nature portfolio

Peer Review File

Effectiveness of BNT162b2 XBB vaccine in the US Veterans Affairs Healthcare System

Corresponding Author: Dr Aisling Caffrey

This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
This manuscript evaluated the effectiveness of XBB vaccines across time periods of XBB and JN.1 sub-lineage predominance among adults in a large US nationwide integrated healthcare system. Particularly, there is a scarcity of data on vaccine effectiveness against JN.1, which is urgently needed to inform regulators and public health policies. However, the current analyses were somewhat rough, and certain details require clearer elaboration.

When the authors mentioned VE, please refer to specific control, e.g. VE against emergency department visit.

Background
Please provide an overview of the utilization of COVID-19 vaccines in the United States, including the types of vaccines available and the distribution coverage of each type.

Methods
1.Setting and Participants: Line 65-66: Introduction of the US Veterans Affairs Healthcare System (VA) should include details such as the number of hospitals or clinics it covers, the size of its patient population, and any distinguishing characteristics compared to other healthcare systems. This could involve discussing the unique demographics served by the VA, such as military veterans, and any specific healthcare needs they may have.
2.Line 124-127, “In secondary analyses, we evaluated adjusted VE by time since BNT162b2 XBB vaccination ... assess the impact of potential waning of protection...We calculated adjusted VE estimates within 60 and 61–133 days since vaccination for the likely XBB and JN.1 time periods”
Was BNT162b2 XBB the final dose of COVID-19 vaccine administered to all participants before the acute respiratory illness (ARI) episode? Alternatively, prior to the ARI episode, did some individuals receive a different COVID-19 vaccine after receiving BNT162b2 XBB, while others did not? Furthermore, why was the cutoff value set at 60 days?
3.Clarify in the “Methods” section whether “Prior COVID-19 infection”, “Virtual visit (outpatient only)”, and “ICU admission (hospitalized only)” were classified as yes/no.
4.In Table 1, what are the definitions of "Area deprivation index" and "VA Frailty index"? How were they evaluated, and how did the authors obtain this information? Consider clarifying these details in the "Methods" section or a supplementary file.
5.Line 472-474 should be removed to Statistical Analyses section.

Results
1.Note the use of thousand separators and other bullet points in Figure 1.
2.Were there any individuals re-enrolled in the analysis? If so, how were they distributed between the case and control groups? This information should be annotated in Figure 1 and clarified in either the "Methods" or "Results" section.
3.Line 86-86, “Within each ARI outcome category, cases were those with a positive SARS-CoV-2 NAAT or RAT result, and controls were those who tested negative”, it seems that there were three independent control groups, you could consider reformatting table1 as following? Hospital admission ED/UC visit Outpatient visits. This format could provide a clearer visualization of the data and the comparison.

4.Table 1 appears lengthy; “Medical History” wasn’t adjusted in primary analysis, secondary analysis, or additional stratified VE analyses. Maybe authors could move data on "Medical History" to a supplementary file.
5.In Table 1, were the categories under "COVID vaccine status" mutually exclusive? Or were they simply categorized as

yes/no for each category?
6.Please provide specific details on the COVID vaccine status of participants, including the number of doses administered (1-dose, 2-dose, 3-dose, etc.), the type of vaccine (mRNA, protein subunit), and the brand of vaccine (Pfizer, Moderna, etc.).
7.Review Table 1 for consistency in the sums of categories under “Body mass index category” and “Area deprivation index”. Additionally, ensure that data on "never smoker" was included under "Smoking status".
8.Lines 152-156, “A higher proportion of those who received the XBB vaccine (compared to those who did not) were…”
Lines 152-156 contain inaccurate information. The 113,174 included participants were those “ARI episodes with corresponding SARS-CoV-2 test results”, rather than the entire or a representative (lack of evidence in current manuscript) population that received the XBB vaccine.
9.Line 172-174, “VE could not be calculated beyond 60 days of BNT162b2 XBB vaccination during the likely XBB period due to the small number of ARI episodes with a time since vaccination longer than 60 days during this time period”.
How many ARI episodes with a time since vaccination longer than 60 days during likely XBB period?
10.Line 470, specify in which variables were compared using Fisher’s Exact test.
11.Were ADI and VA-FI adjusted in the VE analysis?
12.Ensure consistency in decimal formatting throughout the manuscript and supplementary file.
13.Note the unclear vaccination status of participants in the manuscript, particularly regarding their completed vaccination schedule, for the VE analysis. Consider estimating VEs based on detailed vaccination course to provide clearer insights. Current analysis seems to be unmatched. It might be beneficial to add a matched analysis to enhance the robustness of the findings.
References:
•Tseng HF, Ackerson BK, Luo Y, Sy LS, Talarico CA, Tian Y, Bruxvoort KJ, Tubert JE, Florea A, Ku JH, Lee GS, Choi SK, Takhar HS, Aragones M, Qian L. Effectiveness of mRNA-1273 against SARS-CoV-2 Omicron and Delta variants. Nat Med. 2022 May;28(5):1063-1071. doi: 10.1038/s41591-022-01753-y.
•Gazit S, Saciuk Y, Perez G, Peretz A, Pitzer VE, Patalon T. Short term, relative effectiveness of four doses versus three doses of BNT162b2 vaccine in people aged 60 years and older in Israel: retrospective, test negative, case-control study. BMJ. 2022 May 24;377:e071113. doi: 10.1136/bmj-2022-071113.
•Huang Z, Xu S, Liu J, Wu L, Qiu J, Wang N, Ren J, Li Z, Guo X, Tao F, Chen J, Lu D, Sun X, Wang W. Effectiveness of inactivated and Ad5-nCoV COVID-19 vaccines against SARS-CoV-2 Omicron BA. 2 variant infection, severe illness, and death. BMC Med. 2022 Oct 20;20(1):400. doi: 10.1186/s12916-022-02606-8.

Discussion
1.Line 199, for the first reason of “observed reduction in VE during the likely JN.1 period”, could you please provide some references to support this point?
2.Could you elaborate on the results of the subgroup analysis? Specifically, it appears that vaccine effectiveness (VE) was higher in immunocompromised individuals compared to non-immunocompromised individuals for outpatient visits (based on immunocompromised status); VEs were also higher in obese individuals compared to non-obese individuals (based on obesity classification); and VE was higher in current or former smokers compared to non-smokers for hospitalization (based on smoking status).

Conclusions
Line 288-289, “BNT162b2 XBB vaccine was effective at preventing a range of COVID-19 outcomes during the 2023–2024 respiratory virus season”. I couldn't agree with this point until the authors address the questions raised above, including concerns about the representativeness, and providing a detailed vaccination course. Like in line 281-284, the authors mentioned that their findings may not be generalizable to the broader US population or globally, suggesting caution in drawing conclusions.

Reviewer #2

(Remarks to the Author)
I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Nature Communications initiative to facilitate training in peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.

Reviewer #3

(Remarks to the Author)
The authors describe an interesting study on vaccine effectiveness (VE) of the BNT162b2 XBB.1.5-adapted COVID-19 vaccine in a large population using a wealth of data. We were impressed by the number of confounding variables that was adjusted for, including receipt of influenza vaccination and pneumococcal vaccination. We also appreciate the extensive descriptive tables (table 1, supplemental table 2) that were included, which provide a valuable source of information for other researchers that may not have access to such detailed data. The study compares VE of the BNT162b2 XBB.1.5 vaccine during a period of XBB.1.5 dominance and a period of JN.1 dominance, which is also a valuable addition to the literature.

We have a few minor comments and suggestions.

Regarding the exclusion criteria as described in the methods,
1. The phrasing of exclusion criterion 5 and 7 is ambiguous, as ‘within x days’ could be misunderstood as ‘in the x days after’. We recommend writing ‘within x days prior to’.
2. Receiving COVID antivirals within 30 days before the ARI episode was a reason for exclusion many times (figure 1). Can

the authors explain why this occurred so frequently and how this may affect the (interpretation of the) results? For instance, if this was the reason for exclusion so often because persons were given antivirals at ARI encounters at lower levels of care and only the encounter at the highest level of care was included, could there be an association between receiving antivirals in the 30 days prior to the ARI episode and vaccination status (e.g. through age)? How may this have influenced the study results?
3. Receiving an XBB vaccine other than BNT162b2 was a common reason for exclusion. Were Pfizer and Moderna vaccines administered more or less randomly in the US, or was there an association between type of vaccine and patient characteristics that may have influenced the results?

Results: To provide context to the reader, we suggest including a figure depicting BNT162b2 vaccine uptake and the number of ARI episodes over time and indicating the XBB, XBB/JN.1 and JN.1 study periods.

In the second paragraph of the discussion, although we agree that the study suggests that the observed reduction in VE during the likely JN.1 period was not driven by waning, we suggest removing the phrase 'for three reasons'. We think the third reason described is the most compelling and the other two only support the overall argument. We also recommend phrasing the second reason less strongly, because, although confidence intervals overlap, we think that waning of around 10% in only 60 days (table 2) amounts to more than 'only very modest waning'.

The discussion mentions (p11) that there still may have been residual confounding by unmeasured factors. This is indeed unavoidable, but considering the impressive number of confounders that was adjusted for, could the authors be more specific what type of unmeasured confounders (social, behavioral?) they have in mind?

Figure 1: It would be better to replace 'Pfizer XBB.1.5-adapted vaccine' by 'BNT162b2 XBB.1.5-adapted vaccine' and 'recieved' by 'received'.

Reviewer #4

(Remarks to the Author)
I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Nature Communications initiative to facilitate training in peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.

Version 1:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
I agree with the authors that "nearly all individuals in the US have some level of pre-existing immunity and it is now well accepted that there is waning of both infection- and vaccine-induced immunity over time," but I think the variables "the number of doses administered (1-dose, 2-dose, 3- dose, etc.) and COVID vaccine status (authors listed)" are important in evaluating vaccine effectiveness (VE). The current results of VEs of XBB.1.5-adapted vaccines in the paper are not clear. If the authors have collected this information, perhaps they could include a stratified analysis by specific vaccination history in the supplementary files."

Reviewer #2

(Remarks to the Author)

Reviewer #3

(Remarks to the Author)
our concerns have been addressed and we recommend accepting this revised manuscript for publication

Reviewer #4

(Remarks to the Author)
I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Nature Communications initiative to facilitate training in peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.

Response to the Reviewers

Authors response: Thank you for considering a revised version of our manuscript after paying due diligence to the comments of the Editor and Reviewers. We have responded to all comments and queries in a point-by-point response. Our revisions to the manuscript are shown with track changes in the manuscript that we uploaded. Additionally, a clean copy of the updated manuscript without track changes is uploaded.

We appreciate the opportunity to make improvements and clarifications to our manuscript. We believe we have fully addressed all of the comments and we greatly appreciate the improvements in our manuscript as a result.

- We have complied with the *Nature Communications* formatting instructions.
- We have complied with the 'Sex and Gender Equity in Research – SAGER – guidelines'. As indicated in in the reporting summary, sex was collected in our study of existing health records from the Veterans Affairs Healthcare System. The database does not indicate whether sex is self-reported or assigned, which we have specified in the footnote of Table 1. Sex was controlled for in our multivariable analyses, as specified in the footnote of Table 2.

- We have completed the following checklists:
  Editorial policy checklist:
  https://www.nature.com/documents/nr-editorial-policy-checklist.pdf

  Reporting summary:
  https://www.nature.com/documents/nr-reporting-summary.pdf

- A Data Availability section is present in the manuscript.

- The ORCID of the corresponding author has been linked.

REVIEWER COMMENTS

Reviewer #1 (Remarks to the Author):

This manuscript evaluated the effectiveness of XBB vaccines across time periods of XBB and JN.1 sub-lineage predominance among adults in a large US nationwide integrated healthcare system. Particularly, there is a scarcity of data on vaccine effectiveness against JN.1, which is urgently needed to inform regulators and public health policies. However, the current analyses were somewhat rough, and certain details require clearer elaboration.

When the authors mentioned VE, please refer to specific control, e.g. VE against emergency department visit.

Authors response: Thank you for these comments. We have clarified details of our analyses as recommended by the reviewers. Additionally, we have revised the manuscript to clearly indicate vaccine effectiveness against hospitalization, emergency department / urgent care (ED/UC) visits, and outpatient visits.

Background
Please provide an overview of the utilization of COVID-19 vaccines in the United States, including the types of vaccines available and the distribution coverage of each type.

Authors response: We added an overview of the COVID-19 vaccines currently available in the United States (US) (*please see first paragraph of the Background section*). There are 3 COVID-19 vaccines available in the US, that have all been updated to target the SARS-CoV-2 XBB.1.5 sub-lineage. As of the authorization dates of these updated 2023-2024 COVID-19 vaccines, older versions that target the BA.4/BA.5 variants and/or the ancestral SARS-CoV-2 strain were no longer authorized for use in the United States.

As the utilization of COVID-19 vaccines in the United States has already been extensively described in previous work (*please see references below*), we refrained from restating the findings of these studies.

Ioannou G.N., Green P., Locke E.R., Berry K. Factors associated with early receipt of COVID-19 vaccination and adherence to second dose in the Veterans Affairs healthcare system. *PLoS ONE.* 2021;16(12)
Ioannou GN, Locke ER, Green PK, Berry K. Comparison of Moderna versus Pfizer-BioNTech COVID-19 vaccine outcomes: A target trial emulation study in the U.S. Veterans Affairs healthcare system. EClinicalMedicine. 2022 Mar 5;45:101326.
Young-Xu Y, Korves C, Roberts J, et al. Coverage and Estimated Effectiveness of mRNA COVID-19 Vaccines Among US Veterans. *JAMA Netw Open.* 2021;4(10):e2128391.
Bajema KL, Dahl RM, Prill MM, et al. Effectiveness of COVID-19 mRNA Vaccines Against COVID-19–Associated Hospitalization — Five Veterans Affairs Medical Centers, United States, February 1–August 6, 2021. MMWR Morb Mortal Wkly Rep 2021;70:1294–1299.

Methods
1.Setting and Participants: Line 65-66: Introduction of the US Veterans Affairs Healthcare System (VA) should include details such as the number of hospitals or clinics it covers, the size of its patient population, and any distinguishing characteristics compared to other healthcare systems. This could involve discussing the unique demographics served by the VA, such as military veterans, and any specific healthcare needs they may have.

Authors response: We have added details about the VA Healthcare system (*please see Methods Section, Settings and Participants, first paragraph)*. The VA Healthcare system is the largest integrated healthcare system in the US, with over 9 million enrolled Veterans and over 1,300 health care facilities nationwide, including 172 VA Medical Centers (hospitals) and 1,138

outpatient clinics. As mentioned in the limitations paragraph, Veterans are generally older with a higher prevalence of underlying medical conditions than in the general US population.

2.Line 124-127, “In secondary analyses, we evaluated adjusted VE by time since BNT162b2 XBB vaccination ... assess the impact of potential waning of protection...We calculated adjusted VE estimates within 60 and 61–133 days since vaccination for the likely XBB and JN.1 time periods”

Was BNT162b2 XBB the final dose of COVID-19 vaccine administered to all participants before the acute respiratory illness (ARI) episode? Alternatively, prior to the ARI episode, did some individuals receive a different COVID-19 vaccine after receiving BNT162b2 XBB, while others did not? Furthermore, why was the cutoff value set at 60 days?

Authors response: The objective of our study was to estimate the effectiveness of the BNT162b2 XBB.1.5-adapted vaccine in preventing COVID-19-related hospitalizations, emergency department and urgent care visits, and outpatient visits, compared to individuals who did not receive any XBB-adapted vaccine.

It's important to note that the BNT162b2 XBB vaccine was not necessarily the last dose of COVID-19 vaccine administered to all patients before their acute respiratory infection (ARI) episode. Individuals who did not receive the BNT162b2 XBB vaccine might have been either not up to date with current vaccination recommendations or completely unvaccinated.

We have clarified in the Methods section (*please see Exposure, first paragraph*) that the group not exposed to the BNT162b2 XBB vaccine included those who were either not up to date with their vaccinations or were unvaccinated.

For those who did receive an XBB-adapted vaccine, they had to have received the BNT162b2 XBB vaccine specifically. They could not have received any other XBB vaccine, nor could they have received a different vaccine after the BNT162b2 XBB vaccination.

We have updated the Background section to clarify vaccination recommendations from the Centers for Disease Control and Prevention (CDC) (*please see last sentence of the first paragraph)*. In the US, individuals aged 12 years and older are considered up to date with their COVID-19 vaccinations once they have received a single dose of an updated XBB vaccine, regardless of their prior vaccination history, according to CDC recommendations.

The cutoff value was set at 60 days since previous vaccine effectiveness studies of XBB vaccines against symptomatic COVID-19 also used 60 days as the cutoff for time since vaccination (*please see reference below*). Additionally, in our study, the median time since receipt of the XBB vaccine was approximately 60 days (54 days). Typically, vaccine waning does not begin until at least 10 to 12 weeks after vaccination. We have added a citation for the use of the 60-day cutoff in the Methods section (*please see Statistical Analyses, second to last*

paragraph).

Gelles R, Ciesla AA, Mak J, et al. "Early Estimates of Updated 2023–2024 (Monovalent XBB.1.5) COVID-19 Vaccine Effectiveness Against Symptomatic SARS-CoV-2 Infection Attributable to Co-Circulating Omicron Variants Among Immunocompetent Adults — Increasing Community Access to Testing Program, United States, September 2023–January 2024." MMWR Morb Mortal Wkly Rep 2024;73:77–83.

3.Clarify in the “Methods” section whether “Prior COVID-19 infection”, “Virtual visit (outpatient only)”, and “ICU admission (hospitalized only)” were classified as yes/no.

Authors response: We have made these clarifications (*please see Table 1 footnotes*).

4.In Table 1, what are the definitions of "Area deprivation index" and "VA Frailty index"? How were they evaluated, and how did the authors obtain this information? Consider clarifying these details in the "Methods" section or a supplementary file.

Authors response: We have added these definitions and references (*please see Table 1 footnotes*).

5.Line 472-474 should be removed to Statistical Analyses section.

Authors response: We have moved these lines to the Statistical Analyses section (*please see second paragraph*).

Results
1.Note the use of thousand separators and other bullet points in Figure 1.

Authors response: We have formatted the Figure as per formatting guidelines and we defer to the Editor as to whether the Figures should be further revised.

2.Were there any individuals re-enrolled in the analysis? If so, how were they distributed between the case and control groups? This information should be annotated in Figure 1 and clarified in either the "Methods" or "Results" section.

Authors response: In the Methods section, we state that “patients could contribute more than one ARI episode to the study if the episodes were more than 30 days apart” *(Methods section, Settings and Participants, paragraph 2)*. We have added this footnote to Figure 1, as well as the number of cases and controls with multiple events to Figure 1 and the first paragraph of the Results section. Additionally, we have added a Supplemental Figure 1, which indicates study timeframes for assessing exclusion, exposure, covariates and acute respiratory infection episodes.

3.Line 86-86, “Within each ARI outcome category, cases were those with a positive SARS-CoV-

2 NAAT or RAT result, and controls were those who tested negative", it seems that there were three independent control groups, you could consider reformatting table1 as following? Hospital admission ED/UC visit Outpatient visits. This format could provide a clearer visualization of the data and the comparison.

Authors response: To clarify, Table 1 presents the aggregate SARS-CoV-2 positive cases and SARS-CoV-2 negative controls. Multivariable analyses were conducted separately for each ARI outcome category: hospitalization, ED/UC visits, and outpatient visits. Within each of these categories, cases were individuals with a positive SARS-CoV-2 NAAT or RAT result, and controls were those who tested negative. We have added supplemental tables of demographics and clinical characteristics for cases and controls for each VE outcome (*please see Supplemental Tables 3, 4, and 5*).

4.Table 1 appears lengthy; "Medical History" wasn't adjusted in primary analysis, secondary analysis, or additional stratified VE analyses. Maybe authors could move data on "Medical History" to a supplementary file.

Authors response: We have moved "Medical History" from Table 1 to the supplemental material as recommended (*please see Supplemental Table 2)*.

5.In Table 1, were the categories under "COVID vaccine status" mutually exclusive? Or were they simply categorized as yes/no for each category?

Authors response: The categories under "COVID vaccine status" were categorized as present or absent for each category. We have clarified this in the footnotes of Table 1.

6.Please provide specific details on the COVID vaccine status of participants, including the number of doses administered (1-dose, 2-dose, 3-dose, etc.), the type of vaccine (mRNA, protein subunit), and the brand of vaccine (Pfizer, Moderna, etc.).

Authors response: Thank you for your comment and for highlighting the need for more detailed information on the COVID-19 vaccination status of participants. We acknowledge the importance of considering these variables in understanding vaccine effectiveness. However, given the diverse vaccination and infection histories of participants, stratifying by the number of doses, type, and brand of vaccine would significantly complicate the analysis and interpretation of our results. Nearly all individuals in the US have some level of pre-existing COVID-19 immunity stemming from prior vaccination, prior infection, or in many cases, both. Accounting for a full immunologic history is becoming less feasible each year, and COVID-19 vaccine effectiveness will need to transition to an influenza model, where each update to the vaccine will be evaluated without regard to immunologic history. This approach mirrors real world vaccine recommendations and uptake, where the updated vaccine is recommended regardless of prior vaccine or infection history. Additionally, the waning immunity observed over time suggests that the specific details of previous vaccinations might have a reduced impact on the outcomes assessed in our study. Previous work has demonstrated that the VE of prior vaccinations on

symptomatic COVID-19 infections wanes to 0% by about 6 months (*please see reference below*).

In response to your suggestion, we have revised the manuscript (*please see the second limitations paragraph)* to include the following explanation: " Due to heterogeneity in both the number of previous COVID-19 vaccinations received and vaccine manufacturer of previous vaccinations, we did not conduct stratified analyses by specific vaccination history. The impact of specific COVID-19 vaccination history on our results is likely limited given that nearly all individuals in the US have some level of pre-existing immunity and it is now well accepted that there is waning of both infection- and vaccine-induced immunity over time."

Ciesla AA, Wiegand RE, Smith ZR, Britton A, Fleming-Dutra KE, Miller J, Accorsi EK, Verani JR, Shang N, Derado G, Pilishvili T, Link-Gelles R. Effectiveness of Booster Doses of Monovalent mRNA COVID-19 Vaccine Against Symptomatic Severe Acute Respiratory Syndrome Coronavirus 2 Infection in Children, Adolescents, and Adults During Omicron Subvariant BA.2/BA.2.12.1 and BA.4/BA.5 Predominant Periods. Open Forum Infect Dis. 2023 Apr 13;10(5):ofad187. doi: 10.1093/ofid/ofad187.

7.Review Table 1 for consistency in the sums of categories under “Body mass index category” and “Area deprivation index”. Additionally, ensure that data on "never smoker" was included under "Smoking status".

Authors response: Thank you, we have made these updates to the Table.

8.Lines 152-156, “A higher proportion of those who received the XBB vaccine (compared to those who did not) were…”
Lines 152-156 contain inaccurate information. The 113,174 included participants were those “ARI episodes with corresponding SARS-CoV-2 test results”, rather than the entire or a representative (lack of evidence in current manuscript) population that received the XBB vaccine.

Authors response: We have clarified that these comparisons were among those with ARI episodes and corresponding SARS-CoV-2 test result.

9.Line 172-174, “VE could not be calculated beyond 60 days of BNT162b2 XBB vaccination during the likely XBB period due to the small number of ARI episodes with a time since vaccination longer than 60 days during this time period”.
How many ARI episodes with a time since vaccination longer than 60 days during likely XBB period?

Authors response: There was only 1 hospitalization, 4 ED/UC visits, and no outpatient visits over 60 days since XBB vaccination during the likely XBB period.

10.Line 470, specify in which variables were compared using Fisher’s Exact test.

Authors response: We have revised this statement, as no variables were compared using Fisher's Exact test.

11.Were ADI and VA-FI adjusted in the VE analysis?

Authors response: We adjusted for the variables listed in the footnote of Table 2. We did not adjust for ADI and VA-FI as we selected variables for adjustment *a priori* based on previous literature.

12.Ensure consistency in decimal formatting throughout the manuscript and supplementary file.

Authors response: Thank you, we have reviewed all the Tables and Figures throughout the manuscript and supplemental material for consistency, reporting one decimal for percentages, three decimals for p-values, and no decimals for vaccine effectiveness.

13.Note the unclear vaccination status of participants in the manuscript, particularly regarding their completed vaccination schedule, for the VE analysis. Consider estimating VEs based on detailed vaccination course to provide clearer insights. Current analysis seems to be unmatched. It might be beneficial to add a matched analysis to enhance the robustness of the findings.

Authors response: Thank you, please see our response to Item 6 above which addresses this comment.

References:
•Tseng HF, Ackerson BK, Luo Y, Sy LS, Talarico CA, Tian Y, Bruxvoort KJ, Tubert JE, Florea A, Ku JH, Lee GS, Choi SK, Takhar HS, Aragones M, Qian L. Effectiveness of mRNA-1273 against SARS-CoV-2 Omicron and Delta variants. Nat Med. 2022 May;28(5):1063-1071. doi: 10.1038/s41591-022-01753-y.
•Gazit S, Saciuk Y, Perez G, Peretz A, Pitzer VE, Patalon T. Short term, relative effectiveness of four doses versus three doses of BNT162b2 vaccine in people aged 60 years and older in Israel: retrospective, test negative, case-control study. BMJ. 2022 May 24;377:e071113. doi: 10.1136/bmj-2022-071113.
•Huang Z, Xu S, Liu J, Wu L, Qiu J, Wang N, Ren J, Li Z, Guo X, Tao F, Chen J, Lu D, Sun X, Wang W. Effectiveness of inactivated and Ad5-nCoV COVID-19 vaccines against SARS-CoV-2 Omicron BA. 2 variant infection, severe illness, and death. BMC Med. 2022 Oct 20;20(1):400. doi: 10.1186/s12916-022-02606-8.

Discussion
1.Line 199, for the first reason of "observed reduction in VE during the likely JN.1 period", could you please provide some references to support this point?

Authors response: Thank you for providing those references, which demonstrate despite differences in speed of waning based on the specific COVID-19 vaccine administered, doses administered, and SARS-CoV-2 variant targeted, waning typically does not begin until after at least week 10 to 12 weeks. We have noted this in the manuscript (*please see Discussion section, paragraph 2*) and added these citations (*citations #32-#34*).

2.Could you elaborate on the results of the subgroup analysis? Specifically, it appears that vaccine effectiveness (VE) was higher in immunocompromised individuals compared to non-immunocompromised individuals for outpatient visits (based on immunocompromised status); VEs were also higher in obese individuals compared to non-obese individuals (based on obesity classification); and VE was higher in current or former smokers compared to non-smokers for hospitalization (based on smoking status).

Authors response: Discussion of our subgroup analyses have been added, as well as supporting citations (*please see Discussion section, 3rd to last paragraph and citations #12, #43, #44*).

Conclusions
Line 288-289, “BNT162b2 XBB vaccine was effective at preventing a range of COVID-19 outcomes during the 2023–2024 respiratory virus season”. I couldn't agree with this point until the authors address the questions raised above, including concerns about the representativeness, and providing a detailed vaccination course. Like in line 281-284, the authors mentioned that their findings may not be generalizable to the broader US population or globally, suggesting caution in drawing conclusions.

Authors response: The reviewer is correct that the US Veteran population is generally older and has a higher prevalence of underlying medical conditions compared to the general US population. These factors may place US Veterans at a higher risk of COVID-19 hospitalization, making research on VE in this population particularly important.

We have addressed the concerns regarding details of previous vaccinations in our previous responses and have added a description of the VA Healthcare System to further support our conclusions. Additionally, we acknowledge that our findings may not be fully generalizable to the broader US population or globally, as mentioned in our second limitations paragraph.

Reviewer #2 (Remarks to the Author):

I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Nature Communications initiative to facilitate training in peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.

Authors response: Thank you for reviewing our manuscript. We have addressed all of the reviewer comments.

Reviewer #3 (Remarks to the Author):

The authors describe an interesting study on vaccine effectiveness (VE) of the BNT162b2 XBB.1.5-adapted COVID-19 vaccine in a large population using a wealth of data. We were impressed by the number of confounding variables that was adjusted for, including receipt of influenza vaccination and pneumococcal vaccination. We also appreciate the extensive descriptive tables (table 1, supplemental table 2) that were included, which provide a valuable source of information for other researchers that may not have access to such detailed data. The study compares VE of the BNT162b2 XBB.1.5 vaccine during a period of XBB.1.5 dominance and a period of JN.1 dominance, which is also a valuable addition to the literature.

Authors response: Thank you for noting the strengths of this important work, including the large study population, strong and rich data source based on the VA electronic health record, detailed descriptive and supplemental tables, and data during the periods of XBB.1.5 dominance and JN.1 dominance.

We have a few minor comments and suggestions.

Regarding the exclusion criteria as described in the methods,
1. The phrasing of exclusion criterion 5 and 7 is ambiguous, as ‘within x days’ could be misunderstood as ‘in the x days after’. We recommend writing ‘within x days prior to’.

Authors response: We have reworded exclusion criteria 5 and 7 as recommended to improve clarity (*please see the Methods section, Settings and Participants, second paragraph*).

2. Receiving COVID antivirals within 30 days before the ARI episode was a reason for exclusion many times (figure 1). Can the authors explain why this occurred so frequently and how this may affect the (interpretation of the) results? For instance, if this was the reason for exclusion so often because persons were given antivirals at ARI encounters at lower levels of care and only the encounter at the highest level of care was included, could there be an association between receiving antivirals in the 30 days prior to the ARI episode and vaccination status (e.g. through age)? How may this have influenced the study results?

Authors response: Thank you for raising this important point. Receiving COVID antivirals within 30 days before the ARI episode was indeed a common reason for exclusion, as shown in Figure 1. As our study did not intend to assess the combined effectiveness of vaccination and antivirals, we only included those not treated with antivirals. These methods have been used by others assessing vaccine effectiveness (*please see reference below*).

The frequent exclusion due to prior antiviral use might be influenced by several factors, including the clinical practice of prescribing antivirals to high-risk individuals, such as our Veteran population, who are often older and have multiple comorbid conditions.

To address this concern, we acknowledge that the exclusion of individuals who received antivirals might affect the representativeness of our study population, as those who received antivirals are likely to have different health profiles compared to those who did not. Consequently, this could influence the generalizability of our findings. We have added this consideration to the end of the second limitations paragraph.

Tartof SY, Slezak JM, Frankland TB, et al. BNT162b2 XBB1.5-adapted Vaccine and COVID-19 Hospital Admissions and Ambulatory Visits in US Adults. medRxiv. 2023:2023.12.24.23300512. doi:10.1101/2023.12.24.23300512

3. Receiving an XBB vaccine other than BNT162b2 was a common reason for exclusion. Were Pfizer and Moderna vaccines administered more or less randomly in the US, or was there an association between type of vaccine and patient characteristics that may have influenced the results?

Authors response: In the US, "there is no preferential recommendation for the use of any one COVID-19 vaccine over another when more than one licensed or authorized, recommended, and age-appropriate vaccine is available," per the CDC (https://www.cdc.gov/coronavirus/2019-ncov/vaccines/stay-up-to-date.html). The VA is the largest national, comprehensive healthcare system in the US and has administered both mRNA vaccines, Pfizer and Moderna, to a large proportion of its enrollees. The decision to administer either the Pfizer or Moderna vaccine was typically made at the VA medical center level and often varied over time. We are not aware of any associations between type of vaccine administered and patient characteristics that may have influenced the results.

Results: To provide context to the reader, we suggest including a figure depicting BNT162b2 vaccine uptake and the number of ARI episodes over time and indicating the XBB, XBB/JN.1 and JN.1 study periods.

Authors response: We have included a figure as recommended by the reviewer (*please see Supplemental Figure 2)*.

In the second paragraph of the discussion, although we agree that the study suggests that the observed reduction in VE during the likely JN.1 period was not driven by waning, we suggest removing the phrase 'for three reasons'. We think the third reason described is the most compelling and the other two only support the overall argument. We also recommend phrasing the second reason less strongly, because, although confidence intervals overlap, we think that waning of around 10% in only 60 days (table 2) amounts to more than 'only very modest waning'.

Authors response: We have removed the phrase 'for three reasons' and phrased the second reason less strongly, as "modest waning" (*please see the Discussion section, second paragraph)*.

The discussion mentions (p11) that there still may have been residual confounding by unmeasured factors. This is indeed unavoidable, but considering the impressive number of confounders that was adjusted for, could the authors be more specific what type of unmeasured confounders (social, behavioral?) they have in mind?

Authors response: Thank you for raising this important point. Potential unmeasured confounders could include social and behavioral factors that were not captured in our dataset. For instance, variations in health-seeking behavior and adherence to public health recommendations could influence both vaccination status and COVID-19 outcomes. We have updated the manuscript accordingly (*please see the Discussion section, first limitations paragraph)*.

Figure 1: It would be better to replace 'Pfizer XBB.1.5-adapted vaccine' by 'BNT162b2 XBB.1.5-adapted vaccine' and 'recieved' by 'received'.

Authors response: Thank you, we made these changes to Figure 1 as recommended.

Reviewer #4 (Remarks to the Author):

I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Nature Communications initiative to facilitate training in peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.

Authors response: Thank you for reviewing our manuscript. We have addressed all of the reviewer comments.

Response to the Reviewers

REVIEWER COMMENTS
Reviewer #1 (Remarks to the Author):

I agree with the authors that “nearly all individuals in the US have some level of pre-existing immunity and it is now well accepted that there is waning of both infection- and vaccine-induced immunity over time,” but I think the variables “the number of doses administered (1-dose, 2-dose, 3- dose, etc.) and COVID vaccine status (authors listed)” are important in evaluating vaccine effectiveness (VE). The current results of VEs of XBB.1.5-adapted vaccines in the paper are not clear. If the authors have collected this information, perhaps they could include a stratified analysis by specific vaccination history in the supplementary files.”

Authors response: As requested by the reviewer and editor, we conducted stratified analyses by previous COVID-19 vaccination (one or more doses of BA.4/5-adapted bivalent vaccine, 3 or more doses of original wild-type mRNA but no bivalent-adapted vaccines). Our Methods (Page 15 of track changes version), Results (Page 7 of track changes version), and Discussion (Page 9 of track changes version) sections, and Supplemental Information (Pages 39 and 40) have been updated accordingly.

Due to insufficient sample size (cell sizes <5), we were not able to conduct stratified analyses for 1 dose of original wild-type mRNA but no bivalent-adapted vaccines, or non-mRNA but no original wild-type mRNA or bivalent-adapted vaccines. Additionally, stratified analyses for 2 doses of original wild-type mRNA but no bivalent-adapted vaccines, and no original wild-type mRNA or bivalent-adapted or non-mRNA vaccines produced wide confidence intervals (>75 for all outcomes) due to very low sample sizes (cell sizes of 5 and 8). As these VE estimates were unstable, these results are not reported in the revised Supplemental Information.

Reviewer #3 (Remarks to the Author):

our concerns have been addressed and we recommend accepting this revised manuscript for publication

Authors response: Thank you for reviewing our revised manuscript.

Reviewer #4 (Remarks to the Author):

I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Nature Communications initiative to facilitate training in peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.

Authors response: Thank you for reviewing our revised manuscript.