

## **BNT162b2 XBB1.5-adapted Vaccine and COVID-19 Hospital Admissions and Ambulatory**

### **Visits in US Adults**

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## **KEY POINTS**

### **Questions**

Does receiving the BNT162b2 XBB1.5-adapted vaccine offer additional protection against COVID-19 hospital admission and ambulatory visits in US adults  $\geq 18$  years of age compared to not receiving an XBB1.5-adapted vaccine of any kind? Do older versions of COVID-19 vaccine still provide any protection compared to the unvaccinated?

### **Findings**

The BNT162b2 XBB1.5-adapted vaccine (Pfizer-BioNTech 2023–2024 formulation) provided significant additional protection against a range of COVID-19 outcomes during a period when XBB sub-lineages were predominant but JN.1 was also co-circulating and rapidly increasing in prevalence. Older versions of COVID-19 vaccines offered little, if any, additional protection compared to the unvaccinated, including against COVID-19 hospital admission, regardless of the number or type of prior doses received.

### **Meaning**

Our findings reaffirm current recommendations for broad age-based use of annually updated COVID-19 vaccines.

## **ABSTRACT**

### **Importance**

Data describing the early additional protection afforded by recently recommended XBB1.5-adapted COVID-19 vaccines are limited.

### **Objective**

We estimated the association between receipt of BNT162b2 XBB1.5-adapted vaccine (Pfizer-BioNTech 2023–2024 formulation) and medically attended COVID-19 outcomes among adults  $\geq 18$  years of age.

### **Design, Setting, and Participants**

We performed a test-negative case-control study to compare the odds of BNT162b2 XBB1.5-adapted vaccine receipt between COVID-19 cases and test-negative controls among adults in the Kaiser Permanente Southern California health system between October 11 and December 10, 2023. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were estimated from multivariable logistic regression models that were adjusted for patient demographic and clinical characteristics.

### **Exposure**

The primary exposure was receipt of BNT162b2 XBB1.5-adapted vaccine compared to not receiving an XBB1.5-adapted vaccine of any kind, regardless of prior COVID-19 vaccination or SARS-CoV-2 infection history. We also compared receipt of prior (non-XBB1.5-adapted) versions of COVID-19 vaccines to the unvaccinated to estimate remaining protection from older vaccines.

## **Main Outcomes and Measures**

Cases were those with a positive SARS-CoV-2 polymerase chain reaction test, and controls tested negative. Analyses were done separately for COVID-19 hospital admissions, emergency department (ED) and urgent care (UC) encounters, and outpatient visits.

## **Results**

Among 4232 cases and 19,775 controls with median age of 54 years, adjusted ORs for testing positive for SARS-CoV-2 among those who received BNT162b2 XBB1.5-adapted vaccine a median of 30 days ago (*vs* not having received an XBB1.5-adapted vaccine of any kind) were 0.37 (95% CI: 0.20–0.67) for COVID-19 hospitalization, 0.42 (0.34–0.53) for ED/UC visits, and 0.42 (0.27–0.66) for outpatient visits. Compared to the unvaccinated, those who had received only older versions of COVID-19 vaccines did not show significantly reduced risk of COVID-19 outcomes, including hospital admission.

## **Conclusions and Relevance**

Our findings reaffirm current recommendations for broad age-based use of annually updated COVID-19 vaccines given that (1) XBB1.5-adapted vaccines provided significant additional protection against a range of COVID-19 outcomes and (2) older versions of COVID-19 vaccines offered little, if any, additional protection, including against hospital admission, regardless of the number or type of prior doses received.

## Introduction

XBB and its sub-lineages have been the predominant circulating SARS-CoV-2 strains in the United States since January 2023.<sup>1</sup> XBB sub-lineages are antigenically and phylogenetically distinct from Omicron BA4 and BA5 sub-lineages that were predominant in late 2022.<sup>1</sup> Thus, on September 11, 2023, the US Food and Drug Administration authorized or approved updated monovalent mRNA COVID-19 vaccines targeting the XBB1.5 sub-lineage for individuals aged 6 months through 11 years of age and 12 years and older, respectively.<sup>2</sup> This included use of XBB1.5-adapted vaccines for all recommended doses, including primary series and booster doses.<sup>2</sup> XBB1.5-adapted vaccines were made broadly available in the United States on September 15, 2023, following Centers for Disease Control and Prevention (CDC) recommendations for use in all individuals aged 6 months and older in preparation for the winter respiratory virus season.<sup>3</sup> Studies evaluating the association between receipt of XBB1.5-adapted vaccines and the development of clinically relevant COVID-19 endpoints are needed.

## Methods

### *Design, Setting, and Participants*

Similar to our previous reports,<sup>4-8</sup> we performed a test-negative case-control study to compare the odds of receipt of a Pfizer-BioNTech BNT162b2 XBB1.5-adapted monovalent vaccine (2023–2024 formulation) between COVID-19 cases and test-negative controls. We included patients  $\geq 18$  years of age at Kaiser Permanente Southern California (KPSC) who were diagnosed with acute respiratory infection (ARI; **Table S1**) and tested for SARS-CoV-2 using polymerase chain reaction (PCR) during a hospital admission or emergency department (ED), urgent care (UC), or in-person outpatient encounter from October 10, 2023 through December 10, 2023. The

study start date corresponded to 14 days after the date that XBB1.5-adapted vaccines were made available in KPSC (i.e., September 25, 2023). During the study period, XBB sub-lineages were predominantly circulating. JN.1, however, which is a BA2.86 sub-lineage, also began co-circulating and rapidly increasing in prevalence after mid-November.<sup>1</sup>

Participants were required to have  $\geq 1$  year of health plan membership (allowing for a 31-day gap in membership to account for delays in membership renewal) to determine comorbidities and medical history. Encounters in which the patient had the following were excluded: (1) another positive SARS-CoV-2 test  $\leq 90$  days ago, (2) received any type of XBB1.5-adapted vaccine other than BNT162b2 XBB1.5-adapted vaccine, (3) received a XBB1.5-adapted vaccine  $\leq 2$  months after a prior COVID-19 dose, (4) received a BNT162b2 XBB1.5-adapted vaccine  $\leq 14$  days prior to the encounter, (5) received any other non-XBB1.5-adapted booster doses (e.g., BA.4/5-adapted bivalent or wild-type boosters) outside of CDC recommended dosing intervals (i.e., defined as receipt of any mRNA BA4.5 bivalent dose between August 31, 2022 and September 11, 2023 with  $\geq 8$  weeks [ $\geq 56$  days] since their most recent dose of original wild-type COVID-19 mRNA vaccine received and a minimal required interval of  $\geq 28$  days between a second and subsequent wild-type dose), (6) received nirmatrelvir/ritonavir or any other COVID-19 outpatient antiviral or monoclonal antibody (i.e., molnupiravir, remdesivir, bebtelovimab, bamlanivimab, casirivimab, cilgavimab, sotrovimab, tixagevimab) in the 30 days prior to a COVID-19 encounter, or (7) a hospital admission that, despite having an ARI diagnosis with a positive SARS-CoV-2 test, was determined to be likely unrelated to COVID-19 or clearly related to another cause based on medical chart review that was conducted by trained research staff who were blinded to vaccination status and later validated by a blinded physician investigator (BKA; **Supplemental Appendix**).

### *Outcomes*

Cases were those with a positive SARS-CoV-2 PCR test, and controls tested negative. SARS-CoV-2 PCR tests among cases and controls were restricted to those administered  $\leq 14$  days prior to the initial ARI encounter through  $\leq 3$  days after the encounter. Patients could contribute  $\geq 1$  event to the study if events were  $> 30$  days apart.

### *Exposures*

All members were eligible for COVID-19 vaccines at no cost based on FDA authorized or approved indications. KPSC EHRs captured all vaccinations administered within the health system. Records were supplemented with vaccine administration data from the California Immunization Registry, to which all healthcare providers are required by law to report COVID-19 vaccinations within 24 hours. As such, misclassification of vaccination status was unlikely. To be considered vaccinated, the dose had to occur  $> 14$  days before testing for SARS-CoV-2. For the primary analysis, COVID-19 outcomes were evaluated comparing individuals who received BNT162b2 XBB1.5-adapted vaccine to those who did not receive an XBB1.5-adapted vaccine of any kind (including the unvaccinated), regardless of prior COVID-19 vaccination or SARS-CoV-2 infection history. Additional analyses compared those who had received BNT162b2 XBB1.5-adapted vaccine to those who had received (1)  $\geq 1$  dose of BA.4/5-adapted bivalent vaccine but no XBB1.5-adapted vaccine of any kind, (2)  $\geq 3$  or  $\geq 2$  doses of original wild-type mRNA vaccine but no variant-adapted vaccines of any kind (e.g., XBB1.5-adapted or BA.4/5-adapted bivalent doses), and (3) the unvaccinated. Among those who did not receive an XBB1.5-adapted vaccine of any kind, we also evaluated the same COVID-19 outcomes comparing individuals who received  $\geq 1$  dose of BA.4/5-adapted bivalent vaccine or who

received  $\geq 3$  or  $\geq 2$  original wild-type COVID-19 vaccine doses without a bivalent vaccine of any kind to the unvaccinated. These comparisons were used to estimate remaining protection from prior non-XBB1.5-adapted vaccines (i.e., either BA.4/5-adapted or wild-type doses) during the study period.

### *Statistical Analysis*

Odds ratios (ORs) and 95% confidence intervals (CIs; based on the Wald method) were calculated from multivariable logistic regression models that included week of encounter, age (18–49, 50–64, and  $\geq 65$  years), sex (female, male), self-reported race/ethnicity (non-Hispanic Asian/Pacific Islander, non-Hispanic African-American/Black, Hispanic/Latinx, non-Hispanic White, other [including individuals who identified as American Indian or multiple or other race and ethnicity], and unknown), body mass index ( $< 18.5$ , 18.5–24.9, 25.0–29.9, 30.0–34.9,  $\geq 35.0$  kg/m<sup>2</sup>, and unknown), Charlson risk score (0, 1, 2, 3, and  $\geq 4$ ), 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), health-care utilization in the year before admission (i.e., number of hospital admissions and ED or outpatient visits), and documentation of previous SARS-CoV-2 infection confirmed by PCR or antigen test (ever vs never) for pre-delta, delta, and omicron periods. Missing values were treated as separate categories for all variables in all analyses. Analyses were done separately for hospital admissions, ED/UC encounters, and outpatient visits. Primary analyses were further stratified by age group (18–64 vs  $\geq 65$  years). In sensitivity analyses, we examined the impact on the primary analysis of including patients who received COVID-19 antiviral or monoclonal antibody treatment. Analyses were performed using SAS



version 9.4. This study was approved by the KPSC institutional review board which waived the requirement for informed consent.

## Results

Of 26,187 ARI encounters among adults  $\geq 18$  years of age with continuous enrollment and an eligible SARS-CoV-2 PCR test, 24,007 met study selection criteria (**Figure 1**; 2980 [12.4%] hospital admissions, 15,255 [63.5%] ED/UC, and 5624 [23.4%] outpatient visits). Median age was 54 (interquartile range: 37–70). Overall, 17.6% (4232 / 24,007) tested positive for SARS-CoV-2 and 6.6% (1583 / 24,007) received BNT162b2 XBB1.5-adapted vaccine. Of 4232 cases and 19,775 controls, 171 (4.1%) and 1412 (7.4%), respectively, received BNT162b2 XBB1.5-adapted vaccine (**Table 1**). 22,424 (93.4%) never received an XBB1.5-adapted COVID-19 vaccine of any kind and 2717 (11.3%) never received a COVID-19 vaccine of any kind. Among those who received BNT162b2 XBB1.5-adapted vaccine, median time since receipt of their most recent previous dose of COVID-19 vaccine was 363 days (range: 63–998). Overall, median time since receipt of an XBB1.5-adapted vaccine was 30 days (range: 14–73). Adjusted ORs for testing positive for SARS-CoV-2 among those who received a BNT162b2 XBB1.5-adapted vaccine (vs not having received an XBB1.5-adapted vaccine of any kind) were 0.37 (95% CI: 0.20–0.67) for COVID-19 hospital admission, 0.42 (0.34–0.53) for ED/UC visits, and 0.42 (0.27–0.66) for outpatient visits (**Figure 2, Table S2**). In stratified analyses, reductions in risk of testing positive for SARS-CoV-2 among those who received a BNT162b2 XBB1.5-adapted vaccine were similar regardless of comparison group, including those who received (1)  $\geq 1$  BA.4/5-adapted bivalent vaccine and no XBB1.5-adapted vaccine, (2)  $\geq 3$  or  $\geq 2$  doses of original wild-type vaccine without any variant-adapted boosters of any kind (e.g., BA.1-adapted or

BA.4/5-adapted bivalent vaccines or XBB1.5-adapted vaccines), and (3) the unvaccinated, across all settings of care (i.e., hospital admission and ED/UC or outpatient visits; **Figure 2, Table S2**).

Overall, results also appeared generally similar across age groups 18–64 and  $\geq 65$  years with a trend toward greater risk reduction for age  $\geq 65$  for outpatient encounters; however, CIs were wide for 18–64-year-olds which made age-group comparisons difficult (**Tables S2, S3**).

In sensitivity analyses, results were similar when patients who received antiviral or monoclonal antibody treatment in the 30 days prior to their COVID-19 encounter (n=1263) were included (**Table S4**). The most common reasons for hospital admission in cases that were excluded based on chart review (i.e., likely unrelated to COVID-19; n=198) were labor and delivery (13/198 [6.6%]), injuries requiring urgent medical care (10/198 [5.1%]), surgery/neurosurgery (32/198 [16.2%]), sepsis due to another etiology (e.g., urinary tract infection, bacteremia, or other infection; 41/198 [20.7%]), and medical conditions unrelated to possible COVID-19-associated conditions (e.g., bacterial infection without sepsis, malignancy, drug withdrawal, seizures: 93/198 [47.0%]).

Finally, compared to the unvaccinated, individuals who had not received an XBB1.5-adapted vaccine of any kind but had received older versions of COVID-19 vaccines (i.e.,  $\geq 1$  BA.4/5-adapted bivalent dose or  $\geq 3$  or  $\geq 2$  original wild-type doses and no variant-adapted vaccines of any kind) did not show significantly reduced risk of COVID-19 outcomes, including hospital admission, during the study period (**Figure 3**).

## Discussion

In this test-negative case-control study conducted in a large US healthcare system during the early part of the 2023–2024 viral respiratory season in the United States, compared to individuals

who did not receive a XBB1.5-adapted vaccine of any kind, those who received a BNT162b2 XBB1.5-adapted vaccine had a 63% (95%CI: 33–80%) reduced risk of COVID-19 hospital admission, 58% (47–66%) lower risk of COVID-19 ED/UC encounters, and 58% (34–73%) lower risk of in-person outpatient visits for COVID-19 after a median of 30 days since receipt of the XBB1.5-adapted dose. XBB sub-lineages were predominant during our study period, however, during the last several weeks of our study when many cases accrued, JN.1 was rapidly increasing in prevalence across the United States and in the State of California.<sup>1</sup> Preliminary data suggest that BA2.86 and JN.1 show signs of slightly increased immune evasion to XBB1.5-adapted vaccines, however, both strains are still neutralized by BNT162b2 XBB1.5-adapted vaccine.<sup>9,10</sup> Our results help confirm these early pre-clinical studies<sup>9,10</sup> by showing that XBB1.5-adapted vaccine provided additional protection against COVID-19 during a period of XBB and JN.1 co-circulation. However, the majority of cases in our analyses were likely XBB sub-lineages.

Consistent with previous reports of COVID-19 vaccine effectiveness,<sup>4-8</sup> estimated reductions in risk appeared higher for the more severe outcome of hospital admission across all comparison groups (OR point estimates 0.32–0.37) as compared to less severe outcomes like ED/UC and outpatient visits (ORs 0.40–0.57), although CIs overlapped. Importantly, BNT162b2 XBB1.5-adapted vaccine provided similar additional protection in adults regardless of age group and the number of prior COVID-19 vaccine doses received for all COVID-19 outcomes. This latter finding was consistent with our results suggesting that prior receipt of only older versions of COVID-19 vaccines (i.e., receipt of BA.4/5-adapted bivalent vaccine or  $\geq 3$  or  $\geq 2$  original wild-type doses but no XBB1.5-adapted vaccine) provided little, if any, current additional protection compared to the unvaccinated against COVID-19 outcomes, including hospital admission. Thus,

analogous to influenza, although older versions of COVID-19 vaccines once provided high levels of protection, the combination of waning vaccine-induced immunity and continuous SARS-CoV-2 strain evolution eventually renders prior versions of vaccines ineffective. This, in turn, warrants routine updates to COVID-19 vaccines—also like influenza—so long as SARS-CoV-2 continues to circulate and cause disease. For the week ending December 9, 2023, there were 23,432 new COVID-19 hospital admissions in the United States—the highest rate since last winter.<sup>11</sup> This still represents a large public health burden and is roughly three times higher than the number of new weekly influenza hospitalizations that occurred during the same period (7090);<sup>12</sup> albeit fewer than the approximately 150,000 weekly hospitalizations seen at the peak of the Omicron BA.1 wave.<sup>11</sup> Our findings help reaffirm current recommendations for broad age-based use of annually updated COVID-19 vaccines in the United States prior to likely winter peaks in disease activity.<sup>13</sup>

Uptake of XBB1.5-adapted vaccines in the United States to date has been low. As of December 22, 2023 only 19% and 37% of all adults  $\geq 18$  and  $\geq 65$  years of age, respectively, had received an XBB1.5-adapted vaccine.<sup>14</sup> Current COVID-19 vaccine coverage significantly lags that of seasonal influenza vaccines, despite both vaccines being made available during the autumn and winter, and current CDC guidelines that support co-administration of the two vaccines.<sup>15</sup>

Reasons for low COVID-19 vaccine uptake likely include reduced concern about COVID-19 in the general population over time and as pandemic declarations ended, annual COVID-19 vaccination not yet being seen as a “routine health activity,” confusion about risk level regarding COVID-19, and continued skepticism in some populations about the safety and effectiveness of mRNA vaccines.<sup>16</sup>

A recent preprint study showed that among adults  $\geq 65$  years of age in Denmark, receipt of an XBB1.5-adapted vaccine (90% of which were the BNT162b2 XBB1.5-adapted vaccine in the study population) led to a 75% (95%CI: 61–84%) reduced risk of COVID-19 hospital admission over an average follow-up time of 10 days compared to those who did not receive an XBB1.5-adapted vaccine<sup>17</sup>—an estimate that was comparable to ours, albeit slightly higher, against the same outcome and comparison group. However, this study had shorter follow-up time and included data only through the end of October, which was prior to the emergence and rapid growth of the JN.1 strain. Another recent preprint study conducted in the Netherlands also recently showed similar reductions in risk of hospital admission (71% [67–74%]) among adults  $\geq 60$  years of age who were previously vaccinated.<sup>18</sup> Our study helps confirm these early global findings but also describes the association between XBB1.5-adapted vaccine receipt and the development of COVID-19 across a broader range of outcomes and age groups, in a more diverse study population, and during a more recent time period that included when the JN.1 strain was rapidly increasing in prevalence in the United States.

Our study has limitations. Although we controlled for key sociodemographic and clinical characteristics, there may be residual confounding driven by unaccounted for differences in the likelihood of exposure or severity of SARS-CoV-2 infection between vaccinated and unvaccinated individuals. Although individuals who are more likely to get vaccinated against COVID-19 may also be more likely to seek care or testing for SARS-CoV-2, the test-negative design of our study helps mitigate against bias caused by differences in healthcare-seeking behavior—including the propensity to test.<sup>19-21</sup> We also controlled for prior healthcare utilization, age, and underlying comorbid illness to help mitigate the potential for healthy vaccinee bias. A second limitation is that median time since receipt of an XBB1.5-adapted

vaccine was only 30 days, and future studies are needed to evaluate durability of protection. In addition, although we know our study was conducted during a period when XBB sub-lineages were predominant, but JN.1 was also co-circulating and rapidly increasing in prevalence, we did not have genotype information available for all our cases, nor were we able to estimate sub-lineage-specific estimates. Thus, future studies describing the association between receipt of XBB1.5-adapted vaccines and development of strain-specific BA2.86 sub-lineage-related disease (e.g., JN.1) are needed. Another limitation is that there was likely misclassification of previous infections, particularly among those who did not seek testing at KPSC. If undocumented previous infection was more likely in unvaccinated individuals, for example, this could contribute to underestimation of vaccine protection. It remains possible that some healthcare encounters were “with COVID-19” rather than “for COVID-19,” and this could lead to underestimation of the protective effects of vaccination against medically attended disease. To help mitigate this bias, we (1) used medical record review to exclude hospital admissions that were unrelated to COVID-19, and (2) restricted our analyses to patients presenting with ARI for all outcomes.

In conclusion, individuals who did not receive an XBB1.5-adapted vaccine and had received only older versions of COVID-19 vaccines had little, if any, additional protection compared to the unvaccinated against COVID-19 endpoints, including hospital admission, regardless of the number or type of prior doses received. Receipt of a BNT162b2 XBB1.5-adapted vaccine, however, was associated with significantly reduced risk of developing a range of COVID-19 outcomes during the early part of the 2023–2024 viral respiratory season—with the strongest protective effects seen against hospital admission. These two findings help reaffirm current recommendations for broad age-based use of annually updated COVID-19 vaccines. Uptake of

this 2023–2024 formulation of COVID-19 vaccines, however, remains low, and targeted and tailored interventions to continuously improve annual COVID-19 uptake are warranted.

#### *Data statement*

Anonymized data that support the findings of this study may be made available from the investigative team in the following conditions: (1) agreement to collaborate with the study team on all publications, (2) provision of external funding for administrative and investigator time necessary for this collaboration, (3) demonstration that the external investigative team is qualified and has documented evidence of training for human subjects protections, and (4) agreement to abide by the terms outlined in data use agreements between institutions.

#### *Role of the Funding Source*

This study was sponsored by Pfizer. The study design was jointly developed by KPSC and Pfizer. KPSC collected and analyzed 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.

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TBF and JMS had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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### **Figure 1. Selection criteria**

ARI = acute respiratory infection. CDC = Centers for Disease Control and Prevention.

### **Figure 2. Risk of COVID-19 outcome among those who received BNT162b2 XBB1.5-adapted vaccine by comparison group, adults $\geq 18$ years of age**

CI = confidence interval. ED = emergency department; UC = urgent care. Models adjusted for week of encounter, age, sex, self-reported race/ethnicity, BMI, Charlson comorbidity index, prior SARS-CoV-2 infection, and utilization history (flu and pneumococcal vaccination, inpatient, ED, and outpatient encounters in prior year).

### **Figure 3. Risk of COVID-19 outcome among those who received only older (non-XBB1.5-adapted) versions of COVID-19 vaccines compared to the unvaccinated by vaccine regimen received, adults $\geq 18$ years of age**

CI = confidence interval. ED = emergency department; UC = urgent care. Models adjusted for week of encounter, age, sex, self-reported race/ethnicity, BMI, Charlson comorbidity index, prior SARS-CoV-2 infection, and utilization history (flu and pneumococcal vaccination, inpatient, ED, and outpatient encounters in prior year).

26187 ARI encounters among adults ≥18 years of age with continuous enrollment and a SARS-CoV-2 test  
3296 ARI hospital admissions  
16719 ARI emergency department or urgent care visits

157 encounters with positive SARS-CoV-2 ≤90 days ago excluded  
86 encounters with a XBB1.5-adapted vaccine other than BNT162b2 was received excluded  
12 encounters with a XBB1.5-adapted vaccine received ≤2 months after a prior COVID-19 dose  
658 encounters with a BNT162b2 XBB1.5-adapted vaccine received ≤14 days prior to the encounter  
4 encounters with any other non-XBB1.5-adapted booster doses (e.g., BA.4/5-adapted bivalent or wild-type boosters) received outside of CDC recommended dosing intervals  
1263 encounters with COVID-19 antiviral or monoclonal antibody treatment received in the 30 days prior to the encounter excluded

24007 final study population  
2980 ARI hospital admissions  
15255 ARI emergency department or urgent care visits  
5624 ARI in-person outpatient visits

4232 SARS-CoV-2 positive (cases)  
393 ARI hospital admissions  
2470 ARI emergency department or urgent care visits  
1223 ARI in-person outpatient visits

19755 SARS-CoV-2 negative (test-negative controls)  
2587 ARI hospital admissions  
12785 ARI emergency department or urgent care visits  
4401 ARI in-person outpatient visits

171 Received XBB1.5-adapted vaccine  
13 ARI hospital admissions  
96 ARI emergency department or urgent care visits

4061 Did not receive XBB-adapted vaccine of any kind  
380 ARI hospital admissions  
2374 ARI emergency department or urgent care visits

694 Received ≥1 dose of BA.4/5-adapted bivalent vaccine  
75 ARI hospital admissions  
389 ARI emergency department or urgent care visits

2042 Received ≥3 original wild-type COVID-19 vaccine doses without a variant-adapted vaccine of any kind (e.g., XBB1.5- or BA.4/5 bivalent-adapted)  
205 ARI hospital admissions  
1151 ARI emergency department or urgent care visits

2835 Received ≥2 original wild-type COVID-19 vaccine doses without a variant-adapted vaccine of any kind (e.g., XBB1.5- or BA.4/5 bivalent-adapted)  
348 ARI hospital admissions  
1648 ARI emergency department or urgent care visits

437 Unvaccinated  
42 ARI hospital admissions  
282 ARI emergency department or urgent care visits

1412 Received XBB1.5-adapted vaccine  
170 ARI hospital admissions  
870 ARI emergency department or urgent care visits

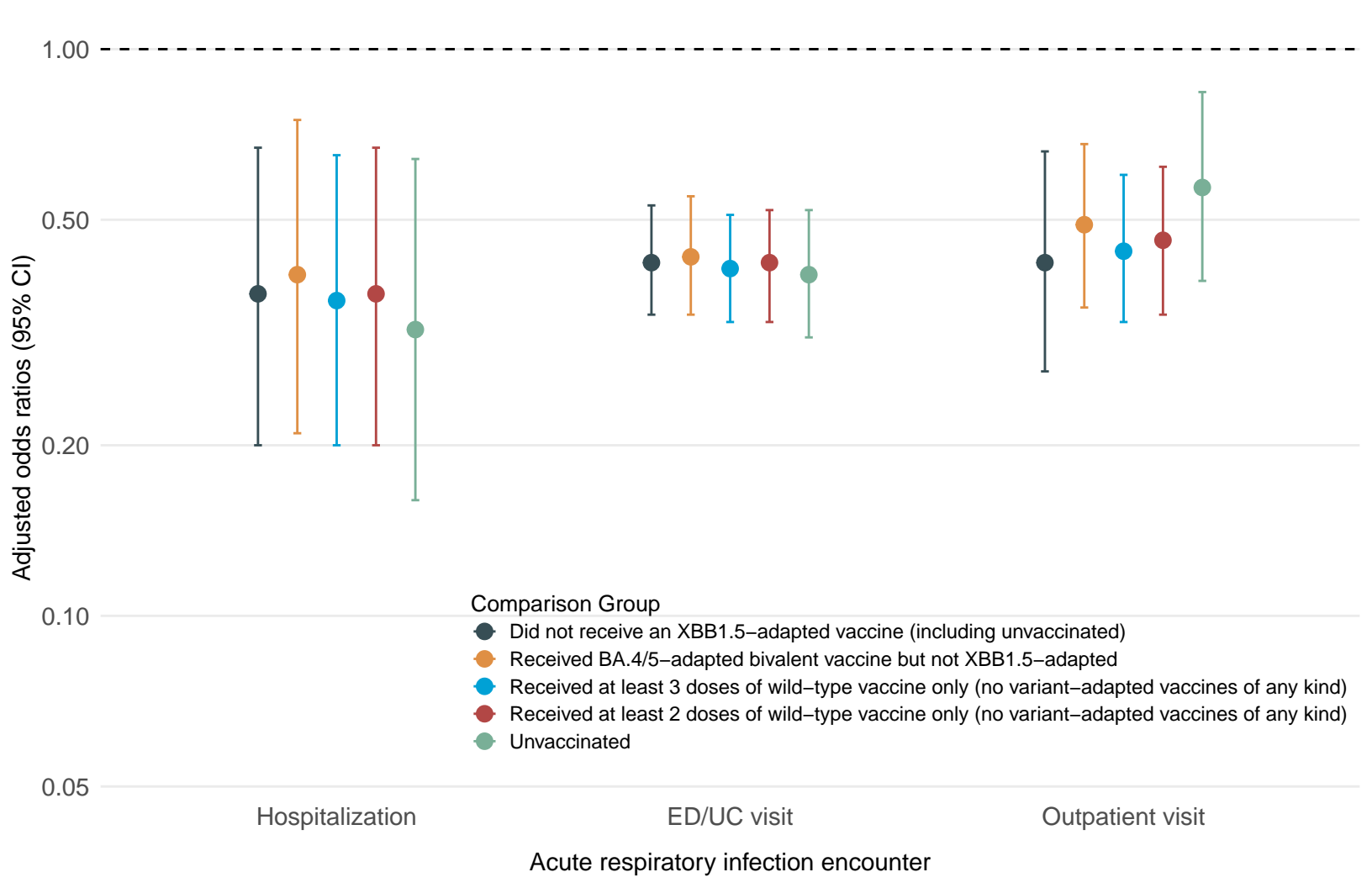
18361 Did not receive XBB-adapted vaccine of any kind  
2417 ARI hospital admissions  
11915 ARI emergency department or urgent care visits

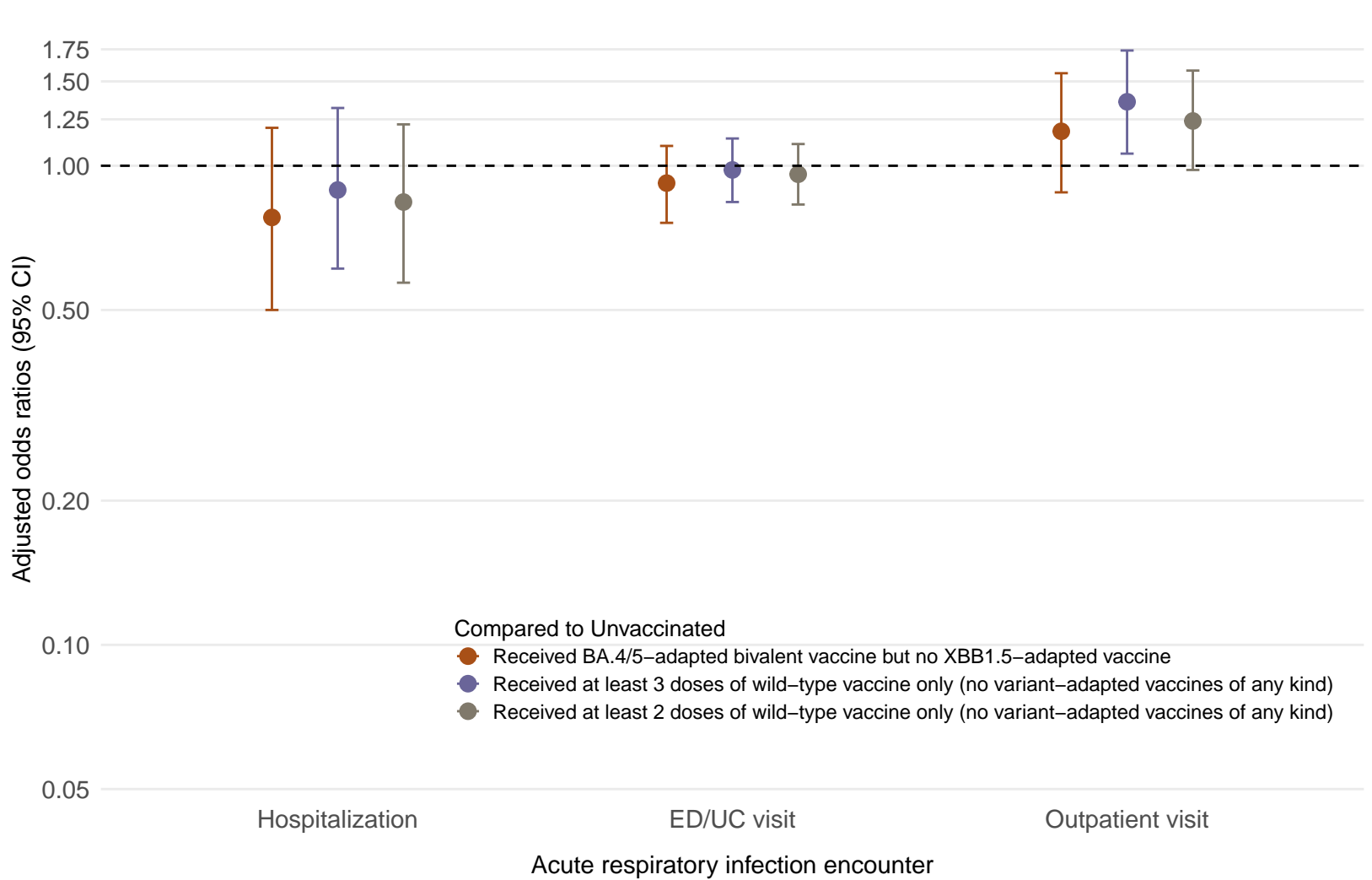
2913 Received ≥1 dose of BA.4/5-adapted bivalent vaccine  
482 ARI hospital admissions  
1755 ARI emergency department or urgent care visits

8410 Received ≥3 original wild-type COVID-19 vaccine doses without a variant-adapted vaccine of any kind (e.g., XBB1.5- or BA.4/5 bivalent-adapted)  
1190 ARI hospital admissions  
5326 ARI emergency department or urgent care visits

12539 Received ≥2 original wild-type COVID-19 vaccine doses without a variant-adapted vaccine of any kind (e.g., XBB1.5- or BA.4/5 bivalent-adapted)  
1609 ARI hospital admissions  
8157 ARI emergency department or urgent care visits

2280 Unvaccinated  
265 ARI hospital admissions  
1556 ARI emergency department or urgent care visits





**Table 1: Characteristics of Study Population**

Characteristic	Did not receive an XBB1.5-adapted vaccine of any kind	Received BNT162b2 XBB1.5-adapted vaccine	SARS-CoV-2 Positive	SARS-CoV-2 Negative	Total
<b>Total N</b>	22424	1583	4232	19775	24007
<b>Prior COVID-19 vaccination</b>					
Unvaccinated	2717 (12.1%)	0 (0%)	437 (10.3%)	2280 (11.5%)	2717 (11.3%)
1 original wild-type dose and no BA.4/5-adapted bivalent doses	713 (3.2%)	0 (0%)	95 (2.2%)	618 (3.1%)	713 (3.0%)
2 original wild-type doses and no BA.4/5-adapted bivalent doses	4922 (22.0%)	32 (2.0%)	797 (18.8%)	4157 (21.0%)	4954 (20.6%)
≥3 original wild-type doses and no BA.4/5-adapted bivalent dose	10452 (46.6%)	757 (47.8%)	2119 (50.1%)	9090 (46.0%)	11209 (46.7%)
≥1 BA.4/5-adapted bivalent doses	3620 (16.1%)	794 (50.2%)	784 (18.5%)	3630 (18.4%)	4414 (18.4%)
<b>Age in years at time of encounter</b>					
18–49	9962 (44.4%)	311 (19.6%)	1562 (36.9%)	8711 (44.1%)	10273 (42.8%)
50–64	5274 (23.5%)	294 (18.6%)	1020 (24.1%)	4548 (23%)	5568 (23.2%)
≥65	7188 (32.1%)	978 (61.8%)	1650 (39%)	6516 (33%)	8166 (34%)
<b>Sex</b>					
Female	13709 (61.1%)	885 (55.9%)	2601 (61.5%)	11993 (60.6%)	14594 (60.8%)
Male	8715 (38.9%)	698 (44.1%)	1631 (38.5%)	7782 (39.4%)	9413 (39.2%)
<b>Self-Reported Race / Ethnicity</b>					
Non-Hispanic African American/Black	2321 (10.4%)	251 (15.9%)	466 (11%)	2106 (10.6%)	2572 (10.7%)
Non-Hispanic Asian/Pacific Islander	2521 (11.2%)	150 (9.5%)	509 (12%)	2162 (10.9%)	2671 (11.1%)
Hispanic/Latinx	10340 (46.1%)	485 (30.6%)	1883 (44.5%)	8942 (45.2%)	10825 (45.1%)
Non-Hispanic White	970 (4.3%)	57 (3.6%)	171 (4%)	856 (4.3%)	1027 (4.3%)
Other/Unknown*	6272 (28%)	640 (40.4%)	1203 (28.4%)	5709 (28.9%)	6912 (28.8%)
<b>Encounter type</b>					
Hospital admission	2942 (13.1%)	186 (11.7%)	539 (12.7%)	2589 (13.1%)	3128 (13%)
Emergency department visit	6444 (28.7%)	424 (26.8%)	1286 (30.4%)	5582 (28.2%)	6868 (28.6%)
Urgent care visit	7845 (35%)	542 (34.2%)	1184 (28%)	7203 (36.4%)	8387 (34.9%)

Characteristic	Did not receive an XBB1.5-adapted vaccine of any kind	Received BNT162b2 XBB1.5-adapted vaccine	SARS-CoV-2 Positive	SARS-CoV-2 Negative	Total
In-person outpatient visit	5193 (23.2%)	431 (27.2%)	1223 (28.9%)	4401 (22.3%)	5624 (23.4%)
<b>Charlson comorbidity index</b>					
0	10562 (47.1%)	456 (28.8%)	1859 (43.9%)	9159 (46.3%)	11018 (45.9%)
1	4227 (18.9%)	285 (18%)	770 (18.2%)	3742 (18.9%)	4512 (18.8%)
2	2088 (9.3%)	227 (14.3%)	445 (10.5%)	1870 (9.5%)	2315 (9.6%)
3	1333 (5.9%)	157 (9.9%)	270 (6.4%)	1220 (6.2%)	1490 (6.2%)
≥4	4214 (18.8%)	458 (28.9%)	888 (21%)	3784 (19.1%)	4672 (19.5%)
<b>Body mass index (BMI; kg/m<sup>2</sup>)</b>					
Underweight (<18.5)	488 (2.2%)	18 (1.1%)	84 (2%)	422 (2.1%)	506 (2.1%)
Normal or healthy weight (18.5–24.9)	5038 (22.5%)	432 (27.3%)	993 (23.5%)	4477 (22.6%)	5470 (22.8%)
Overweight (25.0–29.9)	6737 (30%)	514 (32.5%)	1349 (31.9%)	5902 (29.8%)	7251 (30.2%)
Obese, class 1 (30.0–34.9)	5104 (22.8%)	363 (22.9%)	936 (22.1%)	4531 (22.9%)	5467 (22.8%)
Obese, class 2-3 (≥35.0)	4830 (21.5%)	251 (15.9%)	835 (19.7%)	4246 (21.5%)	5081 (21.2%)
Unknown	227 (1%)	5 (0.3%)	35 (0.8%)	197 (1%)	232 (1%)
<b>Prior documented positive SARS-CoV-2 PCR or antigen tests</b>					
Pre-delta era (March 1, 2020 – June 11, 2021)	2445 (10.9%)	88 (5.6%)	437 (10.3%)	2096 (10.6%)	2533 (10.6%)
Delta era (June 12, 2021 – December 20, 2021)	685 (3.1%)	24 (1.5%)	103 (2.4%)	606 (3.1%)	709 (3%)
Omicron era (December 21, 2021 – current)	6458 (28.8%)	412 (26%)	976 (23.1%)	5894 (29.8%)	6870 (28.6%)
<b>Healthcare Utilization (counts) in year prior to encounter</b>					
<b>Outpatient Visits</b>					
0	1216 (5.4%)	3 (0.2%)	174 (4.1%)	1045 (5.3%)	1219 (5.1%)
1	1291 (5.8%)	31 (2%)	220 (5.2%)	1102 (5.6%)	1322 (5.5%)
2–4	4349 (19.4%)	138 (8.7%)	748 (17.7%)	3739 (18.9%)	4487 (18.7%)
5–9	5616 (25%)	358 (22.6%)	1018 (24.1%)	4956 (25.1%)	5974 (24.9%)
≥10	9952 (44.4%)	1053 (66.5%)	2072 (49%)	8933 (45.2%)	11005 (45.8%)
<b>Emergency Department Visits</b>					
0	14255 (63.6%)	1018 (64.3%)	2729 (64.5%)	12544 (63.4%)	15273 (63.6%)



Characteristic	Did not receive an XBB1.5-adapted vaccine of any kind	Received BNT162b2 XBB1.5-adapted vaccine	SARS-CoV-2 Positive	SARS-CoV-2 Negative	Total
1	4173 (18.6%)	290 (18.3%)	789 (18.6%)	3674 (18.6%)	4463 (18.6%)
≥2	3996 (17.8%)	275 (17.4%)	714 (16.9%)	3557 (18%)	4271 (17.8%)
<b>Hospital Admissions</b>					
0	19405 (86.5%)	1351 (85.3%)	3701 (87.5%)	17055 (86.2%)	20756 (86.5%)
1	1895 (8.5%)	163 (10.3%)	339 (8%)	1719 (8.7%)	2058 (8.6%)
≥2	1124 (5%)	69 (4.4%)	192 (4.5%)	1001 (5.1%)	1193 (5%)
<b>Received influenza vaccine in year prior to encounter</b>					
No	11462 (51.1%)	81 (5.1%)	1888 (44.6%)	9655 (48.8%)	11543 (48.1%)
Yes	10962 (48.9%)	1502 (94.9%)	2344 (55.4%)	10120 (51.2%)	12464 (51.9%)
<b>Received pneumococcal vaccine in 5 years prior to encounter</b>					
No	17107 (76.3%)	1016 (64.2%)	3175 (75%)	14948 (75.6%)	18123 (75.5%)
Yes	5317 (23.7%)	567 (35.8%)	1057 (25%)	4827 (24.4%)	5884 (24.5%)

\* Race/ethnicity is reported by participant. “Other” includes individuals who self-identified as American Indian or “multiple” or “other” race and ethnicity. Race/ethnicity was included as a confounder due to associations with vaccination and COVID-19 healthcare seeking behavior and outcomes.