Vaccine effectiveness and duration of protection of Comirnaty, Vaxzevria and Spikevax against mild and severe COVID-19 in the UK

Nick Andrews[1,2], Elise Tessier[1], Julia Stowe[1], Charlotte Gower[1], Freja Kirsebom[1], Ruth Simmons[1], Eileen Gallagher[1], Meera Chand[1,3], Kevin Brown[1], Shamez N Ladhani[1,4], Mary Ramsay[1,2], Jamie Lopez Bernal[1,2,5]

Affiliations:

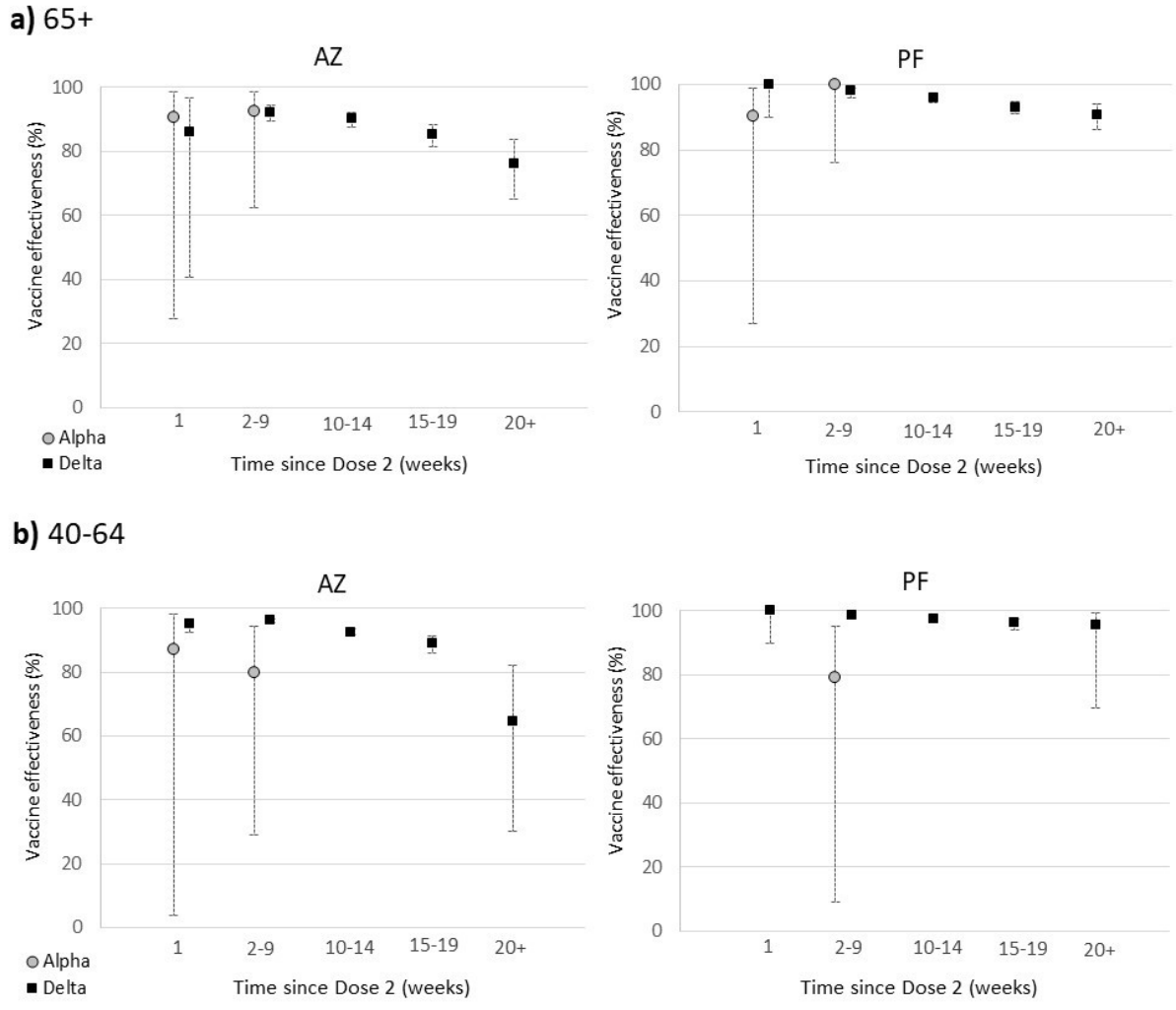
1. Public Health England, London, UK
2. NIHR Health Protection Research Unit in Vaccines and Immunisation, London School of Hygiene and Tropical Medicine, London, UK
3. Guys and St Thomas's Hospital NHS Trust, London, UK
4. Paediatric Infectious Diseases Research Group, St. George's University of London, UK
5. NIHR Health Protection Research Unit in Respiratory Infections, Imperial College London, London, UK

effectiveness estimates of 97.4 (95% CI 97 to 97.7) for Comirnaty and 93.9 (95% CI 93.4 to 94.4) for Vaxzevria for the Delta variant in the 20+ weeks period.

Table 3. Vaccine effectiveness against Delta deaths among individuals with two doses of Vaxzevria, Comirnaty in England at 2 to 9 weeks, 10 to 14 weeks, 15 to 19 weeks and 20+ weeks.

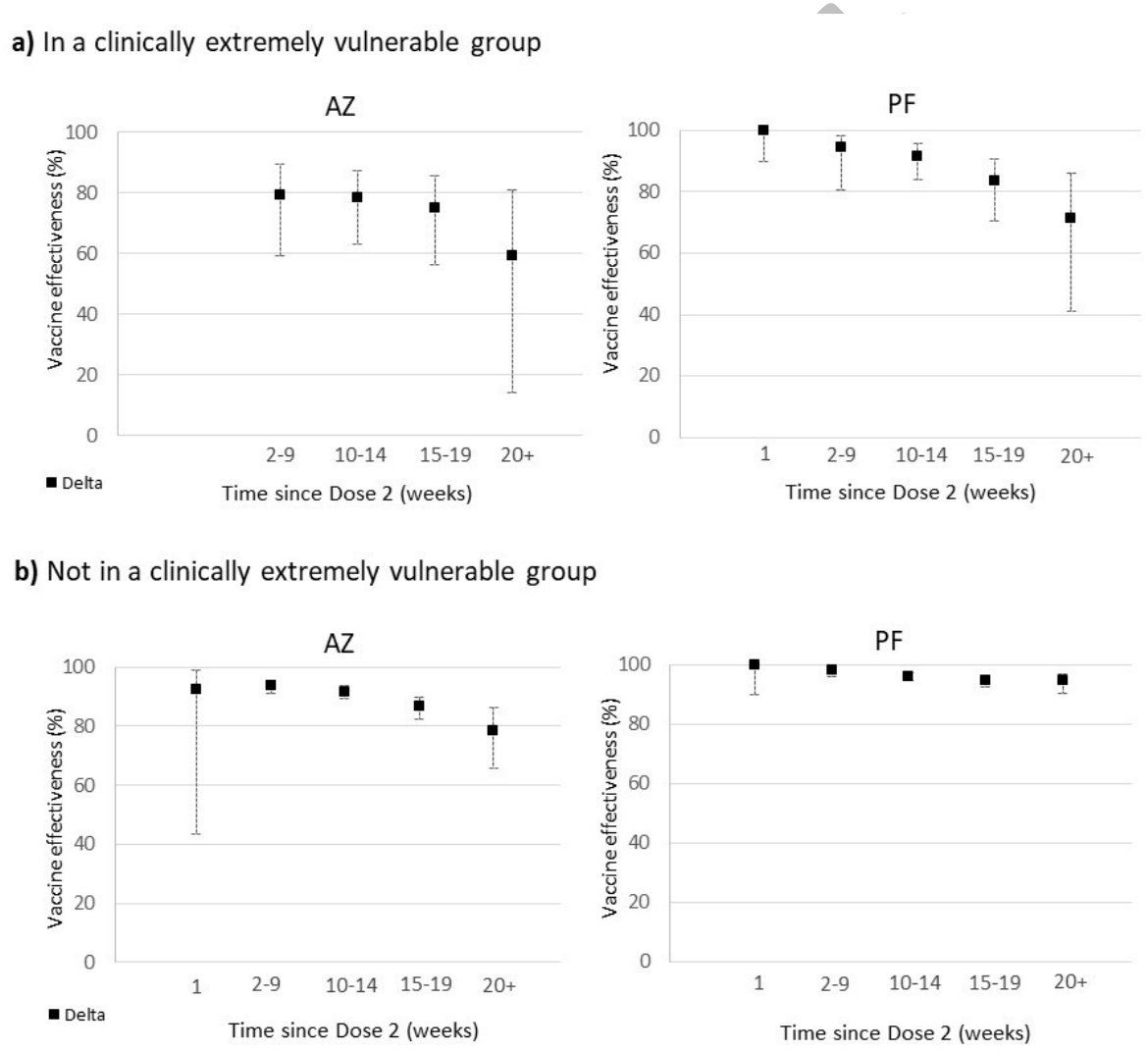
		Dose 2			
Vaccine	Age group	2 to 9 weeks	10 to 14 weeks	15 to 19 weeks	20+ weeks
Vaxzevria	16+	94.1 (91.8 to 95.8)	92.4 (89.7 to 94.4)	89.1 (84.2 to 92.5)	78.7 (52.7 to 90.4)
	65+	92.8 (87.4 to 95.9)	93.1 (89.6 to 95.4)	89.2 (83.3 to 93.0)	79.1 (51.6 to 91.0)
Comirnaty	16+	98.2 (95.9 to 99.2)	95.2 (93.0 to 96.7)	93.9 (91.1 to 95.8)	90.4 (85.1 to 93.8)
	65+	97.0 (91.2 to 99.0)	95.2 (92.3 to 97.0)	94.3 (91.2 to 96.3)	91.0 (85.3 to 94.5)

Figure 2. Vaccine effectiveness against hospitalisation by age group for Vaxzevria (AZ) and Comirnaty (PF), for a) 65+ years and b) 40 to 64 years.



Stratifying by risk group status identified greater waning among 65+ year-olds in a clinically extremely vulnerable group and among 40 to 64-year olds in a clinical risk group or clinically extremely vulnerable group, compared to those who were not in the group (Figure 3 and Supplementary Figure S1). For those aged 40 to 64 years, recipients of either vaccine who were not in a risk group had very high vaccine effectiveness against hospitalisation throughout the follow up period (Figure S1). There was also very little evidence of waning up to 20+ weeks post-vaccination among 65+ year-olds who were not in a CEV group and had received Comirnaty (Figure 3).

Figure 3. Vaccine effectiveness against hospitalisation (age >=65 years) by clinical extremely vulnerable group status for Vaxzevria (AZ) and Comirnaty (PF).



An analysis restricted to 80+ year-olds who had received Comirnaty prior to 04 January 2021 found lower vaccine effectiveness among those with a short (<4 week), compared to an extended interval (≥ 8 weeks) between doses in the latest follow-up periods (beyond 20 weeks after dose 2), although confidence intervals were wide and overlapping (Supplementary Figure S2).

Discussion

Key findings

Our data provide evidence of waning of protection against symptomatic infection following both Vaxzevria and Comirnaty vaccines from 10 weeks after the second dose. Protection against hospitalisation and death, however, was sustained at very high levels for at least 20 weeks after the second dose. Beyond 20 weeks, we observed more waning with Vaxzevria compared to Comirnaty, though the groups who received either vaccine differed. Waning of protection against hospitalisation was greater among older adults and in those in a clinical risk group. Among ≥65 year-olds who were not in a clinical risk group, however, protection against hospitalisation remains close to 95% with Comirnaty and just under 80% with Vaxzevria beyond 20 weeks after the second vaccine dose.

Comparison with existing literature

Our finding of waning in vaccine effectiveness against symptomatic disease is consistent with recent findings from Israel and Qatar reporting an increasing proportion of breakthrough cases among the earliest vaccinated individuals.[9,14-16] In addition to the emergence and rapid spread of the more transmissible Delta variant, the observed waning protection against symptomatic infection with time since vaccination may also be contributing to the increase in COVID-19 cases seen in the UK and elsewhere. Reassuringly, though the number of hospitalisations and, particularly, deaths due to COVID-19 have remained low, especially among vaccinated adults.[17] Our finding of only limited waning of protection against hospitalisation or death in most of the groups studied is consistent with the preserved vaccine effectiveness against hospitalisation reported in Qatar.[9] Studies from the US have also reported sustained high VE against hospitalisation due to COVID-19 despite the emergence and rapid spread of the Delta variant in the community. Across 18 US states, VE following two doses given 3 weeks apart among adults aged ≥18 years (median age 59 years) admitted to 21 hospitals during 11 March to 14 July 2021, was 86% (95% CI = 82%–88%) overall, and 87% (95% CI, 83%–90%) in patients with illness onset during March–May compared to 84% (95% CI, 79%–89%) in those with illness onset during June–July 2021, with no evidence of a significant decline in VE over the 24-week period.[18] A similar study of New York adults during 3 May to 25 July 2021 found hospitalisation rates to be nearly 10-fold lower in vaccinated (>90% received 2 mRNA doses 3 weeks apart) compared to unvaccinated adults (1.31 vs. 10.69 per 100,000 person-days). VE against hospitalisation remained relatively stable (91.9%–95.3%) during the surveillance period, although age-adjusted VE against new COVID-19 cases declined from 91.7% to 79.8%, coinciding with an increase in Delta variant circulation from <2% to >80%.[19] Conversely, there have been reports of an increased proportion of hospitalised cases among the earliest vaccinated adults receiving two doses of Cominarty three weeks apart in Israel.[14] The shorter dosing interval of 3 weeks and, hence, longer follow-up of a population with rapid vaccine uptake in Israel may be a factor in explaining this difference compared to the UK.

Implications

Our findings and those of Qatar and the US raise important questions about the timing of additional boosters in fully vaccinated adults who remain protected against hospitalisation and death for at least 5 months after vaccination. Israel was one of the first countries to immunise adults with the Cominarty and began offering a third dose of the same vaccine to older adults from the end of July

2021.[20] Early data indicate that the third dose was associated with large reductions in SARS-CoV-2 infection within one week of vaccination, with greater reductions in the second week.[20] The duration of protection offered by the third dose, however, remains to be established. The US, the UK and other countries are currently considering recommendations for booster doses for specific age-groups and risk-groups.

Booster doses improve both humoral and cellular immunity against SARS-CoV-2 and have increased neutralising activity against the different variants including Delta, which is likely to improve protection against infection. Given the sustained high VE against hospitalisation and death, the additional benefit of a third dose against these more serious outcomes is limited in the current epidemiological situation. VE may, however, continue to wane over time and it is likely that a booster doses may have a bigger impact on the more severe outcomes with longer intervals between the second and third doses. Decisions on the timing of the third dose will have to balance the rate of waning immunity against disease epidemiology, including the emergence of variants, and prioritisation of those at highest risk of waning immunity. At the same time, it is likely that the third dose will be more reactogenic than previous doses, especially if primed and boosted with different vaccines.[21] Attractive alternatives include half-dose boosters or boosting with variant SARS-CoV-2 strains, which are both under investigation currently.[22]

For the UK and countries such as Canada, another important consideration is that the extended interval schedules of 8 to 12 weeks provide higher serological responses and increased vaccine effectiveness compared to the licensed 3-week interval for mRNA vaccines,[23] thus potentially providing their populations with better longer-term protection.[24] This is supported by our findings comparing short and long intervals in 80+ year olds in the current analysis.

We found that waning was greatest among individuals in clinical risk groups, suggesting that this group should be prioritised for boosters, whenever they are recommended. Other studies have reported lower immune responses and vaccine effectiveness among individuals in clinical risk groups, most notably among immunosuppressed groups.[10,18,25,26] The UK and others have recently recommended a third dose of COVID-19 vaccine for immunocompromised adults as part of their primary immunisation course because of lower immunogenicity following two doses, with improved responses after 3 doses. [27,28]

Limitations

The strengths and limitations of our dataset and an evaluation of vaccine effectiveness using the test negative case control design have been described in detail previously.[1,6] There are some notable limitations worth highlighting that could particularly affect the interpretation of results on waning. First, there are important differences in the groups that received different vaccines as part of the roll-out of the national programme in the UK. For example, Comirnaty was less likely to be used in care homes and among individuals in clinical risk groups, in particular housebound individuals, due to challenges in ultra-low temperature storage and delivery. Instead, Vaxzevria was more likely to be given to these groups but this vaccine was not given to healthy adults under 40 years of age following a recommendation to use alternative vaccines in this age-group because of the risk of vaccine-induced thrombotic thrombocytopenia.[29] While we do adjust for age-group and clinical risk groups in our analysis, this is unlikely to fully mitigate the differences. Second, over time there will be an increasing number of individuals who would have been infected both prior to and after vaccination. Where they have previously tested positive, they will be excluded from the analysis, but many will remain unknown. This means that an increasing proportion of the unvaccinated control

group may have some level of protection from natural infection. This will attenuate vaccine effectiveness over time. Third, testing policies have changed over time. For example, PCR is increasingly being used to confirm positive self-administered lateral flow tests. There is an increased risk of false negative PCRs among those that were lateral flow positive, which will result in misclassification in our study based on PCR results. This would again attenuate vaccine effectiveness.

Conclusions

Our study provides evidence of significant waning against symptomatic disease but limited waning against severe disease over a period of at least 5 after administration of second doses in a programme with an extended interval between first and second doses. Waning appeared to be greater in older age groups and among individuals in clinical risk groups, suggesting that these individuals should be prioritised for booster doses.

References

1. Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. The New England Journal of Medicine 2021;385:585-94.
2. Sharif A. Ismail TGV, Suzanne Elgohari, Julia Stowe, Elise Tessier, Nick Andrews, Amoolya Vusirikala, Mary Ramsay, Sema Mandal, Jamie Lopez Bernal. Effectiveness of BNT162b2 mRNA and ChAdOx1 adenovirus vector COVID-19 vaccines on risk of hospitalisation among older adults in England: an observational study using surveillance data. 2021.
3. Vasileiou E, Simpson CR, Shi T, et al. Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study. The Lancet 2021;397:1646-57.
4. Pritchard E, Matthews PC, Stoesser N, et al. Impact of vaccination on SARS-CoV-2 cases in the community: a population-based study using the UK's COVID-19 Infection Survey. medRxiv 2021:2021.04.22.21255913.
5. Hyams C, Marlow R, Maseko Z, et al. Effectiveness of BNT162b2 and ChAdOx1 nCoV-19 COVID-19 vaccination at preventing hospitalisations in people aged at least 80 years: a test-negative, case-control study. The Lancet Infectious Diseases.
6. Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. BMJ 2021;373:n1088.
7. Pouwels KB, Pritchard E, Matthews PC, et al. Impact of Delta on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK. medRxiv 2021:2021.08.18.21262237.
8. Nanduri S PT, Derado G, et al. Effectiveness of Pfizer-BioNTech and Moderna Vaccines in Preventing SARS-CoV-2 Infection Among Nursing Home Residents Before and During Widespread Circulation of the SARS-CoV-2 B.1.617.2 (Delta) Variant — National Healthcare Safety Network, March 1–August 1, 2021. MMWR Morb Mortal Wkly Rep 2021;70:1163-6.
9. Chemaitelly H, Tang P, Hasan MR, et al. Waning of BNT162b2 vaccine protection against SARS-CoV-2 infection in Qatar. medRxiv 2021:2021.08.25.21262584.
10. Shrotri M, Fragaszy E, Geismar C, et al. Spike-antibody responses to ChAdOx1 and BNT162b2 vaccines by demographic and clinical factors (Virus Watch study). medRxiv 2021:2021.05.12.21257102.
11. Public Health England. SARS-CoV-2 variants of concern and variants under investigation in England Technical briefing 22. 2021.
12. Emergency department: weekly bulletins for 2021. 2021. (Accessed 13/09/2021, at https://www.gov.uk/government/publications/emergency-department-weekly-bulletins-for-2021.)
13. COVID-19 — high risk shielded patient list identification methodology: rule logic. 2020. 13/09/2021, at https://digital.nhs.uk/coronavirus/shielded-patient-list/methodology/rule-logic.)
14. Goldberg Y, Mandel M, Bar-On YM, et al. Waning immunity of the BNT162b2 vaccine: A nationwide study from Israel. medRxiv 2021:2021.08.24.21262423.
15. Israel A, Merzon E, Schäffer AA, et al. Elapsed time since BNT162b2 vaccine and risk of SARS-CoV-2 infection in a large cohort. medRxiv 2021:2021.08.03.21261496.
16. Mizrahi B, Lotan R, Kalkstein N, et al. Correlation of SARS-CoV-2 Breakthrough Infections to Time-from-vaccine; Preliminary Study. medRxiv 2021:2021.07.29.21261317.
17. Public Health England. Weekly national Influenza and COVID-19 surveillance report Week 36 report (up to week 35 data) 9 September 2021. 2021.
18. Mark W. Tenforde M, PhD1,*; Wesley H. Self, MD2,*; Eric A. Naioti, MPH1; Adit A. Ginde, MD3; David J. Douin, MD3; Samantha M. Olson, MPH1;, H. Keipp Talbot MJDC, MD2; Nicholas M. Mohr, MD4; Anne Zepeski, PharmD4; Manjusha Gaglani, MBBS5,6; Tresa McNeal, MD5;, Shekhar Ghamande MNIS, MD7; Kevin W. Gibbs, MD8; D. Clark Files, MD8; David N. Hager, MD, PhD9; Arber Shehu, MD9;, et al. Sustained Effectiveness of Pfizer-BioNTech and Moderna Vaccines Against COVID-19 Associated Hospitalizations Among Adults — United States, March–July 2021. Morbidity and Mortality Weekly Report (MMWR) 2021;70.

19. Eli S. Rosenberg DRH, Vajeera Dorabawila, MaryBeth Conroy, Danielle Greene, Emily Lutterloh, Bryon Backenson, Dina Hoefer, Johanne Morne, Ursula Bauer, Howard A. Zucker. New COVID-19 Cases and Hospitalizations Among Adults, by Vaccination Status — New York, May 3–July 25, 2021. Morbidity and Mortality Weekly Report (MMWR) 2021;70.
20. Israel's COVID-19 boosters are preventing infections, new studies suggest. 2021. (Accessed 13/09/2021, at https://www.science.org/content/article/israel-s-covid-19-boosters-are-preventing-infections-new-studies-suggest.)
21. Powell AA, Power L, Westrop S, et al. Real-world data shows increased reactogenicity in adults after heterologous compared to homologous prime-boost COVID-19 vaccination, March–June 2021, England. 2021;26:2100634.
22. Wu K, Choi A, Koch M, et al. Preliminary Analysis of Safety and Immunogenicity of a SARS-CoV-2 Variant Vaccine Booster. medRxiv 2021:2021.05.05.21256716.
23. Amirthalingam G, Bernal JL, Andrews NJ, et al. Higher serological responses and increased vaccine effectiveness demonstrate the value of extended vaccine schedules in combatting COVID-19 in England. medRxiv 2021:2021.07.26.21261140.
24. Khoury DS, Cromer D, Reynaldi A, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. Nature medicine 2021;27:1205-11.
25. Heather J Whitaker RST, Rachel Byford, Nick J Andrews, Julian Sherlock, Praveen Sebastian Pillai, John Williams, Elizabeth Button, Helen Campbell, Mary Sinnathamby, Georgina Pike, Sneha Anand, Ezra Linley, Jacqueline Hewson, Ashley D Otter, Joanna Ellis, Richard FD Hobbs, Maria Zambon5, Mary Ramsay, Kevin E Brown, Simon de Lusignan, Gayatri Amirthalingam, Jamie Lopez Bernal. Pfizer-BioNTech and Oxford AstraZeneca COVID-19 vaccine effectiveness and immune response among individuals in clinical risk groups. 2021.
26. Monin L, Laing AG, Muñoz-Ruiz M, et al. Safety and immunogenicity of one versus two doses of the COVID-19 vaccine BNT162b2 for patients with cancer: interim analysis of a prospective observational study. The Lancet Oncology 2021;22:765-78.
27. Werbel WA, Boyarsky BJ, Ou MT, et al. Safety and Immunogenicity of a Third Dose of SARS-CoV-2 Vaccine in Solid Organ Transplant Recipients: A Case Series. Annals of Internal Medicine 2021.
28. Longlune N, Nogier MB, Miedougé M, et al. High immunogenicity of a messenger RNA based vaccine against SARS-CoV-2 in chronic dialysis patients. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 2021.
29. Public Health England. COVID-19: the green book, chapter 14a Coronavirus (COVID-19) vaccination information for public health professionals. 2021.

Supplementary tables

Table S1: Analysis sets by age and outcomes

Age at March 31st 2021	Outcome	Period for cases / controls included (Alpha)*	Period for cases/controls included (Delta)**	Period in which first vaccination dose is given if vaccinated at onset
80+	Onset of Symptomatic infection	Onset Dec 8 2020 to June 27 2021	Onset from Apr 12 2021 and tested by Sep 3 2021	Dec 8 2020 – Jan 3 2021
	Hospitalisation within 14 days of test	Onset Dec 8 2020 to June 27 2021	Onset from Apr 12 2021 and tested by Aug 13 2021	Dec 8 2020 – Jan 3 2021
65+	Onset Symptomatic infection	Onset Jan 4 2021 to June 27 2021	Onset from Apr 12 2021 and tested by Sep 3 2021	Jan 4 2021 onwards
	Hospitalisation within 14 days of test	Onset Jan 4 2020 to June 27 2021	Onset from Apr 12 2021 and tested by Aug 13 2021	Jan 4 2021 onwards
	Death within 28 days of test	Onset Jan 4 2021 to June 27 2021	Onset from Apr 12 2021 and tested by July 29 2021	Jan 4 2021 onwards
40 to 64	Onset of Symptomatic infection	Onset Feb 1 2020 to June 27 2021	Onset from Apr 12 2021 and tested by Sep 3 2021	Feb 1 2021 onwards
	Hospitalisation within 14 days of test	Onset Feb 1 2020 to June 27 2021	Onset from Apr 12 2021 and tested by Aug 13 2021	Feb 1 2021 onwards
16 to 39	Onset of Symptomatic infection	Onset May 10 2020 to June 27 2021	Onset from May 10 2021 and tested by Sep 3 2021	May 10 2021 onwards
	Hospitalisation within 14 days of test	Onset May 10 2020 to June 27 2021	Onset from May 10 2021 and tested by Aug 13 2021	May 10 2021 onwards

16+ (All)	Onset of Symptomatic infection	Onset Jan 4 2021 – June 27 2021	Onset from Apr 12 2021 and tested by Sep 3 2021	Jan 4 2021 onwards
	Hospitalisation within 14 days of test	Onset Jan 4 2020 – June 27 2021	Onset from Apr 12 2021 and tested by Aug 13 2021	Jan 4 2021 onwards
	Death within 28 days of test	Onset Jan 4 2021 – June 27 2021 or for 80+ cohort Dec 8 2021 to June 27 2021	Onset from Apr 12 2021 and tested by July 29 2021	Jan 4 2021 onwards if aged <80 or Dec 8 2021 to Jan 3 2021 if aged 80+

*June 27 is for test negative controls and test positive cases if sequencing or s-gene target failure is done, otherwise May 2 is used before which >80% of those tested positive were Alpha

**Apr 12 is for test negative controls and test positive cases if sequencing or s-gene target failure is done , otherwise May 24 is used after which >80% of those tested positive were Delta

Table S2. Descriptive characteristics of positive and negative test results in individuals tested for SARS-CoV-2 in England for the study population. *

		Overall		Positive		Negative	
		n	%	n	%	n	%
	Test Result	**5,233,372**	**100.0**	**1,475,391**	**28.2%**	**3,757,981**	**71.8%**
Vaccination status	Unvaccinated	806,829	15.4%	337,142	22.9%	469,687	12.5%
	Vaxzevria 1 dose	75,466	1.4%	23,742	1.6%	51,724	1.4%
	Vaxzevria 2 doses	2,025,292	38.7%	525,721	35.6%	1,499,571	39.9%
	Comirnaty 1 dose	474,266	9.1%	191,606	13.0%	282,660	7.5%
	Comirnaty 2 doses	1,659,513	31.7%	349,171	23.7%	1,310,342	34.9%
	Spikevax 1 dose	57,509	1.1%	21,535	1.5%	35,974	1.0%
	Spikevax 2 doses	124,934	2.4%	24,328	1.6%	100,606	2.7%
	Mixed course or dose1-2 interval <19 days	9,563	0.2%	2,146	0.1%	7,417	0.2%
Age Group	80+	66,725	1.3%	19,517	1.3%	47,208	1.3%
	65 to 79	284,030	5.4%	68,189	4.6%	215,841	5.7%
	40 to 64	1,942,666	37.1%	517,105	35.0%	1,425,561	37.9%
	16 to 39	2,939,951	56.2%	870,580	59.0%	2,069,371	55.1%
Gender	female	2,923,495	55.9%	754,922	51.2%	2,168,573	57.7%
	male	2,304,400	44.0%	718,775	48.7%	1,585,625	42.2%
	missing	5,477	0.1%	1,694	0.1%	3,783	0.1%
Ethnicity	African	81,929	1.6%	26,710	1.8%	55,219	1.5%
	Another Asian background	67,789	1.3%	21,289	1.4%	46,500	1.2%
	Another Black background	9,431	0.2%	3,170	0.2%	6,261	0.2%
	Another ethnic background	39,912	0.8%	11,198	0.8%	28,714	0.8%
	Arab	22,505	0.4%	6,418	0.4%	16,087	0.4%
	Bangladeshi	46,185	0.9%	17,431	1.2%	28,754	0.8%
	Caribbean	43,118	0.8%	16,490	1.1%	266,284	7.1%
	Chinese	24,955	0.5%	5,401	0.4%	19,554	0.5%

	Indian	183,052	3.5%	51,621	3.5%	131,431	3.5%
	Mixed or multiple ethnic groups	112,294	2.1%	34,119	2.3%	78,175	2.1%
	Pakistani	139,249	2.7%	46,741	3.2%	92,508	2.5%
	Prefer not to say	176,641	3.4%	50,412	3.4%	126,229	3.4%
	White	4,286,312	81.9%	1,184,391	80.3%	3,101,921	82.5%
NHS Region	East of England	572,833	10.9%	146,863	10.0%	425,970	11.3%
	London	769,829	14.7%	209,676	14.2%	560,153	14.9%
	Midlands	1,002,007	19.1%	297,143	20.1%	704,864	18.8%
	North East	871,790	16.7%	274,149	18.6%	597,641	15.9%
	North West	750,159	14.3%	231,517	15.7%	518,642	13.8%
	South East	770,922	14.7%	191,248	13.0%	579,674	15.4%
	South West	495,821	9.5%	124,792	8.5%	371,029	9.9%
	Unknown	11	0.0%	3	0.0%	8	0.0%

*aged 80 and above and either unvaccinated at the time of onset or first vaccinated before 4 January 2021 with onset 8 December 2020 to 3 September 2021 or aged 16 and above and unvaccinated prior to 4 January 2021 with onset 4 January 2021 to 3 September 2021.

Table S3. Counts by variant, hospitalisations and deaths for positive SARS-CoV-2 tests among individuals in England for the study population.

		All	16 to 39	40 to 64	65 to 79	80+
Variant	**Alpha**	543,630	260,209	241,854	31,795	9,772
	Delta	894,965	594,370	261,019	34,175	5,401
	Unknown	36,796	16001	14232	2219	4344
Outcome	**Number of hospitalisations**	20,754	4,766	9,856	3,757	2,375
	Number of deaths	4,540	85	930	1203	2322

Table S4. Vaccine effectiveness against Alpha and Delta symptomatic disease, hospitalisation and death for Comirnaty, Vaxzevria and Spikevax in England.

			Symptomatic disease (tested by Sep 3rd)		Hospitalisation (tested by Aug 13th)		Death (tested by July 29th)	
Age	Vaccine	Dose*	Alpha	Delta	Alpha	Delta	Alpha	Delta
All	Comirnaty	1	45.7 (44 to 47.3)	51.9 (51.4 to 52.4)	85.2 (81.6 to 88.1)	91.8 (90.4 to 93)	73.1 (65 to 79.3)	88.6 (77.3 to 94.3)
from Jan 4		2	95.0 (93.8 to 95.9)	83.5 (83.3 to 83.6)	97.9 (91.4 to 99.5)	96.7 (96.3 to 97)	96.3 (89.9 to 98.6)	95.2 (93.7 to 96.4)
	Vaxzevria	1	44.5 (42.9 to 46.1)	43.3 (42.3 to 44.2)	82.5 (78.7 to 85.7)	81.4 (78.7 to 83.7)	79.1 (68.8 to 86)	88.4 (78.2 to 93.8)
		2	81.7 (79.0 to 84.0)	65.2 (64.9 to 65.6)	93.9 (84.9 to 97.5)	93.0 (92.4 to 93.5)	100 (0 case, 64,518 con)	92.7 (90.7 to 94.3)
	Spikevax	1	54.5 (8.5 to 77.3)	65.9 (65.0 to 66.7)		95.2 (91.8 to 97.1)		
		2		94.8 (94.4 to 95.2)				
	Any	1	45.1 (43.9 to 46.3)	51.8 (51.4 to 52.2)	83.9 (81.2 to 86.2)	88.4 (87.2 to 89.5)	75.3 (68.7 to 80.5)	88.3 (73.5 to 94.9)
		2	89.7 (88.4 to 90.8)	73.3 (73.1 to 73.5)	96.1 (91.5 to 98.2)	94.4 (94.0 to 94.8)	97.0 (91.7 to 98.9)	93.0 (90.3 to 95.0)
16-39	Comirnaty	1		52.6 (52.1 to 53.1)		91.1 (89.4 to 92.5)		
from May 10		2		91.1 (90.9 to 91.4)		98.9 (97.6 to 99.5)		
	Vaxzevria	1		48.5 (44.6 to 52.1)		87.8 (67.4 to 95.4)		
		2		66.0 (61.5 to 69.9)		100.0 (no case, 770 con)		
	Spikevax	1		66.7 (65.9 to 67.6)		95.2 (91.1 to 97.4)		
		2		95.0 (94.3 to 95.6)				
	Any	1		54.1 (53.6 to 54.5)		91.5 (89.9 to 92.8)		

		2		91.0 (90.7 to 91.2)		99.0 (97.7 to 99.5)	
40 to 64 from Feb 1	Comirnaty	1	49.4 (45.7 to 52.9)	45.5 (43.4 to 47.5)	91.4 (82.4 to 95.7)	92.5 (88.7 to 95.0)	
		2	92.9 (87.9 to 95.8)	80.6 (80.1 to 81.1)	79.1 (9.5 to 95.2)	97.9 (97.3 to 98.3)	
	Vaxzevria	1	48.8 (46.2 to 51.4)	34.8 (33.2 to 36.4)	77.6 (68.4 to 84.1)	84.0 (81.2 to 86.4)	
		2	80.9 (75.2 to 85.3)	62.8 (62.1 to 63.5)	79.8 (29.4 to 94.2)	94.8 (94.2 to 95.3)	
	Spikevax	1	61.8 (7.3 to 84.2)	56.0 (52.7 to 59.0)		95.7 (86.5 to 98.6)	
		2		93.9 (93.1 to 94.6)			
	Any	1	49.1 (46.8 to 51.3)	39.2 (37.8 to 40.5)	82.5 (76 to 87.2)	86.5 (84.3 to 88.4)	
		2	85.4 (81.5 to 88.5)	66.2 (65.5 to 66.8)	80.8 (47.3 to 93)	95.5 (95.0 to 95.9)	
65+ from Jan 4	Comirnaty	1	54.4 (50.3 to 58.2)	54.7 (43.2 to 63.9)	79.3 (71.8 to 84.7)	100.0 (no cases 1963 controls)	74.1 (65.7 to 80.4)
		2	94.1 (90.5 to 96.4)	67.4 (64.5 to 70.0)	100.0 (90 to 100)	94.6 (93.3 to 95.7)	96.9 (91.3 to 98.9)
	Vaxzevria	1	54.4 (49.9 to 58.4)	34.0 (22.3 to 43.9)	79.3 (70.8 to 85.3)	86.8 (74.3 to 93.2)	79.9 (68.5 to 87.2)
		2	87.0 (81.2 to 91.0)	49.7 (45.4 to 53.7)	93.1 (66.4 to 98.6)	88.7 (86.2 to 90.7)	100.0 (no cases, 13052 controls)
	Any	1	54.6 (50.9 to 57.9)	41.4 (32.4 to 49.2)	79.8 (73.7 to 84.5)	91.8 (84.1 to 95.7)	75.9 (68.6 to 81.4)
		2	90.6 (87.2 to 93.2)	57.1 (53.4 to 60.5)	96.9 (85.5 to 99.4)	91.3 (89.5 to 92.9)	97.4 (92.6 to 99.1)
80+ early d1 Dec8 to Jan 3	Comirnaty	1	53.8 (45.2 to 61.0)		72.1 (57.0 to 81.9)		
		2	81.0 (75.6 to 85.1)	42.9 (7.9 to 64.7)	93.2 (84.0 to 97.1)	73.4 (53.2 to 84.8)	

*d1: 28 days after first dose to time of second (if given), d2: 14 days after second dose

Table S5. Vaccine effectiveness against Alpha symptomatic disease among individuals with two doses of Vaxzevria, Comirnaty in England at 1 week, 2 to 9 weeks and 10+ weeks.

			Dose 2		
Vaccine	Age group	Subgroup	week 1	2 to 9 weeks	10+
Vaxzevria	All	All	72.3 (66.9 to 76.9)	81.9 (79.2 to 84.3)	76.2 (49.8 to 88.7)
	65+	All	80.2 (69.4 to 87.2)		87.3 (81.5 to 91.4)
	40 to 64	All	74.0 (64.9 to 80.7)		80.7 (74.9 to 85.1)

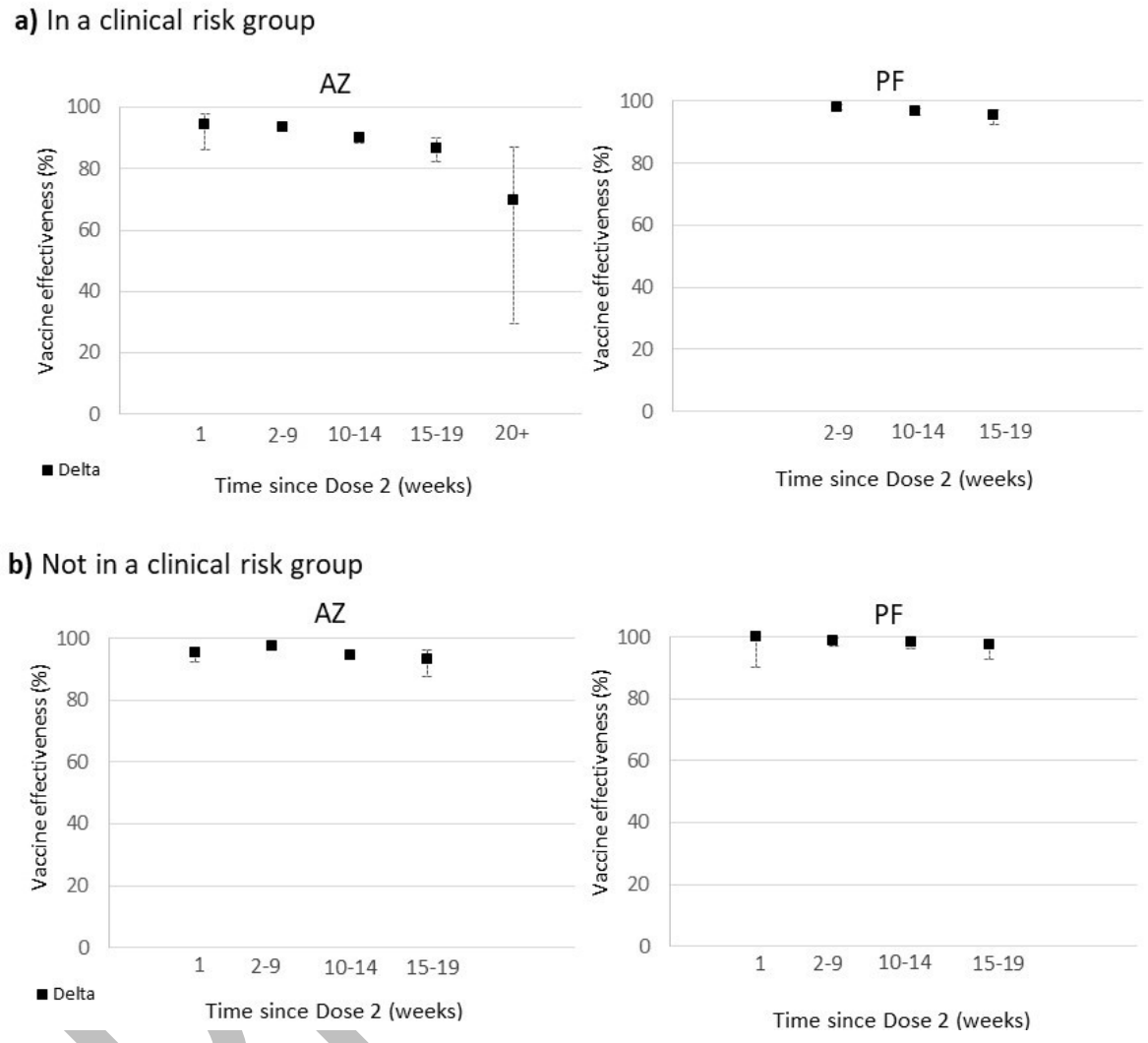
Comirnaty	All		90.3 (87.0 to 92.7)	95.0 (93.8 to 96)	94.8 (88.4 to 97.7)
	80+	All	78.5 (68.1 to 85.5)	81.7 (76.2 to 85.9)	67.1 (31.1 to 84.3)
	65+	All	85.2 (75.3 to 91.1)	94.0 (90.3 to 96.4)	
	40 to 64	All	94.9 (86.4 to 98.1)		92.8 (87.7 to 95.7)

Table S6. Vaccine effectiveness against Alpha hospitalisation among individuals with two doses of Vaxzevria, Comirnaty in England at 1 week, 2 to 9 weeks and 10+ weeks.

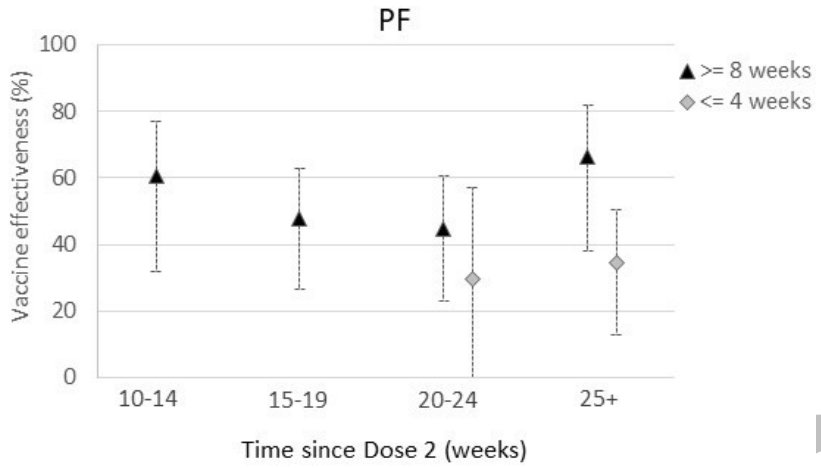
			Dose 2		
Vaccine	Age group	Subgroup	week 1	2 to 9 weeks	10+
Vaxzevria	All	All	90.1 (68.8 to 96.8)		93.8 (84.7 to 97.5)
	65+	All	90.7 (27.8 to 98.8)	92.6 (62.6 to 98.5)	
	40 to 64	All	87.0 (3.7 to 98.2)	79.8 (29.2 to 94.3)	
Comirnaty	All	All	96.5 (75.4 to 99.5)	97.8 (91.0 to 99.5)	
	80+	All	88.7 (64.1 to 96.4)	93.6 (84.1 to 97.4)	91.9 (26.9 to 99.1)
	65+	All	90.4 (27.0 to 98.7)		100.0 (0 case, 877 con)
	40 to 64	All	100.0 (0 cases, 1566 con)	79.1 (8.9 to 95.2)	

Supplementary Figures

Supplementary Figure S1. Vaccine effectiveness against Delta hospitalisation (age 40 to 64 years) by clinical risk group status.



Supplementary Figure S2. Vaccine effectiveness of Comirnaty (PF) against symptomatic disease (Delta variant) in people aged 80+ with either a short (<= 4 weeks) or long (>= 8 weeks) interval between first and second doses.



Supplementary Figure S3. Vaccine effectiveness against hospitalization age ≥ 65, all vaccines combined for intervals afters the second dose