Effectiveness of BNT162b2 BA.4/5 bivalent mRNA vaccine against a range of COVID-19 outcomes in a large health system in the USA: a test-negative case–control study

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Summary

Background XBB-related omicron sublineages have recently replaced BA.4/5 as the predominant omicron sublineages in the USA and other regions globally. Despite preliminary signs of immune evasion of XBB sublineages, few data exist describing the real-world effectiveness of bivalent COVID-19 vaccines, especially against XBB-related illness. We aimed to investigate the effectiveness of the Pfizer–BioNTech BNT162b2 BA.4/5 bivalent vaccine against both BA.4/5-related and XBB-related disease in adults aged 18 years or older.

Methods In this test-negative case–control study, we estimated the effectiveness of the BNT162b2 BA.4/5 bivalent vaccine using data from electronic health records of Kaiser Permanente Southern California health system members aged 18 years or older who received at least two doses of the wild-type COVID-19 mRNA vaccines. Participants sought care for acute respiratory infection between Aug 31, 2022, and April 15, 2023, and were tested for SARS-CoV-2 via PCR tests. Relative vaccine effectiveness (≥2 doses of wild-type mRNA vaccine plus a BNT162b2 BA.4/5 bivalent booster *vs* ≥2 doses of a wild-type mRNA vaccine alone) and absolute vaccine effectiveness (*vs* unvaccinated individuals) was estimated against critical illness related to acute respiratory infection (intensive care unit [ICU] admission, mechanical ventilation, or inpatient death), hospital admission, emergency department or urgent care visits, and in-person outpatient encounters with odds ratios from logistic regression models adjusted for demographic and clinical factors. We stratified vaccine effectiveness estimates for hospital admission, emergency department or urgent care visits, and outpatient encounters by omicron sublineage (ie, likely BA.4/5-related *vs* likely XBB-related), time since bivalent booster receipt, age group, number of wild-type doses received, and immunocompromised status. This study is registered with ClinicalTrials.gov (NCT04848584).

Findings Analyses were conducted for 123 419 encounters (24 246 COVID-19 cases and 99 173 test-negative controls), including 4131 episode of critical illness (a subset of hospital admissions), 14 529 hospital admissions, 63 566 emergency department or urgent care visits, and 45 324 outpatient visits. 20 555 infections were BA.4/5 related and 3691 were XBB related. In adjusted analyses, relative vaccine effectiveness for those who received the BNT162b2 BA.4/5 bivalent booster compared with those who received at least two doses of a wild-type mRNA vaccine alone was an additional 50% (95% CI 23–68) against critical illness, an additional 39% (28–49) against hospital admission, an additional 35% (30–40) against emergency department or urgent care visits, and an additional 28% (22–33) against outpatient encounters. Waning of the bivalent booster from 0–3 months to 4–7 months after vaccination was evident for outpatient outcomes but was not detected for critical illness, hospital admission, and emergency department or urgent care outcomes. The relative effectiveness of the BNT162b2 BA.4/5 bivalent booster for XBB-related infections compared with BA.4/5-related infections was 56% (95% CI 12–78) versus 40% (27–50) for hospital admission; 34% (21–45) versus 36% (30–41) against emergency department or urgent care visits; and 29% (19–38) versus 27% (20–33) for outpatient encounters.

Interpretation By mid-April, 2023, individuals previously vaccinated only with wild-type vaccines had little protection against COVID-19—including hospital admission. A BNT162b2 BA.4/5 bivalent booster restored protection against a range of COVID-19 outcomes, including against XBB-related sublineages, with the most substantial protection observed against hospital admission and critical illness.

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Introduction

On Aug 31, 2022, the US Food and Drug Administration (FDA) granted emergency use authorisation of bivalent mRNA COVID-19 vaccines (which have equal amounts of mRNA encoding the original Wuhan-Hu-1 [hereafter referred to as wild-type] strain and the BA.4/5 omicron sublineage) as a booster dose for individuals aged 18 years or older who received their last vaccine against

Research in context

Evidence before this study

We searched PubMed, medRxiv, and press coverage up to May 15, 2023, using the search terms "BNT162b2", "vaccin*", "COVID-19", "bivalent", "effective*", "impact", "model", "omicron", "BA.4*", and "BA.5" for preprint and published studies, without applying any language restrictions. Available data as of May 15, 2023, have shown substantial waning of effectiveness of the original wild-type mRNA vaccines against the BA.4/5 omicron sublineages, including severe outcomes such as hospital admission, after 3-6 months. Several published reports from the USA and Israel have shown that receipt of a BA.4/5 bivalent booster improves protection early on for those who received a bivalent BA.4/5 mRNA vaccine compared with those who did not against a range of COVID-19 outcomes during periods when BA.4/5-related omicron subvariants (eg, BA.4, BA.5, BQ.1 and BQ.1.1) were predominant. Due to the timing of publications, most reports were unable to describe vaccine effectiveness against the newly emerged XBB-related omicron sublineages or ascertain the durability of BA.4/5 bivalent vaccines. To the best of our knowledge, no studies have published effectiveness estimates against XBB-related severe disease. Studies evaluating the longer-term effectiveness of BA.4/5 bivalent mRNA vaccines and their effectiveness against XBB-related sublineages, especially for severe outcomes, are currently needed.

Added value of this study

In this test-negative case–control study covering a large, diverse population in the USA, we show that individuals previously vaccinated only with wild-type vaccines (with the last dose received at least 6 months ago) had little protection against COVID-19, including hospital admission. A BNT162b2 BA.4/5 bivalent booster restored protection against a range of COVID-19 outcomes, including against XBB-related sublineages, with the most substantial and durable protection observed against severe outcomes. In the first 7 months after receipt of the BNT162b2 BA.4/5 bivalent vaccine, relative effectiveness (*vs* those who received ≥2 doses of a wild-type COVID-19 mRNA vaccine) against hospital admission or critical illness was 34–53%, depending on the time since the last wild-type dose—with no signs of waning. Relative effectiveness against less severe outcomes, such as emergency department, urgent care, and outpatient visits, was generally similar but appeared to show early signs of waning after 3 months for outpatient illness and XBB-related disease. Estimates of absolute vaccine effectiveness of a BNT162b2 BA.4/5 bivalent booster (*vs* unvaccinated individuals) ranged from 56% to 69% against critical illness or hospital admission and showed similar patterns of waning in the outpatient setting as seen with relative effectiveness estimates. These are some of the earliest and most comprehensive data showing the effectiveness of the BNT162b2 BA4/5 bivalent vaccine against a wide range of BA.4/5 and XBB-related outcomes that include severe disease.

Implications of all the available evidence

Although the long-term durability of BA.4/5 bivalent boosters is currently unknown, after 6–7 months, protection against severe illness caused by XBB-related sublineages—which showed initial signs of immune escape and have since become predominant in the USA and other regions globally—appears intact.

the wild-type strain at least 2 months ago.[1] The BNT162b2 BA.4/5 bivalent mRNA vaccine (Pfizer–BioNtech) was also authorised as a booster for children aged 12–17 years on the same date.[1]

At the time of the emergency use authorisation, the need for updated vaccines targeting the BA.4/5 sublineage of omicron was based on emerging data showing substantial waning of effectiveness of the wild-type mRNA vaccines against the newly emerged BA.4/5 omicron sublineage after only 3–6 months, even against severe outcomes such as hospital admission;[2–4] an expected uptick of disease during the winter respiratory virus season;[5] and emerging preclinical data suggesting that a better-matched BA.4/5 bivalent mRNA vaccine could provide higher neutralising activity against BA.4/5 and other more contemporary omicron sublineages compared with wild-type vaccines.[6,7]

Since that time, immunogenicity data from clinical trials confirmed early findings observed in the preclinical setting and showed that neutralising antibody responses for bivalent vaccines in adults aged 18 years or older were substantially higher for those who received the bivalent BA.4/5 vaccine than for those who received the wild-type vaccine, with a similar safety and tolerability profile.[8–10] Additionally, several published studies from the USA[11–14] and three preprint studies, one conducted in the USA,[15] another in Israel,[16] and the third in Denmark, Finland, Norway, and Sweden,[17] have evaluated the effectiveness of mRNA vaccines and shown improved protection soon after vaccination for those who received a bivalent BA.4/5 mRNA vaccine compared with those who did not against a range of COVID-19 outcomes during periods when BA.4/5-related omicron subvariants (eg, BA.4, BA.5, BQ.1, and BQ.1.1) were predominant. Only one preliminary report of bivalent BA.4/5 mRNA vaccine effectiveness against XBB omicron sublineages has been published; however, estimates of bivalent vaccine effectiveness were limited to the outpatient pharmacy setting in this report.[18]

Thus, published studies to date have not thoroughly evaluated omicron sublineage-specific effectiveness across a range of COVID-19 outcomes, and data describing the effectiveness of bivalent BA.4/5 vaccines against XBB sublineages, which have since become dominant in the USA,[19] are scarce. In both the preclinical and clinical settings, bivalent BA.4/5 vaccines have

shown significantly lower levels of neutralising activity against XBB-related sublineages.[6,8,20] Accordingly, real-world XBB-specific effectiveness data for bivalent BA.4/5 vaccines are urgently needed to help inform decision making about whether updated vaccines targeting this new omicron sublineage are needed. Vaccine-specific estimates of effectiveness are also needed, as all previous reports have evaluated the effectiveness of receiving one of the two bivalent BA.4/5 mRNA vaccines. To fill these important knowledge gaps and help inform evolving policy for updating COVID-19 vaccines, we aimed to investigate the effectiveness of the Pfizer–BioNTech BNT162b2 BA.4/5 bivalent vaccine, which has been the most widely used bivalent BA.4/5 mRNA vaccine in the USA and globally, against both BA.4/5-related and XBB-related disease in adults aged 18 years or older in a large US health system; we explored vaccine effectiveness across a range of COVID-19 outcomes, including critical illness (intensive care unit [ICU] admission, mechanical ventilation, or inpatient death), hospital admission, emergency department or urgent care visits, and outpatient encounters.

Methods

Study design and participants

Kaiser Permanente Southern California (KPSC) is a large, integrated health-care system with more than 4·7 million members in southern California, USA.[21] People join through employer-paid, Medicare, or Medicaid programmes or private pay. The KPSC population is representative of the demographic profile of the southern California population.[22] KPSC has an integrated electronic health record system that includes data for members across all health-care settings. We conducted a case–control study with a test-negative design of KPSC members aged 18 years or older who were diagnosed with acute respiratory infection (based on International Classification of Diseases, Tenth Revision [ICD-10] codes) and were tested for SARS-CoV-2 infection via a PCR test in either the hospital, emergency department or urgent care, or in-person outpatient setting from Aug 31, 2022 (the day bivalent mRNA boosters were approved for adults in the USA), to April 15, 2023. During the first part of this period, BA.4/5 was the predominant sublineage in the USA, with some BA.2-related sublineages (including BA.2·12.1) co-circulating with the BA.4/5 sublineage. Beginning the week of Jan 22, 2023, XBB-related sublineages became predominant in the USA and globally.[23] Participants were required to have at least 1 year of health plan membership to ascertain comorbidities and medical history. A 45-day gap in membership was allowed to account for any delays in renewal of membership. This study was approved by the KPSC Institutional Review Board, which granted a waiver of informed consent.

Exposures

All members were eligible for COVID-19 vaccines at no cost on the basis of FDA-authorised or approved indications. KPSC electronic health records (EHRs) captured all vaccinations administered within KPSC and were updated daily with vaccine administration data from the California Immunization Registry, to which all health-care providers are required by law to report COVID-19 vaccinations within 24 h. As such, misclassification of vaccination status is unlikely.

Patients were included only if they were unvaccinated against COVID-19 (ie, never received a COVID-19 vaccine of any type) or received at least two doses of a wild-type mRNA COVID-19 vaccine (either BNT162b2 [Pfizer–BioNTech] or mRNA-1273 [Moderna]). An individual's vaccination status was ascertained on the basis of doses received at least 14 days before the encounter. Minimal required intervals between doses varied by recommendation and were defined on the basis of recommendations[24–27] as at least 28 days between a second and third dose; at least 3 months (≥84 days) between a third and fourth dose; and at least 4 months (≥112 days) between a fourth and fifth dose. Vaccination with a bivalent booster was defined as receipt of the BNT162b2 BA.4/5 bivalent vaccine at least 8 weeks (≥56 days) after the most recent dose of wild-type COVID-19 mRNA vaccine received. Individuals who were vaccinated with mRNA-1273.222 (the Moderna BA.4/5 bivalent booster) were censored upon its receipt. Individuals who received only one wild-type COVID-19 mRNA dose, more than five doses of wild-type COVID-19 vaccines, or any non-mRNA COVID-19 vaccine were excluded from analyses. Those who received nirmatrelvir or ritonavir or any other COVID-19 outpatient antiviral or monoclonal antibody (ie, molnupiravir, remdesivir, bebtelovimab, bamlanivimab, casirivimab, cilgavimab, sotrovimab, or tixagevimab) before their COVID-19 encounter were also excluded.

Outcomes

The effectiveness of the BNT162b2 BA.4/5 bivalent vaccine was evaluated by comparing the odds of vaccination between COVID-19 cases and test-negative controls. Cases and controls were patients with critical illness related to acute respiratory infection (leading to ICU admission, mechanical ventilation, or inpatient death), hospital admission, emergency department or urgent care visit, or outpatient encounter with a SARS-CoV-2 PCR test administered up to 14 days before the initial encounter or up to 3 days after the encounter. Cases were defined as those with a positive SARS-CoV-2 PCR test, and controls were those who tested negative and had no evidence of a positive SARS-CoV-2 test in the 90 days before the encounter. Patients could contribute more than one event to the study if the events were more than 90 days apart.

When ascertaining omicron sublineage, we defined XBB-related cases as those that that were confirmed to be an XBB sublineage by whole genome sequencing, or tested with the ThermoFisher TaqPath COVID-19 Combo Kit (ThermoFisher; Waltham, MA, USA) and showed an absence of S protein target failure (SGTF) after Nov 20, 2022 (ie, the date when XBB-related sublineages became the predominant strains showing absence of SGTF [*vs* other BA.2 sublineages]). This date was consistent with when the prevalence of XBB-related sublineages surpassed that of BA.2 sublineages based on the US Centers for Disease Control and Prevention (CDC) variant proportions tracker for the western region (Region 9), which includes California.[19] This approach was also consistent with a CDC definition used in their recent XBB sublineage-specific analysis.[18] Based on variant epidemiology at the time of study conduct, samples showing the presence of SGTF were considered to be BA.5 related (eg, BA.4, BA.5, BQ.1, or BQ.1.1).

Statistical analysis

Patient and clinical characteristics were compared across cases and test-negative controls and by vaccination status with the χ^2 test for categorical variables and Fisher's exact test for binary variables. Continuous variables were compared with the Wilcoxon rank-sum test. All crude and adjusted effectiveness estimates were constructed and compared with odds ratios (ORs) and 95% CIs

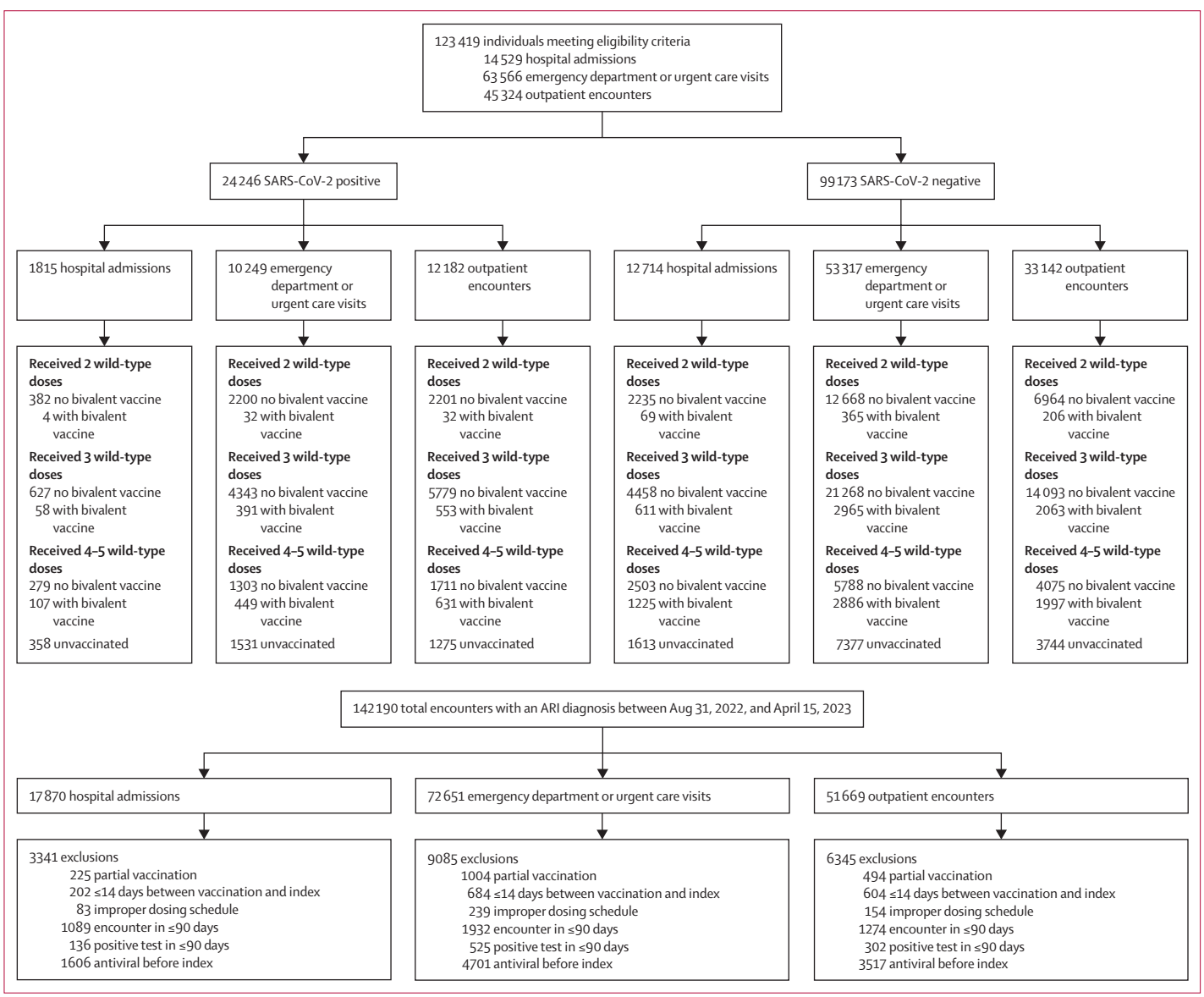

Figure 1: **Flowchart for study population**
ARI=acute respiratory infection.

from logistic regression models (separately for each encounter type). Vaccine effectiveness was calculated as 1–OR multiplied by 100%, with corresponding 95% CIs calculated with the Wald method. Adjusted ORs and 95% CIs were estimated by adjusting for month of encounter, age (18–49, 50–64, and ≥65 years), self-reported sex (male and female), self-reported race or ethnicity (Hispanic, non-Hispanic white, non-Hispanic Black, non-Hispanic Asian/Pacific Islander, and other or unknown), BMI (<18·5, 18·5–24·9, 25·0–29·9, 30·0–34·9, ≥35·0 kg/m², and unknown), Charlson comorbidity index (0, 1, 2, 3, and ≥4), receipt of influenza vaccine in the year before admission (yes or no), receipt of pneumococcal vaccine in the 5 years before admission (yes or no; to adjust for health-care seeking behaviour), health-care utilisation in the year before admission (ie, number of inpatient, emergency department, or outpatient visits) and documentation of previous SARS-CoV-2 infection (ever *vs* never) for pre-delta, delta, and omicron periods in multivariable logistic regression models. For analyses of XBB-related variants, we adjusted for week of encounter (rather than month) because the analysis period was shorter and had more variable rates of COVID-19.

Effectiveness estimates for the BNT162b2 BA.4/5 bivalent vaccine were generated with two comparison frameworks. First, we estimated relative effectiveness by comparing the odds of being a COVID-19 case for individuals who received at least two doses of a wild-type mRNA vaccine and a BNT162b2 BA.4/5 bivalent booster versus individuals who received at least two doses of a wild-type COVID-19 mRNA vaccine but did not receive a COVID-19 bivalent booster of any kind. Second, we generated absolute vaccine effectiveness estimates that used unvaccinated individuals as the reference group.

Effectiveness estimates for critical illness, hospital admission, emergency department or urgent care visits, and outpatient encounters were stratified by time since BNT162b2 BA.4/5 bivalent booster (0–3 months *vs* 4–7 months), age group (18–64 and 40–49 years *vs* 50–64 years and ≥65 years), number of wild-type mRNA doses received, and immunocompromising status (defined as the absence of any immunocompromising conditions including leukaemia, lymphoma, congenital immunodeficiencies, asplenia or hyposplenia, HIV/AIDS, history of haematopoietic stem-cell or solid organ transplantation, or receipt of immunocompromised medication with previously published approaches).[26] Effectiveness estimates for hospital admission, emergency department or urgent care visits, and outpatient encounters were stratified by omicron sublineage (likely BA.4/5 related *vs* likely XBB related, as defined previously); lineage-specific models did not converge for the critical illness outcome. To further assess differences in vaccine effectiveness by omicron sublineage, we also performed two adjusted logistic regression analyses with a BNT162b2

	COVID-19 cases (n=24 246)	Test-negative controls (n=99 173)	Total (n=123 419)	p value
Age, years				
18–49	10 821 (44·6%)	45 836 (46·2%)	56 657 (45·9%)	<0·0001
50–64	6780 (28·0%)	22 477 (22·7%)	29 257 (23·7%)	..
≥65	6645 (27·4%)	30 860 (31·1%)	37 505 (30·4%)	..
Self-reported sex				
Female	15 009 (61·9%)	61 408 (61·9%)	76 417 (61·9%)	0·96
Male	9236 (38·1%)	37 760 (38·1%)	46 996 (38·1%)	..
Unknown	1 (<0·1%)	5 (<0·1%)	6 (<0·1%)	..
Race or ethnicity				
Asian	3001 (12·4%)	10 403 (10·5%)	13 404 (10·9%)	<0·0001
Black	2384 (9·8%)	9908 (10·0%)	12 292 (10·0%)	..
Hispanic	12 076 (49·8%)	46 550 (46·9%)	58 626 (47·5%)	..
Other or unknown	1077 (4·4%)	4023 (4·1%)	5100 (4·1%)	..
White	5708 (23·5%)	28 289 (28·5%)	33 997 (27·5%)	..
BMI, kg/m²				
Underweight (<18·5)	374 (1·5%)	2073 (2·1%)	2447 (2·0%)	<0·0001
Normal or healthy weight (18·5–24·9)	5439 (22·4%)	22 416 (22·6%)	27 855 (22·6%)	..
Overweight (25·0–29·9)	7584 (31·3%)	29 273 (29·5%)	36 857 (29·9%)	..
Obese, class 1 (30·0–34·9)	5505 (22·7%)	22 515 (22·7%)	28 020 (22·7%)	..
Obese, class 2–3 (≥35·0)	5061 (20·9%)	21 906 (22·1%)	26 967 (21·8%)	..
Unknown	283 (1·2%)	990 (1·0%)	1273 (1·0%)	..
Comorbidities				
Hypertension	7794 (32·1%)	36 363 (36·7%)	44 157 (35·8%)	<0·0001
Congestive heart failure	1088 (4·5%)	9097 (9·2%)	10 185 (8·3%)	<0·0001
Myocardial infarction	602 (2·5%)	4095 (4·1%)	4697 (3·8%)	<0·0001
Peripheral vascular disease	3780 (15·6%)	20 927 (21·1%)	24 707 (20·0%)	<0·0001
Cerebrovascular disease	808 (3·3%)	4809 (4·8%)	5617 (4·6%)	<0·0001
Diabetes				
Diabetes; unknown glycated haemoglobin	231 (1·0%)	1118 (1·1%)	1349 (1·1%)	<0·0001
Diabetes; glycated haemoglobin <7·5%	3136 (12·9%)	13 845 (14%)	16 981 (13·8%)	..
Diabetes; glycated haemoglobin ≥7·5%	1820 (7·5%)	8335 (8·4%)	10 155 (8·2%)	..
Chronic obstructive pulmonary disease	3706 (15·3%)	22 089 (22·3%)	25 795 (20·9%)	<0·0001
Renal disease	2238 (9·2%)	12 753 (12·9%)	14 991 (12·1%)	<0·0001
Malignancy	1054 (4·3%)	6416 (6·5%)	7470 (6·1%)	<0·0001
Organ transplant	98 (0·4%)	544 (0·5%)	642 (0·5%)	0·005
Charlson comorbidity index				
0	13 488 (55·6%)	48 721 (49·1%)	62 209 (50·4%)	<0·0001
1	4627 (19·1%)	18 351 (18·5%)	22 978 (18·6%)	..
2	2190 (9·0%)	9133 (9·2%)	11 323 (9·2%)	..
3	1147 (4·7%)	5582 (5·6%)	6729 (5·5%)	..
≥4	2794 (11·5%)	17 386 (17·5%)	20 180 (16·4%)	..
Outpatient encounters in previous year				
0	1223 (5·0%)	5150 (5·2%)	6373 (5·2%)	<0·0001
1	1537 (6·3%)	6357 (6·4%)	7894 (6·4%)	..
2–4	5256 (21·7%)	20 195 (20·4%)	25 451 (20·6%)	..
5–9	6728 (27·7%)	26 051 (26·3%)	32 779 (26·6%)	..
≥10	9502 (39·2%)	41 420 (41·8%)	50 922 (41·3%)	..

(Table continues on next page)

	COVID-19 cases (n=24 246)	Test-negative controls (n=99 173)	Total (n=123 419)	p value
(Continued from previous page)				
Emergency department encounters in previous year				
0	17 621 (72·7%)	65 427 (66·0%)	83 048 (67·3%)	<0·0001
1	4090 (16·9%)	18 714 (18·9%)	22 804 (18·5%)	..
≥2	2535 (10·5%)	15 032 (15·2%)	17 567 (14·2%)	..
Inpatient encounters in previous year				
0	22 452 (92·6%)	86 895 (87·6%)	109 347 (88·6%)	<0·0001
1	1350 (5·6%)	8224 (8·3%)	9574 (7·8%)	..
≥2	444 (1·8%)	4054 (4·1%)	4498 (3·6%)	..
NDI z-score (higher values mean more deprivation)				
Mean (SD)	0·3 (0·87)	0·3 (0·88)	0·3 (0·88)	<0·0001
Median (IQR)	0·2 (−0·4 to 0·9)	0·2 (−0·4 to 0·8)	0·2 (−0·4 to 0·8)	..
Range	−2·0 to 5·3	−2·0 to 5·3	−2·0 to 5·3	..
Influenza vaccine year before admission	13 331 (55·0%)	54 437 (54·9%)	67 768 (54·9%)	0·80
Pneumococcal vaccine 5 years before admission	5238 (21·6%)	23 250 (23·4%)	28 488 (23·1%)	<0·0001
Previous pre-delta SARS-CoV-2 infection	2608 (10·8%)	12 335 (12·4%)	14 943 (12·1%)	<0·0001
Previous delta SARS-CoV-2 infection	638 (2·6%)	3303 (3·3%)	3941 (3·2%)	<0·0001
Previous omicron SARS-CoV-2 infection	2774 (11·4%)	22 129 (22·3%)	24 903 (20·2%)	<0·0001
Doses received before encounter				
Unvaccinated	3164 (13%)	12 734 (12·8%)	15 898 (12·9%)	<0·0001
2 monovalent doses	4783 (19·7%)	21 867 (22·0%)	26 650 (21·6%)	..
2 monovalent doses plus bivalent booster	68 (0·3%)	640 (0·6%)	708 (0·6%)	..
3 monovalent doses	10 749 (44·3%)	39 819 (40·2%)	50 568 (41·0%)	..
3 monovalent doses plus bivalent booster	1002 (4·1%)	5639 (5·7%)	6641 (5·4%)	..
4–5 monovalent doses	3293 (13·6%)	12 366 (12·5%)	15 659 (12·7%)	..
4–5 monovalent doses plus bivalent booster	1187 (4·9%)	6108 (6·2%)	7295 (5·9%)	..

Data are n (%), unless otherwise stated. NDI=Neighborhood Deprivation Index.

Table: **Characteristics of COVID-19 cases and test-negative controls among individuals diagnosed with acute respiratory infection from Aug 31, 2022, to April 15, 2023**

BA.4/5 bivalent booster as the main exposure (one with unvaccinated individuals serving as the reference group and the other with those receiving at least two wild-type vaccines but no bivalent booster as the reference) and omicron sublineage (BA.4/5 related *vs* XBB related) as the outcome.[28] Missing values were treated as separate categories for all variables in all analyses.

See Online for appendix

All analyses were done with SAS Enterprise Guide statistical software (version 8.2). This study is registered with ClinicalTrials.gov (NCT04848584).

Role of the funding source

This study was sponsored by Pfizer. The study design was developed by KPSC but approved by Pfizer. KPSC collected and analysed the data. Pfizer did not participate in the collection or analysis of data. KPSC and Pfizer participated in the interpretation of data, in the writing of the report, and in the decision to submit the paper for publication.

Results

During the study period, after removal of 18 771 encounters meeting exclusion criteria, there were 4131 critical illnesses (a subset of hospital admissions), 14 529 hospital admissions, 63 566 emergency department or urgent care visits (28 110 emergency department and 35 456 urgent care), and 45 324 in-person outpatient encounters with an acute respiratory infection diagnosis and a documented SARS-CoV-2 PCR test (figure 1), resulting in a final study population of 123 419 encounters, comprising 24 246 COVID-19 cases and 99 173 test-negative controls. The median age of the study population was 52 years (IQR 36–68). Overall, of 24 246 COVID-19 cases, 20 555 (1724 inpatient, 8964 emergency department or urgent care, and 9867 outpatient) infections were BA.4/5 related and 3691 (91 inpatient, 1285 emergency department or urgent care, and 2315 outpatient) were XBB related. Compared with those who tested positive for SARS-CoV-2, those who tested negative tended to be younger and have evidence of previous SARS-CoV-2 infection, among other differences (table). In total, 3136 people contributed multiple events (6276 events; 3132 with two events, and four with three events).

Overall, 15 898 (12·9%) of 123 419 individuals were unvaccinated, 26 650 (21·6%) had received only two wild-type COVID-19 mRNA doses, 708 (0·6%) had received two wild-type mRNA doses plus a BNT162b2 BA.4/5 bivalent vaccine, 50 568 (41·0%) had received three wild-type mRNA doses, 6641 (5·4%) had received three wild-type mRNA doses plus a BNT162b2 BA.4/5 bivalent dose, 15 659 (12·7%) had four or five wild-type mRNA doses, and 7295 (5·9%) had received four or five wild-type mRNA doses plus a BNT162b2 BA.4/5 bivalent booster (table). Overall, 14 644 participants received a BNT162b2 BA.4/5 bivalent vaccine.

Compared with participants who had received two or more doses of wild-type mRNA vaccine with or without the BNT162b2 BA.4/5 bivalent booster, unvaccinated participants were younger, more likely to be Black, less likely to have comorbidities, and less likely to have previously received an influenza or pneumococcal vaccine (appendix pp 1–2). Among vaccinated individuals, the median time from receipt of the last wild-type dose was 350 days (IQR 261-455) for those who did not receive a bivalent booster and 331 days (246-423) for those who did. For those with at least two wild-type mRNA doses, the median time between receipt of a wild-type dose and a BNT162b2 BA.4/5 bivalent booster was 230 days (IQR 164-340). The median time since receipt of a bivalent booster was 77 days (IQR 46-119; range 14-218; appendix p 2). Because the vast majority (13 868 [94·7%] of 14 644) of

individuals who received the BNT162b2 BA.4/5 bivalent booster received their last wild-type dose at least 6 months ago, we did not stratify bivalent booster effectiveness analyses by time since receipt of the last wild-type dose.

Among all participants, the relative effectiveness of the BNT162b2 BA.4/5 bivalent booster compared with those who received at least two doses of a wild-type mRNA vaccine alone was an additional 50% (95% CI 23–68) against critical illness, an additional 39% (28–49) against hospital admission, an additional 35% (30–40) against emergency department or urgent care visits, and an additional 28% (22–33) against outpatient encounters (figure 2; appendix p 3). Point estimates were generally consistent across age groups and time since BNT162b2 BA.4/5 bivalent dose across all outcomes (appendix p 3). In further stratified age groups, vaccine effectiveness appeared to be lower against hospital admission among individuals aged 50–64 years versus those aged 40–49 years, but 95% CIs were largely overlapping (appendix p 3). Waning of vaccine effectiveness from 0–3 months after the BNT162b2 BA.4/5 bivalent dose to 4–7 months after the BNT162b2 BA.4/5 bivalent dose was observed only for outpatient encounters and was not observed against emergency department or urgent care visits, hospital admission, or critical illness outcomes (figure 3; appendix p 3). Overall, vaccine effectiveness estimates were similar when restricted only to immunocompetent adults (appendix pp 3–4).

Adjusted absolute effectiveness (which used unvaccinated individuals as the reference group) was higher for those who received the BNT162b2 BA.4/5 bivalent booster than for those who did not for critical illness (67% [95% CI 44 to 81] *vs* 34% [8 to 53]) hospital admission (59% [49 to 68] *vs* 28% [11 to 42]), emergency department or urgent care visits (45% [39 to 50] *vs* 13% [6 to 19]), and outpatient encounters (29% [21 to 36] *vs* 2% [–6 to 9]; figure 2; appendix p 4). BNT162b2 BA.4/5 bivalent vaccine effectiveness against outpatient visits appeared to wane substantially, from 35% (95% CI 28 to 42) at 0–3 months since receipt of a bivalent booster to 6% (–9 to 19) 4–7 months after a bivalent booster (figure 3; appendix p 4). Waning was not yet evident, however, for vaccine effectiveness against critical illness or hospital admission, nor for emergency department or urgent care outcomes, when comparing outcomes 0–3 months versus 4–7 months since a bivalent booster. Overall, vaccine effectiveness estimates were consistent across age groups (appendix p 4) and when restricted only to immunocompetent adults (appendix pp 3–4). Among those who were previously vaccinated with at least two doses of wild-type mRNA vaccines but had not received a bivalent booster, effectiveness against hospital admission (compared to unvaccinated individuals) was only 33% (95% CI 22–42). Against emergency department or urgent care visits, effectiveness was 15% (95% CI 9–20) and no protection was observed against outpatient illness (appendix p 4).

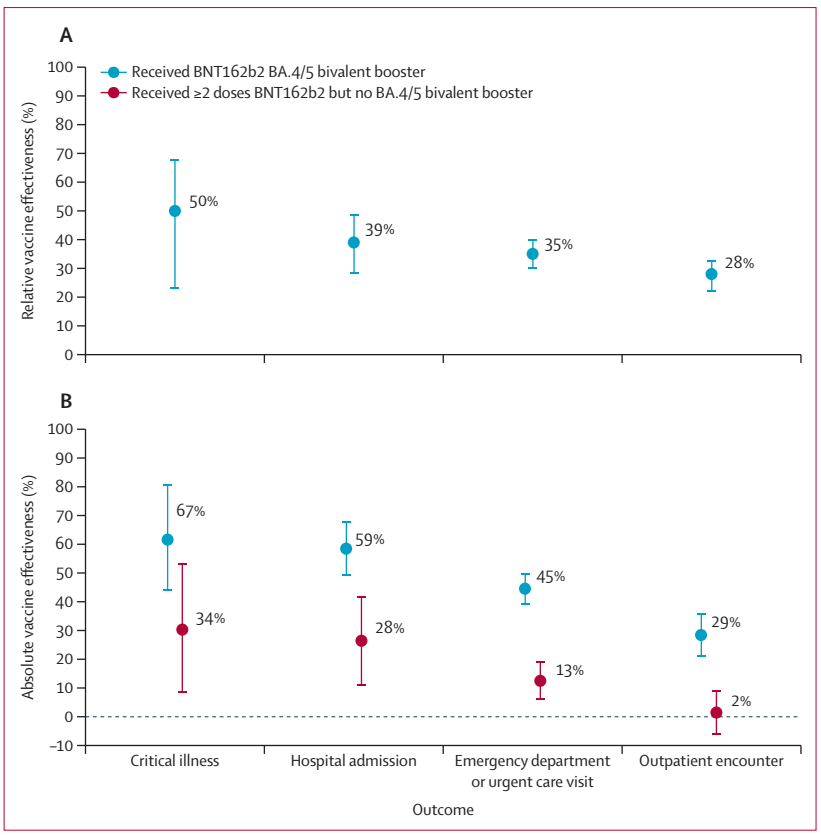

Figure 2: **Adjusted effectiveness of the BNT162b2 BA.4/5 bivalent booster compared with those vaccinated with at least two doses of original wild-type mRNA vaccine (A), and compared with unvaccinated individuals (B), by outcome, from Aug 31, 2022, to April 15, 2023**
Estimates adjusted for month of encounter, age, sex, race or ethnicity, BMI, Charlson comorbidity index, previous influenza vaccination, previous pneumococcal vaccination, previous health-care utilisation, and documentation of previous SARS-CoV-2 infection. Error bars represent 95% CIs.

When stratified by the number of wild-type vaccines received, estimates of the relative and absolute effectiveness of BNT162b2 BA.4/5 bivalent showed a benefit of receiving the BNT162b2 BA.4/5 bivalent vaccine across all outcomes (appendix pp 4–5). Point estimates of relative vaccine effectiveness showed a 29–66% additional benefit of the bivalent dose against critical illness, hospital admission, and emergency department or urgent care outcomes. Absolute vaccine effectiveness point estimates without a bivalent booster were 29–40% against critical illness, 27–42% against hospital admission, and 12–20% against emergency department or urgent care encounters, but among those who received the BNT162b2 BA.4/5 bivalent vaccine the absolute vaccine effectiveness point estimates were 47–79% against critical illness, 59–74% against hospital admission, and 44–60% against emergency department or urgent care encounters (appendix pp 4–5). Notably, the absolute effectiveness of receiving three wild-type doses plus a bivalent booster yielded better protection than receiving four or five doses of a wild-type vaccine only across emergency department or urgent care and outpatient outcomes, but not for hospital admission as

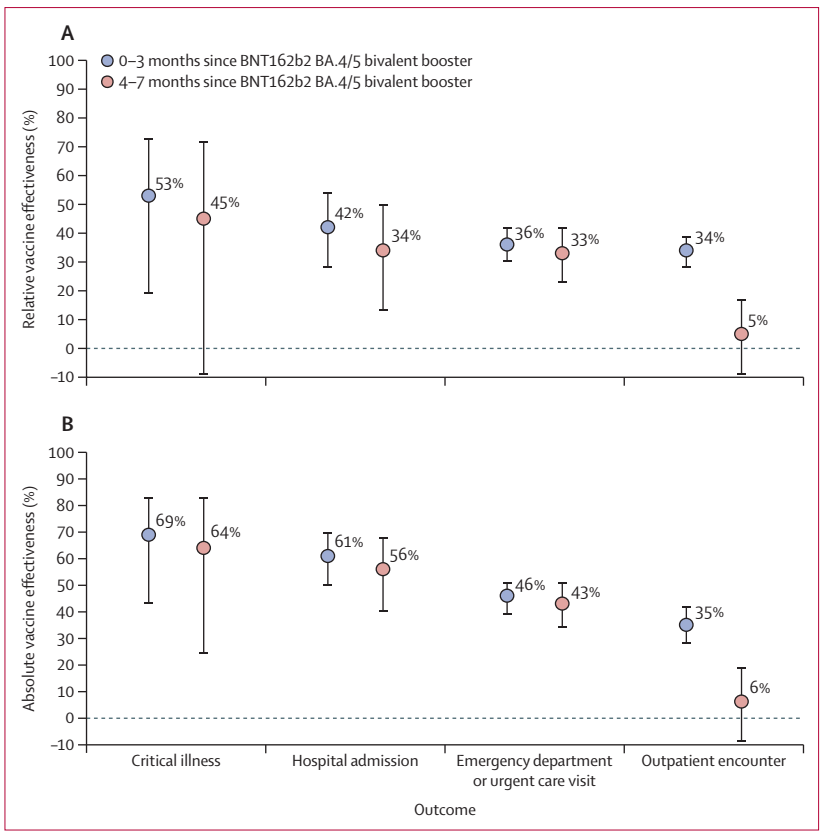

Figure 3: **Adjusted effectiveness of the BNT162b2 BA.4/5 bivalent booster by time since vaccination, compared with those vaccinated with at least two doses of original wild-type mRNA vaccine (A), and compared with unvaccinated individuals (B) by outcome, from Aug 31, 2022, to April 15, 2023**
Estimates adjusted for month of encounter, age, sex, race or ethnicity, BMI, Charlson comorbidity index, previous influenza vaccination, previous pneumococcal vaccination, previous health-care utilisation, and documentation of previous SARS-CoV-2 infection. Error bars represent 95% CIs.

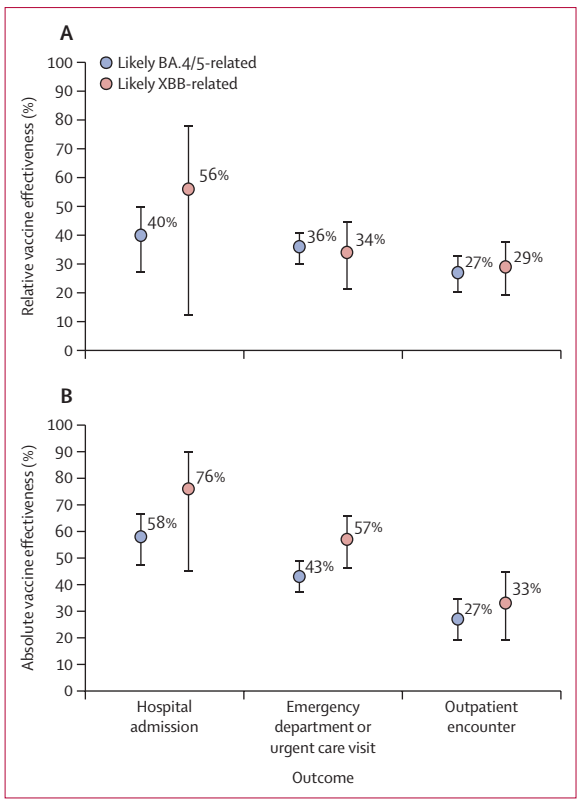

Figure 4: **Adjusted effectiveness of the BNT162b2 BA.4/5 bivalent booster compared with those vaccinated with at least two doses of original wild-type mRNA vaccine (A), and compared with unvaccinated individuals (B), and omicron sublineage, from Aug 31, 2022, to April 15, 2023**
Estimates adjusted for month of encounter, age, sex, race or ethnicity, BMI, Charlson comorbidity index, previous influenza vaccination, previous pneumococcal vaccination, previous health-care utilisation, and documentation of previous SARS-CoV-2 infection. Error bars represent 95% CIs. Confidence Intervals for vaccine effectiveness against critical illness not available for "Likely BA.4/5" category due to the small sample size, estimates were 100% for both absolute and relative vaccine effectiveness.

evidenced by overlapping confidence intervals. Among individuals who received four or five doses of wild-type vaccines only, absolute effectiveness was low (vaccine effectiveness of roughly 40% or lower) against all outcomes but was improved after a bivalent booster (appendix p 5). However, this direct comparison might not have fully accounted for potential differences in time since receipt of the last booster dose or differences in patient characteristics between the two groups (ie, individuals who were recommended to receive more than three wild-type doses were more likely to be at high risk of developing severe COVID-19).

Results from relative effectiveness analyses that stratified effectiveness by omicron sublineage (ie, BA.4/5-related *vs* XBB-related) showed comparable performance of a BNT162b2 BA.4/5 bivalent booster across sublineages (appendix p 6): effectiveness against hospital admission was 56% (95% CI 12–78) for XBB-related infections versus 40% (27–50) for BA.4/5-related infections; effectiveness against emergency department or urgent care visits was 34% (21–45) versus 36% (30-41); and effectiveness against outpatient encounters was 29% (19–38) versus 27% (20-33; figure 4; appendix p 6). The absolute effectiveness of a BNT162b2 BA.4/5 bivalent booster against XBB-related strains was also comparable to that against BA.4/5-related infections (figure 4; appendix p 6).

The likelihood of being infected with BA.4/5-related sublineages relative to XBB-related strains was similar for those with a bivalent booster when using unvaccinated individuals as the reference group (OR 0·44 [95% CI 0·09–2·19]) or when using those receiving at least two doses of the wild-type vaccine but not bivalent booster as the reference group (0·70 [0·16–3·09]). Waning of immunity following a bivalent booster was observed most prominently in the outpatient setting across both sublineages, was only evident in the emergency department or urgent care setting against XBB-related infections, and was not yet evident for hospital admission or critical illness outcomes, as 95% CIs between timepoints overlapped for this endpoint (appendix p 6).

Discussion

In this test-negative case–control study conducted in an adult population in a large US health-care system that was predominantly vaccinated with wild-type COVID-19 vaccines, the Pfizer–BioNTech BNT162b2 BA.4/5 bivalent booster improved protection against a range of COVID-19 outcomes, including critical illness, hospital admission, emergency department or urgent care visits, and outpatient encounters. During our study period (from September, 2022, to mid-April, 2023), protection against COVID-19 afforded by wild-type mRNA vaccines alone, for which most individuals had received their last dose at least 6 months ago, was low. Among those who received at least two doses of a wild-type mRNA vaccine, a BNT162b2 BA.4/5 bivalent booster improved protection against COVID-19-related critical illness by an additional 50% (95% CI 23–68), against hospital admission by an additional 39% (28–49), against emergency department or urgent care visits by an additional 35% (30–40), and against any in-person outpatient encounter by an additional 28% (22–33) among adults aged 18 years or older. These findings were consistent across both younger (<65 years) and older (≥65 years) adults and regardless of how many doses of wild-type COVID-19 vaccines were previously received. If this pattern continues year after year, the recent proposal by the FDA for an annual or seasonal COVID-19 vaccination programme targeted to the most recently circulating strains seems prudent, particularly for those at highest risk of severe outcomes, to ensure that protection is bolstered before the winter viral respiratory season.

Direct head-to-head comparisons of the effectiveness of bivalent boosters versus wild-type boosters are not available. Monitoring effectiveness in high-risk individuals over time will be crucial to help inform the FDA's current decision-making about whether certain high-risk groups might need more than one dose of updated, better-matched vaccines annually to ensure high levels of protection—especially against severe disease.

Our results are concordant with other preliminary studies describing the effectiveness of bivalent mRNA vaccines administered as a booster. Two published CDC reports previously showed that the effectiveness of a bivalent booster (compared to unvaccinated individuals) against outpatient illness and emergency department or urgent care visits was likely to be between 25% and 55%,[11,12] a range that was nearly identical to ours (approximately 29–45%; appendix p 4). Furthermore, the most recent data from the IVY Network presented by the CDC at the Vaccines and Related Biological Products Advisory Committee (VRBPAC) on Jan 26, 2023, showed that the BNT162b2 BA.4/5 bivalent booster had an effectiveness of 72% (95% CI 54–83) against hospital admission among immunocompetent adults aged 65 years or older[29]—an estimate that was generally similar to our results (vaccine effectiveness 59% [95% CI 46–70]; appendix p 3) in the same population and during a similar time period. The IVY network estimate included up to 3 months of follow-up compared with up to 7 months in our study, which might contribute to our estimate being slightly lower. Preliminary preprint data from the USA,[15] Israel,[16] and a study conducted in Denmark, Finland, Norway, and Sweden[17] have also confirmed the added benefit of bivalent vaccines, with point estimates in line with those reported by the CDC[11–13,29] and observed in our study. Our study provides relative and absolute vaccine-specific estimates for the BNT162b2 BA.4/5 bivalent vaccine across a range of COVID-19 outcomes that were all evaluated in the same setting and with the same methodology, which allows for better comparisons of vaccine effectiveness across outcomes.

Another important and novel finding was that improved protection after a bivalent booster was observed for the most recent omicron sublineages, including against BA.4/5-related and XBB-related illness, and there was no early evidence of reduced effectiveness against XBB-related sublineages, despite evidence that bivalent vaccines have lower neutralising activity against XBB than against earlier omicron subvariants.[6,20] These data confirm the findings of a preliminary report from the CDC showing that the effectiveness of a bivalent booster against testing positive for SARS-CoV-2 in the outpatient pharmacy setting was similar for XBB-related sublineages and earlier omicron subvariants.[18] Our study, however, adds XBB-specific estimates of effectiveness across a wider range of COVID-19 outcomes. Taken together, these findings suggest that neutralising antibody data are not a perfect correlate of protection, and that current BA.4/5-based bivalent boosters are providing sufficient early protection against XBB-related disease.

Although we observed waning effectiveness against outpatient COVID-19 illness 4–7 months after receipt of a bivalent booster, we did not observe waning effectiveness of a bivalent booster against more severe outcomes. Durability data beyond 6–7 months, however, could not be estimated. Historically, waning against more severe outcomes tends to occur later than that seen against less severe illness—usually more than 6 months after a booster dose.[30–32] Notably, other reports have highlighted early signs of waning effectiveness—even against severe outcomes—following a bivalent booster.[18,33–37] Given how antigenically distant XBB-related sublineages are compared with previous omicron strains,[38] this waning effectiveness should be continually monitored over time to inform upcoming decisions about the need for vaccine updates (ie, strain selection) and the administration of additional booster doses.

Like all observational research, our study has limitations. First, despite our use of a test-negative design and regression analyses to help mitigate against the potential for confounding due to differences in health-care seeking behaviour, proclivity to test, and

clinical or sociodemographic factors, some potential confounders were not included.[39] For example, those who choose to receive bivalent boosters might be more or less likely to take other precautions to reduce SARS-CoV-2 exposure, and we were unable to measure this directly. Therefore, our study might still be subject to unmeasured confounding. Second, although we restricted our COVID-19 outcomes to those that were related to acute respiratory infection and confirmed with a positive SARS-CoV-2 PCR test, it is possible that some of the encounters we classified as COVID-19-related were not. If this occurred frequently, however, it would probably bias vaccine effectiveness towards the null. Third, it is likely that we misclassified previous infection, as many infections are either undiagnosed or diagnosed at home and not reported. Thus, our effectiveness estimates should be interpreted as the additional protection that bivalent vaccines add in the context of widespread immunity and might partially explain why vaccine effectiveness estimates from the omicron period are generally lower than those observed early in the pandemic when most of the population had little or no immunity from SARS-CoV-2 infection. Furthermore, due to the high likelihood of previous infection, which might occur disproportionately among unvaccinated individuals, our results might be biased towards the null from depletion of susceptibles.[40] Fourth, a concern of studies with a test-negative design is the potential for collider bias, wherein conditioning analyses on testing can create spurious associations between the exposure and outcome of interest.[41] However, collider bias is most likely to arise in the context of ambulatory care settings, in which health-care seeking behaviour is causally associated with probability of testing, and is less likely to introduce bias in the inpatient or ICU setting, in which severe infection is more likely to be reported. Thus, we present a range of outcomes to inform the potential impact of BA.4/5-based bivalent boosters, including critical illness and hospital admission, and it is unlikely that unmeasured confounding alone explains our findings against severe COVID-19.

A fifth limitation is that because we relied primarily on SGTF status to identify omicron sublineages, we could not differentiate between XBB sublineages or generate XBB.1.5-specifc estimates, nor were we able to estimate differences in effectiveness between BA.4/5, BQ.1, and BQ.1.1 strains. Furthermore, vaccine effectiveness estimates for XBB-related hospital admission had wide confidence intervals and were limited by the small sample size. Finally, we were unable to evaluate the long-term durability of the BNT162b2 BA.4/5 bivalent vaccine; future studies will be required to carefully monitor the potential for waning of protection from BNT162b2 BA.4/5 bivalent vaccination over time, as new variants or omicron sublineages are likely to emerge in the months ahead.

In summary, protection conferred from wild-type vaccines waned considerably by the end of 2022—even against severe endpoints such as hospital admission. Although rates of hospital admission and deaths due to COVID-19 have not returned to peak levels despite waning immunity from wild-type vaccines, COVID-19 continues to cause a substantial amount of morbidity and mortality. For example, at the time of writing, approximately 200–300 deaths and 5000 hospital admissions due to COVID-19 still occur each day in the USA, with similar rates seen globally.[42] In the current study, relative effectiveness estimates confirmed a significant incremental benefit of receiving a BNT162b2 BA.4/5 bivalent dose compared with receiving only a wild-type mRNA series against a range of COVID-19 outcomes caused by the most recent omicron strains. The most substantial additional protection was observed against critical illness, up to 7 months after receipt of a BNT162b2 BA.4/5 bivalent booster, depending on the time since the last vaccine dose, age group, risk status, and omicron sublineage. Although the long-term durability of bivalent boosters is currently unknown, thus far early protection against XBB-related severe illness—which showed initial signs of immune escape and has since become predominant in the USA and other regions globally—appears intact.

Contributors

SYT, JMS, LP, LJ, and JMM conceived this study. JMS, TBF, VH, and FX conducted the analysis, had access to the raw data, and verified the data. SYT, JMS, JMM, and LP wrote the first draft of the protocol. SYT, LP, and JMM wrote the first draft of the manuscript. All authors contributed to the study design, drafting the protocol, and edited the manuscript for important intellectual content. All authors gave final approval of the version to be published and had final responsibility for the decision to submit the manuscript for publication.

Declaration of interests

SRV, LJ, LP, JMZ, and JMM are employees of and hold stock, or stock options, or both, in Pfizer. SYT, TBF, OAO, JMS, VH, FX, and BKA received research support from Pfizer during the conduct of this study that was paid directly to Kaiser Permanente Southern California. BKA received research support for work unrelated to this study, provided by Pfizer, Moderna, Dynavax, Seqirus, GlaxoSmithKline, and Genentech. JMS received research support from ALK, Dynavax, and Novavax for work unrelated to this study. TBF previously owned stock in Pfizer. SYT received research support from Genentech for work unrelated to this study. All other authors declare no competing interests.

Data sharing

Anonymised data that support the findings of this study can be made available from the investigative team under the following conditions: agreement to collaborate with the study team on all publications, provision of external funding for administrative and investigator time necessary for this collaboration, demonstration that the external investigative team is qualified and has documented evidence of training for human subjects protections, and agreement to abide by the terms outlined in data use agreements between institutions. Data requests should be made via email to the corresponding author.

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