Effectiveness of the Sanofi/GSK (VidPrevtyn Beta) and Pfizer-BioNTech (Comirnaty Original/Omicron BA.4-5) bivalent vaccines against hospitalisation in England

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Summary

Background The Sanofi/GSK AS03-adjuvanted (VidPrevtyn Beta) vaccine and the Pfizer-BioNTech mRNA (Comirnaty Original/Omicron BA.4-5) bivalent vaccine were offered to adults aged 75 years and over in England from 3rd April 2023. This is the first time an adjuvanted COVID-19 vaccine has been administered as part of a UK COVID-19 vaccination programme. In clinical trials, antibody levels generated were comparable with mRNA vaccines but there are no real-world data on the effectiveness or duration of protection.

Methods We used a test-negative case–control study design to estimate the incremental vaccine effectiveness of the Sanofi/GSK and Pfizer bivalent BA.4-5 boosters against hospitalisation amongst those aged 75 years and older in England. Cases (those testing positive) and controls (those testing negative) were identified from the national COVID-19 PCR testing data undertaken in hospital settings. The study period included tests from 3rd April 2023 to 27th August 2023. Tests were linked to the COVID-19 vaccination register and to the national hospital admission database, restricting to those with an acute respiratory infection coded in the primary diagnosis field. Vaccine effectiveness was estimated using multivariable logistic regression amongst those who had last received an autumn 2022 booster given at least 3 months prior. The test result was the outcome and vaccination status the exposure. Analyses were adjusted for week of test, gender, age, clinical risk group status, care home resident status, region, index of multiple deprivation, ethnicity, influenza vaccination status and recent COVID-19 positivity.

Findings There were 14,169 eligible tests from hospitalised individuals aged 75 years and older; 3005 cases (positive tests) and 11,164 controls (negative tests). Effectiveness was highest in the period 9–13 days post vaccination for both manufacturers at about 50%; 43.7% (95% CI, 20.1–60.3%) and 56.1% (95% CI, 25.2–74.2%) for Sanofi/GSK and Pfizer BA.4-5, respectively. There was evidence of waning with a reduction to about 30% for both manufacturers after 5–9 weeks. The longest time interval post vaccination for which we were able to estimate effectiveness was 10+ weeks post vaccination, at which point vaccine effectiveness was 17.6% (95% CI, –3.6 to 34.5%) and 37.9% (95% CI, 13.2–55.5%) for the Sanofi/GSK and Pfizer BA.4-5 boosters, respectively.

Interpretation Both boosters provided good protection against hospitalisation amongst older adults. The finding that the adjuvanted vaccine targeting the distant Beta strain had similar effectiveness to the bivalent mRNA vaccine targeting more closely matched Omicron sub-lineages is notable and highlights the need for further real-world studies into the effectiveness of vaccines from different vaccine platforms and formulations in the presence of matched and unmatched strains.

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Research in context

Evidence before this study
COVID-19 vaccines provide good protection against severe disease, however, due to waning of the vaccines, many countries have opted for frequent booster programmes to maintain a high level of protection in the most vulnerable populations. As part of the UK's spring 2023 COVID-19 booster vaccination programme, all adults aged 75 years and older and the immunosuppressed were offered a booster dose of either the Sanofi/GSK AS03-adjuvanted monovalent beta variant (VidPrevtyn Beta) booster vaccine or the Pfizer-BioNTech mRNA (Comirnaty Original/Omicron BA.4-5) bivalent vaccine. The programme commenced from 3rd April 2023, with care home residents being prioritised for vaccination.

We searched PubMed using the terms 'COVID-19', 'bivalent BA.4-5', 'Sanofi', and 'vaccine effectiveness' with no date restrictions in September 2023 and used the snowball process to identify additional relevant publications. We also scoped preprint databases (MedXriv) for relevant COVID-19 vaccine effectiveness studies undertaken during the spring/summer of 2023.

This is the first time the Sanofi/GSK vaccine has been administered as part of a UK COVID-19 vaccination programme, and the first time an adjuvanted COVID-19 vaccine has been used in the UK. Adjuvanted vaccines against influenza have been shown to have higher effectiveness and longer duration of protection but to our knowledge there are no real-world data on the effectiveness of an adjuvanted vaccine against COVID-19. In clinical trials, the antibody levels generated against different Omicron sub-variants by the Sanofi/GSK vaccine were comparable to levels generated by COVID-19 mRNA vaccines.

Added value of this study
We used a test-negative case control study design using national-level electronic healthcare records to assess vaccine effectiveness against hospitalisation amongst England's population aged 75 years and older, between 3rd April 2023 and 27th August 2023. To our knowledge these are the first real-world effectiveness data for an adjuvanted COVID-19 vaccine. We found that the incremental vaccine effectiveness of a booster dose with either vaccine peaked at around 30–50% protection against hospitalisation, in addition to any remaining protection from prior vaccination with a booster given as part of the autumn 2022 programme.

Implications of all the available evidence
Overall, these results provide reassuring evidence that both the adjuvanted Sanofi/GSK (VidPrevtyn Beta) and Pfizer mRNA BA.4-5 booster vaccines provide a substantial boost in protection against hospitalisation with COVID-19 amongst adults aged 75 years and older for at least 10 weeks after vaccination. The finding that the adjuvanted vaccine targeting the distant Beta strain had similar effectiveness to the bivalent mRNA vaccine targeting more closely matched Omicron sub-lineages is notable and highlights the need for further real-world studies into the effectiveness of vaccines from different vaccine platforms and formulations in the presence of matched and unmatched strains.

Introduction

COVID-19 vaccines provide good protection against severe disease,[1–5] however, due to waning of the vaccines, many countries have opted for frequent booster programmes to maintain a high level of protection in the most vulnerable populations. COVID-19 continues to evolve and over the past 18 months sub-lineages of Omicron have emerged including BA.1, BA.2,[6] BA.4, BA.5,[7] BQ.1, CH.1.1, numerous sub-lineages related to XBB[8,9] and most recently BA.2.86.[10,11] Manufacturers have developed modified vaccines which target the spike protein on different COVID-19 variants.

COVID-19 booster vaccinations were offered in the UK in autumn 2021 (all adults), spring 2022 (over 75 year olds and immunosuppressed individuals), autumn 2022 and spring 2023.[12] The autumn 2022 booster programme commenced the 5th September 2022[13] and bivalent BA.1 boosters with either Pfizer BioNTech (Original/Omicron BA.1 Comirnaty®) or Moderna (Spikevax® bivalent Original/Omicron BA.1 vaccine) were offered to all adults aged 50 years and over and vulnerable individuals.[14] The spring 2023 booster programme targeted all adults aged 75 years and older, and

the immunosuppressed.[15] The vaccines advised included the Sanofi/GSK AS03-adjuvanted monovalent beta variant (VidPrevtyn Beta) booster vaccine, the Pfizer-BioNTech mRNA (Comirnaty Original/Omicron BA.4-5) bivalent vaccine and the Moderna mRNA (Spikevax bivalent Original/Omicron BA.4-5) bivalent vaccine. The programme commenced from 3rd April 2023, with care home residents being prioritised for vaccination. The Sanofi/GSK booster was rolled out first, followed around 3 weeks later by Pfizer BA.4-5 and some doses of Moderna BA.4-5, although very few individuals received Moderna BA.4-5.

This is the first time the Sanofi/GSK vaccine has been administered as part of a UK COVID-19 vaccination programme, and the first time an adjuvanted COVID-19 vaccine has been used in the UK. It is a protein sub-unit vaccine containing the beta spike protein in combination with the AS03 adjuvant.[15] This vaccine was approved by the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK for use in adults (aged over 18 years) who have already received an mRNA or adenoviral vector COVID-19 vaccine. Adjuvanted vaccines against influenza have been shown

to have higher effectiveness and longer duration of protection.[16,17] In clinical trials, the antibody levels generated against different Omicron sub-variants by the Sanofi/GSK vaccine were comparable to levels generated by COVID-19 mRNA vaccines.[18]

Our aim was to estimate vaccine effectiveness (VE) against hospitalisation amongst those aged 75 years and older of the Sanofi/GSK and Pfizer BA.4-5 boosters administered as part of the spring 2023 booster programme in England using a test-negative case control (TNCC) study design. During this period, XBB-related sub-lineages dominated in England.[9]

Methods

Study design

To estimate VE against hospitalisation, a TNCC study design was used where all positive PCR tests from individuals aged 75 years and older hospitalised with a respiratory code in the primary diagnosis field in England are cases while all negative PCR tests from such individuals are controls, as previously described.[1–5]

Data sources

A data flow diagram is shown in Supplementary Figure S1.

COVID-19 testing data

Cases and controls were identified from the national database containing all positive and negative tests (all PCR tests and self-reported lateral flow tests) undertaken in England. The study period included all positive and negative PCR tests undertaken in hospital settings (Pillar 1) from 3rd April 2023 to 27th August 2023.

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 a subsequent positive test were also excluded as chances are high that these are false negatives. Tests within 90 days of a previous positive test were also excluded as these likely represent the same episode. The date of an individual's most recent prior positive test was identified from all historic testing data (PCR and self-reported lateral flow tests). Individuals contributed a maximum of one negative control test (selected at random). Further details on the reasons for these exclusions are described previously.[19]

National immunisation management system (NIMS)

The National Immunisation Management System (NIMS) is a national vaccine register containing demographic information on the whole population of England registered with a GP, used to record all COVID-19 vaccinations.[20] To ensure completeness of data, individual

level data is enriched from the NHS Spine (a centralised IT infrastructure allowing NHS services to exchange information across local and national NHS teams). Individuals not registered with a GP practice in England and that do not have an NHS number will be allocated a number upon receiving their vaccine. UKHSA receives a daily feed of new vaccination records.

Testing data were linked to NIMS using combinations of the unique individual NHS number, date of birth, surname, first name, and postcode using deterministic linkage. NIMS was accessed for dates of vaccination and manufacturer, sex, date of birth, ethnicity, care home residency and residential address. Care home status is provided by the NHS. We identified those being resident in a care home as of March 2023. Postcodes (enriched from the NHS Spine) were used to determine index of multiple deprivation (IMD) quintile (small area measures of relative deprivation based on postcode) and NHS region. Data on risk group status (those identified as at risk previously in the pandemic and those identified recently as requiring an autumn booster by NHS CaaS (Cohorting as a Service)[21]), clinically extremely vulnerable status and severely immunosuppressed status were also extracted from the NIMS. Booster doses given as part of the autumn 2022 and spring 2023 booster programmes were classified based on SNOMED coding and timing (autumn booster doses were those coded as bivalent BA.1 doses (Moderna or Pfizer) administered from 5th September 2022, spring booster doses were those coded as bivalent BA.4-5 (Moderna or Pfizer) or Sanofi/GSK administered from 3rd April 2023).

Only individuals who had received at least two doses (a primary vaccination course) prior to the 3rd April 2023 and whose last dose prior to the 3rd April was given as part of the autumn booster programme were included. Those with less than a 12-week interval between the autumn booster dose and the spring booster dose and those who received more than one dose coded as a spring booster dose were excluded. There were insufficient data to estimate VE of the Moderna BA.4-5 booster as very few doses were administered, so these doses were also excluded. Additionally, those who received a booster dose after the 3rd April 2023 which wasn't a Sanofi/GSK or Pfizer/Moderna BA.4-5 dose were excluded.

Hospital admission data

Secondary Uses Service (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.[22] SUS is an administrative database used by commissioners and providers of NHS-funded care for purposes including healthcare planning and National Tariff reimbursement. As such, data on admissions are considered very complete although there is a lag of a few weeks. For this reason, we restricted the

testing data to 3 weeks prior to the date the testing data was linked to SUS. Hospital inpatient admissions for a range of acute respiratory illnesses (ARI) were identified from the SUS and linked to the testing data using NHS number and date of birth. Length of stay was calculated as date of discharge minus the date of admission. Admissions were restricted to those with an ICD-10 coded acute respiratory illness (ARI) discharge diagnosis in the primary diagnosis field (Supplementary Table S1), who were admitted for at least 2 days, where the date of test was 1 day before and up to 2 days after the admission.

Covariates and adjustment

Variables investigated for confounding were week of test date (categorical), gender, age (five-year age bands), risk group status, care home status, NHS region, IMD (index of multiple deprivation) quintile, ethnicity, influenza vaccination status this season (2022/2023) and the likely variant of an individual's most recent prior infection. Only week of test had a major confounding effect. We included the other variables in the model as inclusion did not impact the precision of our estimates and this allowed us to look at the effect of these variables on the probability of positivity. Less than 5% of data were missing in any category. Missing data for ethnicity were included in models as a separate category while missing data for gender and IMD were omitted (<1.5% were missing in each category).

Statistical methods

Multivariable logistic regression was used with the test result as the outcome, vaccination status as the primary exposure variable of interest and with confounder adjustment as described above. VE was calculated as 1-odds ratio and given as a percentage. To compare VE estimates, statistical significance was concluded where 95% CIs did not overlap.

In recent studies of vaccine effectiveness by our group and others, we have estimated effectiveness as the extra protection of a booster dose in addition to the protection already provided by previous vaccinations.[5,8,23,24] Since most of the adult population in England has now received multiple COVID-19 vaccine doses as part of primary and booster vaccination campaigns, very few individuals remain unvaccinated. We consider it most relevant therefore to estimate the additional benefit of a booster vaccine in addition to the protection an individual has from past doses which have waned in effectiveness. Thus, we here estimated the incremental vaccine effectiveness of the spring boosters amongst those who had received a bivalent BA.1 booster dose as part of the autumn 2022 programme, where the previous dose was given at least 3 month prior. The effectiveness estimated here is therefore the additional protection of the spring booster in addition to the protection conferred by at least two doses where the last dose received was a bivalent BA.1 booster.

Incremental VE was estimated at the following intervals since booster vaccination; 0–2 days, 3–8 days, 9–13 days, 2–4 weeks, 5–9 weeks and 10 or more weeks. We split the data 0–2 days and 3–8 days to distinguish any very early protective effect from the deferral of vaccination in individuals who were already aware of their COVID-19 positive status from home lateral flow testing or a healthy vaccinee effect in which those with early symptoms of COVID-19 were more unwell than controls and were less likely to be vaccinated from the period 3–8 days where we do not expect to see a true protective effect from vaccination. Analyses were stratified by manufacturer.

Additionally, stratified analyses were conducted restricting to those who were not resident in a care home as the initial roll-out of the vaccines was primarily with the Sanofi/GSK boosters with residents of care homes being prioritised for vaccination. Sensitivity analyses were also undertaken to assess the effect of not adjusting for prior infection.

Microsoft SQL Server Management Studio v18.11 and Stata/SE 17.0 software were used for data management and statistical analysis.

Ethics committee approval

The study protocol was subject to an internal review by the UK Health Security Agency Research Ethics and Governance Group and was found to be fully compliant with all regulatory requirements. As no regulatory issues were identified, and ethical review is not a requirement for this type of work, it was decided that a full ethical review would not be necessary. UKHSA has legal permission, provided by Regulation 3 of The Health Service (Control of Patient Information) Regulations 2002, to process patient confidential information for national surveillance of communicable diseases and as such, individual patient consent is not required to access records.

Role of funding source

None.

Results

Overall, there were 14,169 eligible tests from hospitalised individuals aged 75 years and older, with 3005 being cases and 11,164 being controls. Full descriptive characteristics are available in Supplementary Table S2. The distribution of cases and controls over time is shown in Supplementary Figure S2. The roll-out of the Sanofi/GSK booster vaccine started approximately three weeks before the roll-out of the Pfizer BA.4-5 boosters; the distribution of time since spring booster vaccination by manufacturer for tests included in the study is shown in Supplementary Figure S3.

Both the Sanofi/GSK and Pfizer BA.4-5 boosters provided good protection against hospitalisation in older

adults in England; odds ratios and corresponding vaccine effectiveness estimates are given in Supplementary Table S3 and Fig. 1. The odds of vaccination by the Sanofi/GSK and by Pfizer BA.4-5 boosters just prior to testing (0–2 days) was significantly below one, yielding apparent positive vaccine effectiveness (69.6% (95% CI, 36.5–85.4%) and 51.1% (95% CI, 0.0–76.1%) for Sanofi/GSK and Pfizer BA.4-5 boosters, respectively). The odds increased to closer to one and were non-significant in the period 3–8 days post vaccination indicating no vaccine association (15.7% (95% CI, −13.5 to 37.4%) and 25.0% (95% CI, −15.1 to 51.2%) for Sanofi/GSK and Pfizer BA.4-5 boosters, respectively).

From 9 days after vaccination, VE against hospitalisation was highest in the earliest period post-vaccination (9–13 days post vaccination) at about 50% for both manufacturers; 43.7% (95% CI, 20.1–60.3%) and 56.1% (95% CI, 25.2–74.2%) for Sanofi/GSK and Pfizer BA.4-5 boosters, respectively (Supplementary Table S3 and Fig. 1). In the period from 2 to 4 weeks post vaccination, the VE point estimate was lower for the Sanofi/GSK booster at 33.1% (95% CI, 18.7–44.9%) compared to the Pfizer BA.4-5 booster at 52.9% (95% CI, 36.2–65.2%) though confidence intervals overlapped so this difference was not statistically significant. After 5–9 weeks there was some evidence of waning; VE was lower than at 9–13 days post vaccination for both manufacturers at 33.1% (95% CI, 16.8–46.3%) for the Sanofi/GSK booster and 28.7% (95% CI, 7.0–45.4%) for the Pfizer BA.4-5 booster. From 10 weeks or more post vaccination (the longest follow-up period available) there was some non-significant evidence of further waning for the Sanofi/GSK booster but not the Pfizer BA.4-5 booster, although confidence intervals were wide and overlapping between the manufacturers. The effect of the other variables included in the model are reported in Supplementary Table S4. Notably, influenza vaccine status this season (2022/2023) did not affect the odds of testing positive. Previous infection had a protective effect, with the greatest protection being from more recent Omicron infections recorded after PCR testing was only available in hospital settings (likely indicating a severe infection in the last year).

When the analysis was stratified to only include individuals who are not currently living in a care home (Table 1), VE estimates against hospitalisation for the Sanofi/GSK booster and Pfizer BA.4-5 booster were similar to those obtained using all cases and controls (Supplementary Table S3 and Fig. 1). There were no statistically significant differences by manufacturer in either of the analyses, but point estimates were more similar for the Sanofi/GSK and Pfizer BA.4-5 boosters when we stratified by those not currently resident in a care home (Table 1). In the period 9–13 days post vaccination, VE against hospitalisation for those not resident in a care home was 51.2% (95% CI, 26.3–67.7%) and 54.9% (95% CI, 21.7–74.0%) for the Sanofi/GSK and Pfizer BA.4-5 boosters, respectively (Table 1). In the longest follow-up period post-vaccination available (10 or more weeks), VE had waned to 14.9% (95% CI, −8.3 to 33.1%) and 38.8% (95% CI, 13.8–56.6%) for the Sanofi/GSK and Pfizer BA.4-5 boosters, respectively, amongst those not resident in a care home. In sensitivity analyses where the adjustment for past positivity was removed, point estimates differed from the primary analysis by less than 2% in the time intervals from 9 days post vaccination (data not shown).
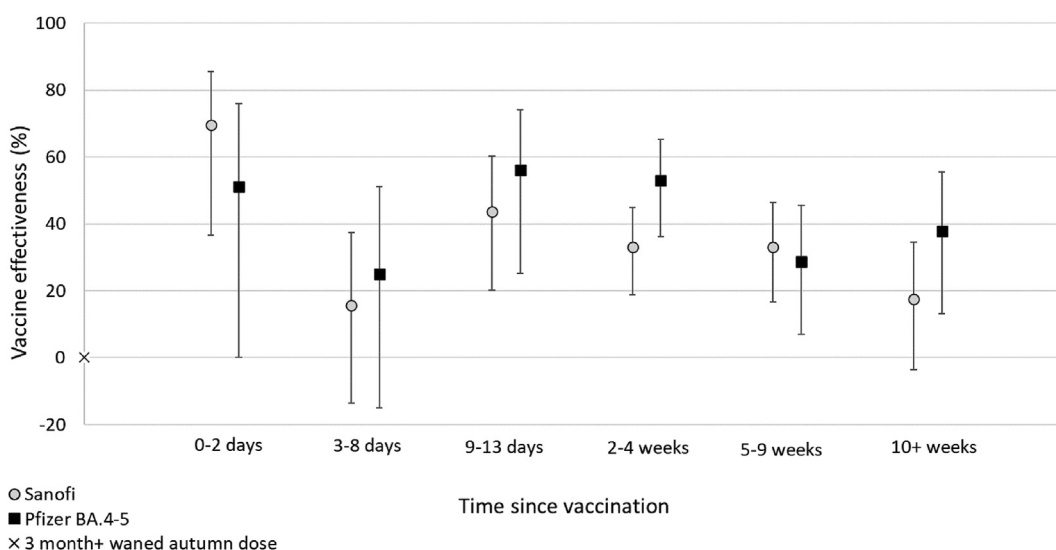

Fig. 1: Vaccine effectiveness (VE) against hospitalisation amongst those aged 75 years and older in England, stratified by spring booster manufacturer. The error bars represent the 95% confidence intervals. The data behind these estimates are presented in Supplementary Table S3.

Spring booster[a]	Interval	Controls	Cases	Odds Ratio	VE (95% C.I.)
None	–	5898	2036	Baseline	Baseline
Sanofi/GSK	0–2 days	51	5	0.27 (0.11–0.69)	72.9 (31.5–89.3)
	3–8 days	158	54	0.90 (0.65–1.24)	10.5 (–23.9 to 35.3)
	9–13 days	153	29	0.49 (0.32–0.74)	51.2 (26.3–67.7)
	2–4 weeks	629	132	0.69 (0.55–0.85)	31.4 (15.3–44.5)
	5–9 weeks	789	111	0.68 (0.53–0.86)	32.3 (14.2–46.5)
	10+ weeks	638	181	0.85 (0.67–1.08)	14.9 (–8.3 to 33.1)
Pfizer BA.4-5	0–2 days	55	7	0.41 (0.18–0.91)	59.4 (9.4–81.8)
	3–8 days	116	25	0.77 (0.49–1.21)	22.7 (–21.0 to 50.7)
	9–13 days	120	15	0.45 (0.26–0.78)	54.9 (21.7–74.0)
	2–4 weeks	447	51	0.49 (0.36–0.67)	50.9 (33.1–63.9)
	5–9 weeks	524	83	0.71 (0.54–0.93)	29.0 (6.7–45.9)
	10+ weeks	242	60	0.61 (0.43–0.86)	38.8 (13.8–56.6)

[a]All individuals had received a bivalent BA.1 booster vaccine as part of the autumn 2022 booster programme, which was at least 3 months prior to their test.

Table 1: Vaccine effectiveness (VE) against hospitalisation amongst those aged 75 years and older not resident in a care home, stratified by spring booster manufacturer.

Discussion

In this test-negative case–control study, we estimated the protection conferred by the Sanofi/GSK and Pfizer BA.4-5 booster vaccines against hospitalisation amongst England's population of adults aged 75 years and older–the main target group of the COVID-19 spring booster campaign due to the increased vulnerability of older adults to severe COVID-19. During the study period, XBB sub-lineages dominated in England. We found that the incremental vaccine effectiveness of a booster dose with either vaccine peaked at around 50% protection against hospitalisation in addition to any remaining protection from prior vaccination with the bivalent BA.1 booster given as part of the autumn 2022 programme.

To our knowledge these are the first real-world effectiveness data for an adjuvanted COVID-19 vaccine. Immunogenicity studies have found that the Sanofi/GSK vaccine elicited as high or higher neutralizing-antibody titres as the original Pfizer mRNA vaccine did against the original strain and against the Beta, Delta, and Omicron BA.1 variants when these vaccines were given as booster doses.[25] Unpublished data from the UKHSA CONSENSUS study found antibody responses to be broadly similar between the two vaccines. The efficacy of an adjuvanted bivalent vaccine (ancestral/Beta) by Sanofi/GSK against symptomatic COVID-19 was 75% in SARS-CoV-2 non-naive participants when given as a second dose in a clinical trial.[26]

Overall, we found both vaccines provided good protection against hospitalisation (around 30–50% in addition to the protection from a waned autumn booster) and we did not find significant differences (as evidenced by the overlapping 95% confidence intervals between VE estimates) in the effectiveness of the boosters by manufacturer. The most prevalent strains in the UK during this analysis period were XBB sub-lineages which are more closely related to the BA.4/5 lineages which this mRNA bivalent vaccine is based on. The similar level of protection with the more distant Sanofi/GSK vaccine based on the Beta strain may be attributable to the adjuvant in the Sanofi product or the different vaccine platform. It is also possible that reduced VE occurs with bivalent vaccines targeting the original strain and a variant strain due to immunological imprinting whereby the presence of ancestral spike in the vaccine prevents broadening of antibodies to the updated variant strain component. Further comparisons of real-world protection from different vaccine platforms and formulations in the presence of matched and unmatched strains are warranted.

Other studies have assessed the real-world effectiveness of the Pfizer BA.4-5 bivalent booster vaccine and found broadly similar results to us; one study from the United States found the incremental effectiveness against hospitalisation of a BA.4-5 bivalent booster was 42% when the last dose was monovalent and given 5–7 months prior,[23] while another found the relative effectiveness against hospitalisation was 52% when the last dose was monovalent.[27] Meanwhile a recent Italian study found the relative effectiveness of bivalent BA.4-5 boosters was 50.6% against severe disease when the last dose was given at least 120 days prior.[28]

The Sanofi/GSK booster was delivered first, with those living in care homes being prioritised for vaccination.[15] Those living in care homes may be older and at higher clinical risk; effectiveness may be expected to be lower in these individuals which could have biased estimates for the Sanofi/GSK booster to be lower as this booster was the main product given to care home residents. In addition to adjusting for care home resident status in the main analysis, we also undertook stratified analyses where we only included those who were not

known to be resident in a care home as of March 2023. We did not find a significant difference in effectiveness by manufacturer in either analysis.

We observed an apparent protective effect of booster vaccination with both manufacturers in the first couple of days post vaccination. The lower odds of vaccination in cases compared to controls in the 0–2 days prior to testing is likely related to a combination of deferral of vaccination in individuals who were already aware of their COVID-19 positive status from home lateral flow testing and a healthy vaccinee effect in which those with early symptoms of COVID-19 were more unwell than controls and were less likely to be vaccinated. These effects would only be expected to be transient as indicated by the fact that the odd ratio was close to one for the 3–8 day period (expected in a period before vaccine induced immunity is expected). The true protective effect of booster vaccination appeared to peak at 9–13 days post vaccination. Previously, we have found that the effectiveness of booster vaccination against hospitalisation wanes over time.[5] Here we also observe evidence of waning, this did not differ significantly by manufacturer although the point estimate beyond 10 weeks after vaccination was lower for the Sanofi/GSK vaccine. It is important to note that the vaccines were used over slightly different time periods, with the Sanofi vaccine being the predominant one used in the first weeks of the programme and so this observation may be confounded by time. Further follow-up would be needed to fully assess waning over time of the Sanofi/GSK and Pfizer BA.4-5 booster vaccines.

The TNCC study design has been widely used to assess influenza vaccine effectiveness, and since the emergence of COVID-19 it has also been used by many groups to assess vaccine effectiveness against COVID-19. In comparison with conventional cohort or case–control study designs, a strength of using the TNCC study design to estimate vaccine effectiveness is that it helps to address unmeasured confounders related to differences in health-seeking behaviours and infectious-disease exposure between vaccinated and unvaccinated people. The TNCC study design requires testing to be independent of vaccination status, which is likely to be the case in a hospital setting.

However, there are also several limitations to our study. In England, PCR tests are only undertaken in hospital settings and symptom onset date is not recorded. The sensitivity of PCR testing is not 100%, particularly if there has been a long interval between the infection date and the date of the test. It is possible that an individual may not have any PCR tests prior to admission, but with a long gap between the infection and development of severe disease they may test negative upon admission and therefore be included as a control although they were a case. If this is a random mis-classification this would bias VE estimates slightly towards the null.[29] As an observational study, there may

have been unmeasured confounders which we were not able to adjust for. Immunity driven by prior infections may affect vaccine effectiveness and most infections have been undocumented since freely available community testing ended in England. In previous studies[5,8] and here we found that when we do not adjust for past positivity our results are similar to those of the main analyses suggesting that these missing data were not likely to have caused a large bias. Including those with past infection is most relevant to public health policy as most of the population have now been infected.

A further limitation is that our study relied on linkage of national-level datasets which will result in some missing data. Additionally, errors in hospital coding may have resulted in the inclusion of some non-respiratory cases and controls in our study.[4] Lack of long term follow up is a further limitation. We were only able to assess VE up to 10 or more weeks post vaccination where we found there was still some protection. Nonetheless, it is clear from these data that the highest level of protection from the boosters is maintained for a relatively short period of time. Policy decisions around the timing of seasonal booster programmes for those at highest risk of severe disease must aim to factor in the likely timeframe in which individuals need to be at their most protected. This remains a challenge as, unlike influenza, COVID-19 has not become a seasonal virus with a predictable annual peak. Disease waves occur throughout the year largely driven by novel sub-lineages, the emergence of which are challenging to predict.

Overall, these results provide reassuring evidence that both the adjuvanted Sanofi/GSK (VidPrevtyn Beta) and Pfizer mRNA BA.4-5 booster vaccines provide a substantial boost in protection against hospitalisation with COVID-19 amongst adults aged 75 years and older for at least 10 weeks after vaccination. Further follow up is needed to better understand the duration of boosted protection with these two vaccines.

Articles

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102587.

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