2), excluding tests within 90 days, was extracted for all individuals to allow adjustment for prior infection.

Vaccination data

The National Immunization Management System (NIMS) contains demographic information on the whole population of England who are registered with a general practice physician in England and is used to record all COVID-19 vaccinations. NIMS was accessed for dates of vaccination and manufacturer, sex, date of birth, ethnicity, and residential address. Addresses were used to determine index of multiple deprivation quintile and were also linked to Care Quality Commission registered care

homes using the unique property reference number. Data on geography (NHS region), risk group status, clinically extremely vulnerable status, and health/social care worker were also extracted from the NIMS. Clinical risk groups included a range of chronic conditions as described in the Green Book (1), whereas the clinically extremely vulnerable group included persons who were considered to be at the highest risk for severe COVID-19, including those with immunosuppressed conditions and those with severe respiratory disease. Third doses were given at least 84 days after a second dose and administered after 13 September 2021. Individuals with a heterologous primary schedule or fewer than 19 days between their first and second dose were excluded. Fourth doses given from 1 January 2022 and at least 84 days after a third dose were counted, with those given the dose with shorter intervals or prior to 1 January 2022 excluded.

Testing data were linked to NIMS on 1 August 2022 using combinations of the unique individual National Health Service (NHS) number, date of birth, surname, first name, and postcode using deterministic linkage.

Identification of Omicron variants and assignment to cases

Sequencing of PCR positive samples is undertaken through a network of laboratories, including the Wellcome Sanger Institute. Whole-genome sequences are assigned to UKHSA definitions of variants based on mutations (2). Cases were defined as BA.2, BA.4 or BA.5 based on whole genome sequencing. From 18 April 2022 to 23 May 2022 the positive predictive value (PPV) of a sequenced test being BA.2 was at least 80% so not sequenced tests were classified as BA.2. From 20 June 2022 onwards, the PPV of a sequenced test being either BA.4 or BA.5 was at least 80%, so from then on tests not sequenced were classified as BA.4 or BA.5 and included in analyses which combined BA.4 and BA.5 cases. Where subsequent positive tests within 14 days included sequencing information, this information was used to classify the variant.

Hospital admission data

Secondary care hospital admission data (SUS)

SUS is the national electronic database of hospital admissions that provides timely updates of ICD-10 codes for completed hospital stays for all NHS hospitals in England. Up to 24 ICD-10 diagnoses fields can be completed in SUS for each admission with the first diagnosis field indicating the primary reason for admission. Hospital inpatient admissions for a range of acute respiratory illnesses were identified from SUS and were linked to the testing data on 08 August 2022 using NHS number and date of birth as previously described (3). Admissions with an ICD-10 coded ARI discharge diagnosis (Supplementary Table 1) in any diagnosis field were identified where the sample was taken 1 day before and up to 2 days after the admission. Length of stay was calculated as date of discharge – date of admission. Where multiple admissions linked to the same sample date, the first admission after the sample date was retained and episode length calculated by summing the stay length for each admission. Data were then restricted to those with ARI in the first diagnosis field and where the length of stay was at least 2 days. The data was restricted to tests up to 17 July 2022 to account for delays in the SUS data recording.

Statistical analysis

Logistic regression was used, with the PCR test result as the dependent variable and cases being those testing positive (stratified in separate analyses as either BA.2, BA.4, BA.5, or BA.4 and BA.5) and controls being those testing negative.

Vaccination status at the date of test (or onset if available) was included as an independent variable and effectiveness defined as 1- odds of vaccination in cases/odds of vaccination in controls.

Vaccine effectiveness was adjusted in logistic regression models for age (ages 18-19, then 20 through to 89 in five-year bands, then everyone age 90 years or older), sex, index of multiple deprivation (quintile), ethnic group, care home residence, , geographic region (NHS region), period (week of test), health and social care worker status, clinical risk group status, clinically extremely vulnerable, and variant of most recent previous infection (none, wild-type, Alpha, Delta or Omicron – variant status determined by date of test). These factors were all considered potential confounders so were included in all models.

Analysis combined all vaccine manufacturers (ChAdOx1, BNT162b2 or mRNA-1273 for 1 dose or 2 doses, and BNT162b2 or mRNA-1273 (half-dose) for third and fourth doses) or were stratified by the manufacturer of the third and fourth dose (whichever was the final dose). Heterologous primary schedules and ChAdOx1 primary course followed by ChAdOx1 third dose recipients were excluded.

Vaccine effectiveness was assessed in the unvaccinated, in dose 1 recipients, in intervals of 0 to 1 weeks, 2 to 14 weeks and 15 to 24 weeks post a second dose, and in intervals of 0 to 1 weeks, 2 to 14 weeks, 15 to 24 weeks and 25 or more weeks post a third or fourth dose. Vaccine effectiveness was estimated relative to those with waned immunity (25 or more weeks post their second dose).

Supplementary Table 1. SUS Acute respiratory illness ICD10 code list.

SUS Acute respiratory illness ICD10 code list	
J04*	Acute laryngitis and tracheitis
J09*	Influenza due to identified avian influenza virus
J10*	Influenza with pneumonia, other influenza virus identified
J11*	Influenza with pneumonia, virus not identified
J12*	Viral pneumonia, not elsewhere classified
J13*	Pneumonia due to <i>Streptococcus pneumoniae</i>
J14*	Pneumonia due to <i>Haemophilus influenzae</i>
J15*	Bacterial pneumonia, not elsewhere classified
J16*	Pneumonia due to other infectious organisms, not elsewhere classified
J17*	Pneumonia in diseases classified elsewhere
J18*	Pneumonia, organism unspecified
J20*	Acute bronchitis
J21*	Acute bronchiolitis
J22*	Unspecified acute lower respiratory infection
J80*	ARDS (related to respiratory infection)
U07*	COVID-19, virus identified and not identified
U04*	Severe acute respiratory syndrome (SARS)

Supplementary Table 2. Vaccine effectiveness estimates against hospitalisation with BA.2 for individuals aged 18 years and older in England. Third and fourth dose VE is estimated relative to a second dose at least 25 weeks prior.

Doses	Interval (weeks)	Controls	Cases	VE % (95% CI)
Unvaccinated		1,235	349	-72.0 (-109 to -41.5)
Dose 1	>0	406	73	-21.8 (-65.7 to 10.4)
Dose 2	0-1	4	1	n too small
	2-14	35	3	n too small
	15-24	78	8	45.5 (-24.4 to 76.1)
	25+	1,645	258	Baseline
Dose 3	0-1	54	3	61.9 (-27.8 to 88.6)
	2-14	520	46	56.7 (38.6 to 69.4)
	15-24	4,636	928	27.5 (14.7 to 38.4)
	25+	8,004	1,079	9.6 (-6.4 to 23.1)
Dose 4	0-1	1,389	160	51.3 (38.8 to 61.2)
	2-14	7,280	486	51.7 (42.2 to 59.7)
	15+	576	38	18.4 (-20.5 to 44.7)

Supplementary Table 3. Descriptive characteristics of eligible tests from hospitalised individuals.

		Overall		Negative		BA.2		BA.4		BA.5		BA.4 or BA.5		
		n	%	n	%	n	%	n	%	n	%	n	%	
	Test Result	32,845	100.0%	25,862	78.7%	3,432	10.4%	273	0.8%	947	2.9%	2,331	7.1%	
	Interval (weeks)													
Vaccination Status and intervals after vaccine	Unvaccinated	1,993	6.1%	1,235	4.8%	349	10.2%	33	12.1%	107	11.3%	269	11.5%	
	Dose 1*	>0	577	1.8%	406	1.6%	73	2.1%	4	1.5%	24	2.5%	70	3.0%
	Dose 2*	0-1	5	0.0%	4	0.0%	1	0.0%	0	0.0%	0	0.0%	0	0.0%
		2-14	41	0.1%	35	0.1%	3	0.1%	1	0.4%	1	0.1%	1	0.0%
		15-24	97	0.3%	78	0.3%	8	0.2%	2	0.7%	2	0.2%	7	0.3%
		25+	2,186	6.7%	1,645	6.4%	258	7.5%	20	7.3%	75	7.9%	188	8.1%
	Dose 3 or 4**	0-1	525	1.6%	446	1.7%	64	1.9%	1	0.4%	3	0.3%	11	0.5%
		BNT162b2	2-14	4,739	14.4%	3,959	15.3%	335	9.8%	29	10.6%	125	13.2%	291
		15-24	5,282	16.1%	4,223	16.3%	805	23.5%	24	8.8%	71	7.5%	159	6.8%
		25+	9,746	29.7%	7,375	28.5%	1,052	30.7%	107	39.2%	360	38.0%	852	36.6%
	Dose 3 or 4** mRNA-1273	0-1	1,140	3.5%	997	3.9%	99	2.9%	4	1.5%	13	1.4%	27	1.2%
		2-14	4,508	13.7%	3,841	14.9%	197	5.7%	32	11.7%	125	13.2%	313	13.4%
		15-24	1,199	3.7%	989	3.8%	161	4.7%	5	1.8%	14	1.5%	30	1.3%
25+		807	2.5%	629	2.4%	27	0.8%	11	4.0%	27	2.9%	113	4.8%	
Age	18-19	80	0.2%	61	0.2%	3	0.1%	1	0.4%	4	0.4%	11	0.5%	
	20-24	228	0.7%	142	0.5%	32	0.9%	4	1.5%	15	1.6%	35	1.5%	
	25-29	323	1.0%	195	0.8%	48	1.4%	9	3.3%	20	2.1%	51	2.2%	
	30-34	406	1.2%	289	1.1%	41	1.2%	13	4.8%	22	2.3%	41	1.8%	
	35-39	465	1.4%	353	1.4%	51	1.5%	7	2.6%	14	1.5%	40	1.7%	
	40-44	475	1.4%	369	1.4%	35	1.0%	5	1.8%	23	2.4%	43	1.8%	
	45-49	683	2.1%	527	2.0%	71	2.1%	3	1.1%	20	2.1%	62	2.7%	
	50-54	1,068	3.3%	855	3.3%	85	2.5%	13	4.8%	31	3.3%	84	3.6%	

	55-59	1,542	4.7%	1,220	4.7%	133	3.9%	16	5.9%	45	4.8%	128	5.5%
	60-64	2,061	6.3%	1,648	6.4%	189	5.5%	17	6.2%	55	5.8%	152	6.5%
	65-69	2,688	8.2%	2,112	8.2%	273	8.0%	20	7.3%	69	7.3%	214	9.2%
	70-74	3,815	11.6%	2,983	11.5%	382	11.1%	32	11.7%	122	12.9%	296	12.7%
	75-79	4,844	14.7%	3,878	15.0%	510	14.9%	30	11.0%	117	12.4%	309	13.3%
	80-84	5,211	15.9%	4,119	15.9%	568	16.6%	34	12.5%	166	17.5%	324	13.9%
	85-89	4,825	14.7%	3,791	14.7%	544	15.9%	37	13.6%	139	14.7%	314	13.5%
	>=90	4,131	12.6%	3,320	12.8%	467	13.6%	32	11.7%	85	9.0%	227	9.7%
Gender	Female	16,450	50.1%	12,998	50.3%	1,651	48.1%	136	49.8%	500	52.8%	1,165	50.0%
	Male	16,258	49.5%	12,732	49.2%	1,778	51.8%	137	50.2%	447	47.2%	1,164	49.9%
	Missing	137	0.4%	132	0.5%	3	0.1%	0	0.0%	0	0.0%	2	0.1%
Ethnicity	African	221	0.7%	154	0.6%	29	0.8%	3	1.1%	7	0.7%	28	1.2%
	Any other Asian background	272	0.8%	189	0.7%	36	1.0%	3	1.1%	10	1.1%	34	1.5%
	Any other Black background	100	0.3%	67	0.3%	10	0.3%	5	1.8%	4	0.4%	14	0.6%
	Any other White background	1,576	4.8%	1,231	4.8%	160	4.7%	15	5.5%	53	5.6%	117	5.0%
	Any other ethnic group	308	0.9%	214	0.8%	35	1.0%	1	0.4%	9	1.0%	49	2.1%
	Any other mixed background	102	0.3%	73	0.3%	15	0.4%	1	0.4%	4	0.4%	9	0.4%
	Bangladeshi or British Bangladeshi	143	0.4%	109	0.4%	13	0.4%	0	0.0%	7	0.7%	14	0.6%
	British, Mixed British	26,771	81.5%	21,305	82.4%	2,771	80.7%	204	74.7%	749	79.1%	1,742	74.7%
	Caribbean	251	0.8%	161	0.6%	33	1.0%	4	1.5%	11	1.2%	42	1.8%
	Chinese	54	0.2%	37	0.1%	9	0.3%	0	0.0%	1	0.1%	7	0.3%
	Indian or British Indian	667	2.0%	464	1.8%	88	2.6%	7	2.6%	15	1.6%	93	4.0%
	Irish	376	1.1%	300	1.2%	36	1.0%	2	0.7%	11	1.2%	27	1.2%
	Pakistani or British Pakistani	473	1.4%	366	1.4%	39	1.1%	4	1.5%	21	2.2%	43	1.8%
	White and Asian	38	0.1%	26	0.1%	3	0.1%	0	0.0%	5	0.5%	4	0.2%
	White and Black African	25	0.1%	14	0.1%	7	0.2%	0	0.0%	1	0.1%	3	0.1%
	White and Black Caribbean	58	0.2%	40	0.2%	6	0.2%	1	0.4%	2	0.2%	9	0.4%
	Missing	1,410	4.3%	1,112	4.3%	142	4.1%	23	8.4%	37	3.9%	96	4.1%

NHS Region	East of England	2,955	9.0%	2,396	9.3%	309	9.0%	14	5.1%	68	7.2%	168	7.2%
	London	3,863	11.8%	2,810	10.9%	423	12.3%	31	11.4%	106	11.2%	493	21.1%
	Midlands	7,696	23.4%	6,059	23.4%	737	21.5%	64	23.4%	260	27.5%	576	24.7%
	North East	5,841	17.8%	4,535	17.5%	689	20.1%	43	15.8%	142	15.0%	432	18.5%
	North West	5,214	15.9%	4,257	16.5%	491	14.3%	48	17.6%	114	12.0%	304	13.0%
	South East	4,157	12.7%	3,366	13.0%	396	11.5%	46	16.8%	165	17.4%	184	7.9%
	South West	3,119	9.5%	2,439	9.4%	387	11.3%	27	9.9%	92	9.7%	174	7.5%
	Missing	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
IMD Quintiles	1	7,918	24.1%	6,236	24.1%	818	23.8%	63	23.1%	213	22.5%	588	25.2%
	2	6,923	21.1%	5,428	21.0%	728	21.2%	51	18.7%	198	20.9%	518	22.2%
	3	6,371	19.4%	5,049	19.5%	676	19.7%	55	20.1%	173	18.3%	418	17.9%
	4	6,232	19.0%	4,921	19.0%	645	18.8%	50	18.3%	191	20.2%	425	18.2%
	5	5,317	16.2%	4,168	16.1%	557	16.2%	53	19.4%	168	17.7%	371	15.9%
	Missing	84	0.3%	60	0.2%	8	0.2%	1	0.4%	4	0.4%	11	0.5%
Vaccine priority groups	HSCW	244	0.7%	172	0.7%	28	0.8%	4	1.5%	8	0.8%	32	1.4%
	At risk***	5,396	16.4%	4,172	16.1%	540	15.7%	57	20.9%	178	18.8%	449	19.3%
	Severely Immunosuppressed	4,044	12.3%	3,108	12.0%	463	13.5%	37	13.6%	138	14.6%	298	12.8%
	CEV	15,813	48.1%	12,472	48.2%	1,719	50.1%	120	44.0%	407	43.0%	1,095	47.0%
Variant of most recent previous infection	None	27,270	83.0%	20,795	80.4%	3,212	93.6%	254	93.0%	870	91.9%	2,139	91.8%
	Wild-type	972	3.0%	872	3.4%	51	1.5%	2	0.7%	15	1.6%	32	1.4%
	Alpha	1,214	3.7%	1,086	4.2%	64	1.9%	5	1.8%	17	1.8%	42	1.8%
	Delta	1,186	3.6%	1,052	4.1%	53	1.5%	7	2.6%	21	2.2%	53	2.3%
	Omicron	2,203	6.7%	2,057	8.0%	52	1.5%	5	1.8%	24	2.5%	65	2.8%
Week Number	16	3,692	11.2%	2,638	10.2%	1,054	30.7%	0	0.0%	0	0.0%	0	0.0%
	17	3,337	10.2%	2,614	10.1%	718	20.9%	3	1.1%	2	0.2%	0	0.0%
	18	3,152	9.6%	2,593	10.0%	553	16.1%	4	1.5%	2	0.2%	0	0.0%
	19	3,002	9.1%	2,540	9.8%	449	13.1%	6	2.2%	7	0.7%	0	0.0%

20	2,830	8.6%	2,471	9.6%	348	10.1%	4	1.5%	7	0.7%	0	0.0%
21	2,332	7.1%	2,254	8.7%	55	1.6%	5	1.8%	18	1.9%	0	0.0%
22	2,330	7.1%	2,206	8.5%	62	1.8%	23	8.4%	39	4.1%	0	0.0%
23	2,320	7.1%	2,158	8.3%	57	1.7%	33	12.1%	72	7.6%	0	0.0%
24	2,162	6.6%	1,910	7.4%	56	1.6%	60	22.0%	136	14.4%	0	0.0%
25	2,501	7.6%	1,604	6.2%	42	1.2%	49	17.9%	241	25.4%	565	24.2%
26	2,075	6.3%	1,220	4.7%	24	0.7%	46	16.8%	163	17.2%	622	26.7%
27	1,804	5.5%	946	3.7%	12	0.3%	25	9.2%	156	16.5%	665	28.5%
28	1,308	4.0%	708	2.7%	2	0.1%	15	5.5%	104	11.0%	479	20.5%

*Dose 1 and 2 is recipients of ChAdOx1-S, BNT162b2 or mRNA-1273.

**Dose 3 or 4 is recipients of BNT162b2 or mRNA-1273 following any primary immunisation course.

***At risk is only those under 65

Percentages are column percentages. First row is shows row percentages.

Supplementary Table 4. Vaccine effectiveness estimates against hospitalisation for individuals aged 18 years and older in England (estimates from Figure 1a).

Doses	Interval (weeks)	Controls	Cases	VE % (95% CI)	Cases	VE % (95% CI)	Cases	VE % (95% CI)
			BA.2		BA.4		BA.5	
Unvaccinated		1,235	349	-72.2 (-109.3 to -41.7)	33	-91.0 (-243.3 to -6.2)	107	-76.8 (-148.1 to -26.0)
Dose 1	>0	406	73	-21.9 (-65.8 to 10.4)	4	30.1 (-112.3 to 77.0)	24	-10.5 (-86.0 to 34.3)
Dose 2	0-1	4	1	n too small	0	n too small	0	n too small
	2-14	35	3	53.0 (-62.5 to 86.4)	1	n too small	1	n too small
	15-24	78	8	45.4 (-24.7 to 76.1)	2	n too small	2	n too small
	25+	1,645	258	Baseline	20	Baseline	75	Baseline
Final dose (Dose 3 or 4)	0-1	1,443	163	51.7 (39.4 to 61.5)	5	51.3 (-34.8 to 82.4)	16	58.9 (26.7 to 77.0)
	2-14	7,800	532	52.4 (43.2 to 60.1)	61	56.8 (24.0 to 75.4)	250	59.9 (45.6 to 70.5)
	15-24	5,212	966	27.2 (14.4 to 38.1)	29	22.2 (-42.8 to 57.6)	85	38.7 (12.8 to 56.9)
	25+	8,004	1079	9.8 (-6.0 to 23.3)	118	1.5 (-63.1 to 40.5)	387	23.3 (-1.5 to 42.1)

Supplementary Table 5. Vaccine effectiveness estimates against hospitalisation for individuals aged 18 years and older in England (estimates from Figure 1b and 1c).

Doses	Interval (weeks)	Controls	Cases	VE % (95% CI)	Cases	VE % (95% CI)
			BA.2		BA.4 and BA.5	
Unvaccinated		1,235	349	-72.1 (-109.1 to -41.6)	409	-69.9 (-113.7 to -35.1)
Dose 1	>0	406	73	-21.8 (-65.6 to 10.4)	98	-17.7 (-65.2 to 16.1)
Dose 2	0-1	4	1	n too small	0	n too small
	2-14	35	3	53.0 (-62.6 to 86.4)	3	n too small
	15-24	78	8	45.4 (-24.7 to 76.1)	11	-17.2 (-169.2 to 49.0)
	25+	1,645	258	Baseline	283	Baseline
Final dose (Dose 3 or 4) BNT162b2	0-1	446	64	44.8 (24.8 to 59.6)	15	38.9 (-16.0 to 67.8)
	2-14	3,959	335	50.3 (39.8 to 58.9)	445	49.6 (37.5 to 59.4)
	15-24	4,223	805	26.5 (13.2 to 37.7)	254	36.3 (19.1 to 49.8)
	25+	7,375	1,052	9.5 (-6.5 to 23.1)	1,319	16.7 (-0.3 to 30.7)
Final dose (Dose 3 or 4) mRNA-1273	0-1	997	99	55.2 (41.8 to 65.6)	44	55.4 (33.7 to 70.0)
	2-14	3,841	197	55.7 (45.1 to 64.2)	470	62.2 (53.2 to 69.4)
	15-24	989	161	30.3 (12.6 to 44.4)	49	42.5 (14.3 to 61.4)
	25+	629	27	23.5 (-17.5 to 50.2)	151	42.0 (24.5 to 55.5)

References

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