PEER REVIEW HISTORY

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Medicine. The paper was subsequently accepted for publication at BMJ Medicine.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Comparative effectiveness of the monovalent XBB.1.5-containing covid-19 mRNA vaccine: a target trial emulation using registry data across three Nordic countries
AUTHORS	Andersson, Niklas; Thiesson, Emilia; Pihlström, Nicklas; Perälä, Jori; Faksová, Kristýna; Gram, Mie; Poukka, Eero; Leino, Tuija; Ljung, Rickard; Hviid, Anders

VERSION 1 - REVIEW

REVIEWER NAME	Reviewer 1
REVIEWER AFFILIATION	
REVIEWER CONFLICT OF INTEREST	None
DATE REVIEW RETURNED	14-Jun-2024

GENERAL COMMENTS	Andersson and colleagues have used national record-linkage to construct a cohort study to assess the effectiveness of the monovalent XBB.1.5 vaccine recommended in the autumn-winter of 2023-24 in population 65 years or older, in Finland, Sweden and Denmark. Authors have used target trial emulation, a robust methodology that has been used extensively in the assessment of COVID-19 vaccines. Moreover, one of the strengths of the study is that they provide absolute risk differences, an impact estimate of great relevance for policy makers. The article is clear and well written. I send a few comments that I consider could improve the quality of the work. Authors have explained with great detail the matching procedure. One point that is not addressed but is normally included in target trial emulations is whether for the analysis of subperiods (i.e. discarding X time since the beginning of follow-up) they used all individuals on follow-up on that date or only complete pairs that remained on follow-up. If they have done the first option, because of unequal distribution of events and other reasons for censoring, the population in which the analysis of those sub-periods is based is no longer balanced by matching factors, and therefore results cannot be considered properly adjusted for these variables. To maintain the matching (and confounding adjustment), they should use only pairs in which both members are still on follow-up at day 8 (for the main analysis), or at days in which they start contributing to any of the groups in Figure 2, or on the day when the BA.2.86 period starts to be assessed (and possible others?). It would be essential information to include the number of individuals on follow-up and number of events in the survival curves in Figure 1.

	Regarding the management of competing events, the approach proposed by the authors, in practical terms, mean that those experiencing the competing event are kept in the risk set as immortal. This is one valid approach but then results need to be interpreted as the effectiveness of the vaccine in a hypothetical world were no one died. Moreover, because overall death is generally associated with vaccination (this has been observed for influenza and COVID-19), the management of these competing events is delicate. Authors could improve the credibility of their results by including a sensitivity analysis where individuals experiencing the competing event are censored free of event. With regards to generalizability of results to populations different to the ones included in this study, in the discussion, authors should highlight that these are estimates among the fraction of the population 65+ years who had received already 4 vaccine doses on 1 October 2023. Other populations with different background level of previous immunisations may not expect the effect seen in this work. In that sense, could authors add which proportion of all population 65+ fulfilled the elegibility criteria of this study? Maybe add it in the flowchart? One other eligibility criteria is no prior hospital admission related to covid-19. What is the time framework of this? Since the beginning of the pandemic? In the last X months? Please add. If this is since the beginning of the pandemic also would be good to know what proportion of population exited the eligible group due to this criterion and comment on what it means for generalizability. Regarding the interpretation of results, I do think that differences in point estimates by previous number of doses and by period of predominance of XBB or BA.2.86 should be highlighted in the text, despite the wide confidence intervals. Also, in line 30 of page 12, regarding the difference in effectiveness by variant it says "… and this potential difference was also not reflected in the absolute risk estimates". It is strange that while incidence seems lower in the BA.2.86 period and effectiveness is also lower, the absolute number of cases averted by vaccination should be also lower in the BA.2.86 period. Is there any explanation for the lack of difference in absolute terms? Minor comments Authors have decided to call their estimate "comparative" effectiveness. This is not so usual, why not "relative" effectiveness or just "effectiveness"? All estimates of effectiveness are comparative by nature. In the introduction, authors state "evaluations of the vaccine effectiveness with respect to the prevention of severe covid.19, however, are rare". Please explain what "rare" means in this context and give examples? In the last sentence of the introduction (line 31): "… with 12 weeks of follow-up", I think it should be, "to a maximum of 12 weeks" or "up to 12 weeks", because not all individuals had exactly 12 weeks of follow-up since it depended on the timing of vaccination. In the first Methods subheading: study data sources, design and cohort" is there a word missing? "cohort specification" or something like that? Where there many health-care personnel in this cohort of 65+ people? Can Sweden extend the follow-up period for the next submission, to match the study period of the other two countries? It would be relevant to rule out that differences by variants or waning is not due to different populations contributing. Page 10 line 23 says "3-three week".

REVIEWER NAME	Wang, Xiaofeng
REVIEWER AFFILIATION	Cleveland Clinic
REVIEWER CONFLICT OF INTEREST	None
DATE REVIEW RETURNED	14-Jun-2024

GENERAL COMMENTS	Review Report on "Comparative effectiveness of the monovalent XBB.1.5-containing COVID-19 mRNA vaccine across three Nordic countries" The paper evaluates the effectiveness of the monovalent XBB.1.5-containing COVID-19 mRNA vaccine in reducing COVID-19 related hospital admissions and deaths among individuals aged 65 and older across Denmark, Finland, and Sweden. Using a target trial emulation approach, the study compares outcomes between vaccinated individuals and matched non-recipients over a 12-week period during autumn and winter 2023-2024. This study provides useful evidence on the effectiveness of the monovalent XBB.1.5-containing COVID-19 mRNA vaccine in reducing severe outcomes among older adults across three Nordic countries. While the study's strengths include its large cohort size and the use of target trial emulation, it lacks novelty. Similar studies (Huiberts et al., Hansen et al., Lin et al.) have already published comparable findings and conclusions on this topic. My specific comments are as follows: Strengths: 1. Multiple Country Study and Large Cohort: The inclusion of data from three Nordic countries and a large cohort of 1,867,448 matched pairs enhances the generalizability and robustness of the findings. The large sample size provides substantial statistical power to detect differences in outcomes and allows for comprehensive subgroup analyses. 2. Target Trial Emulation: The use of target trial emulation for the observational study design is a significant strength. This method attempts to mimic the conditions of a randomized controlled trial (RCT), thereby reducing biases typically associated with observational studies. Weaknesses: 1. Antiviral Treatment Effects: Omission of Key Treatments: The study does not consider the effects of antiviral treatments such as Paxlovid and Lagevrio, which are crucial in preventing severe outcomes of COVID-19. Ignoring these treatments could lead to an overestimation or underestimation of the vaccine's effectiveness. It is essential to include data on the usage of these antivirals and adjust for their effects in the analysis to accurately assess the vaccine's true effectiveness. Comparison to Existing Literature: Studies like Lin et al. (2024) have demonstrated the significant impact of antiviral treatments on severe COVID-19 outcomes. The omission of these treatments in the current study limits the comprehensiveness and accuracy of its

	findings. 2. Confounding Variables: Lack of Comprehensive Confounding Control: There is limited discussion and adjustment for potential confounding variables, such as region of residency, socio-economic factors, and variations in healthcare access. These factors can significantly influence the outcomes of COVID-19 hospitalizations and deaths. Existing Literature Comparison: Huiberts et al. (2024) and Hansen et al. (2024) have shown the importance of adjusting for a wide range of confounders to accurately estimate vaccine effectiveness. The current study could enhance its robustness by incorporating a more comprehensive set of confounding variables. 3. Lack of Novel Insights: The conclusions of this study align with those reported in other studies, such as Huiberts et al. (2024), Hansen et al. (2024), and Lin et al. (2024). The study does not provide new insights into vaccine effectiveness beyond what has already been established. 5. Meta-Analysis and Heterogeneity: Potential Variations Across Countries/regions: The study combines country-specific estimates using random-effects meta-analysis but does not adequately address potential heterogeneity between countries. Reporting and discussing the heterogeneity measures (e.g., I^2 statistics) would provide more insight into the consistency of the findings across different settings. Reference: Huiberts, A.J., Hoeve, C.E., de Gier, B., Cremer, J., van der Veer, B., de Melker, H.E., van de Wijgert, J.H., van den Hof, S., Eggink, D. and Knol, M.J., 2024. Effectiveness of Omicron XBB. 1.5 vaccine against infection with SARS-CoV-2 Omicron XBB and JN. 1 variants, prospective cohort study, the Netherlands, October 2023 to January 2024. Eurosurveillance, 29(10), p.2400109. Hansen, C.H., Moustsen-Helms, I.R., Rasmussen, M., Søborg, B., Ullum, H. and Valentiner-Branth, P., 2024. Short-term effectiveness of the XBB. 1.5 updated COVID-19 vaccine against hospitalisation in Denmark: a national cohort study. The Lancet Infectious Diseases, 24(2), pp.e73-e74. Lin, D.Y., Huang, S., Milinovich, A., Duggal, A. and Wang, X., 2024. Effectiveness of XBB. 1.5 vaccines and antiviral drugs against severe outcomes of omicron infection in the USA. The Lancet Infectious Diseases, 24(5), pp.e278-e280.

VERSION 1 – AUTHOR RESPONSE

COMMENTS FROM REVIEWERS

REVIEWER: 1

1) Andersson and colleagues have used national record-linkage to construct a cohort study to assess the effectiveness of the monovalent XBB.1.5 vaccine recommended in the autumn-

winter of 2023-24 in population 65 years or older, in Finland, Sweden and Denmark. Authors have used target trial emulation, a robust methodology that has been used extensively in the assessment of COVID-19 vaccines. Moreover, one of the strengths of the study is that they provide absolute risk differences, an impact estimate of great relevance for policy makers. The article is clear and well written. I send a few comments that I consider could improve the quality of the work.

Authors have explained with great detail the matching procedure. One point that is not addressed but is normally included in target trial emulations is whether for the analysis of subperiods (i.e. discarding X time since the beginning of follow-up) they used all individuals on follow-up on that date or only complete pairs that remained on follow-up. If they have done the first option, because of unequal distribution of events and other reasons for censoring, the population in which the analysis of those sub-periods is based is no longer balanced by matching factors, and therefore results cannot be considered properly adjusted for these variables. To maintain the matching (and confounding adjustment), they should use only pairs in which both members are still on follow-up at day 8 (for the main analysis), or at days in which they start contributing to any of the groups in Figure 2, or on the day when the BA.2.86 period starts to be assessed (and possible others?).

Response: We thank the reviewer for the kind review and the many useful comments and suggestions. We appreciated this well-thought-out reviewer question. With our design, the matching of pairs, as the reviewer correctly argues, is completed at day 8 (start of follow-up) as we match on this date. To make this fully clear for readers, we have modified the following sentence.

“Individuals receiving an XBB.1.5-containing vaccine dose during the study period (1 October 2023 to 21 April 2024) were matched on day 8 after the day of vaccination (after 1 week; to ensure full immunisation) with individuals who had not received an additional dose up until and including this day.” (Methods, page 6)

2) It would be essential information to include the number of individuals on follow-up and number of events in the survival curves in Figure 1.

Response: We thank the reviewer for this suggestion. In response to this comment, we have included the numbers of events and individuals at-risk during follow-up in supplementary table S5 (i.e., we suggest including these numbers in the form of a supplementary table to allow more space for details that would be difficult to include in Figure 1 as it is already a quite large figure).

3) Regarding the management of competing events, the approach proposed by the authors, in practical terms, mean that those experiencing the competing event are kept in the risk set as immortal. This is one valid approach but then results need to be interpreted as the effectiveness of the vaccine in a hypothetical world were no one died. Moreover, because overall death is generally associated with vaccination (this has been observed for influenza and COVID-19), the management of these competing events is delicate. Authors could improve the credibility of their results by including a sensitivity analysis where individuals experiencing the competing event are censored free of event.

Response: As suggested, we have included a sensitivity analysis where we compute the effectiveness estimates based on cumulative incidences obtained from the Kaplan-Meier estimator (please see Supplementary Table S6). Results were comparable to those obtained using the Aalen-Johansen estimator.

4) With regards to generalizability of results to populations different to the ones included in this study, in the discussion, authors should highlight that these are estimates among the fraction of the population 65+ years who had received already 4 vaccine doses on 1 October 2023. Other populations with different background level of previous immunisations may not expect the effect seen in this work. In that sense, could authors add which proportion of all population 65+ fulfilled the elegibility criteria of this study? Maybe add it in the flowchart?

Response: We thank the reviewer for this comment. In response to this reviewer comment, we have modified the following sentence and added a flow chart presenting the number of individuals enrolled and excluded during the construction of the study cohort (please see supplementary figure S3).

“Accordingly, these results may only indirectly support evaluations within populations not represented in the analyses (e.g., individuals younger than 65 years old, having received less than 4 covid-19 vaccine doses before receiving the XBB.1.5-containing vaccine, or previously hospitalised for covid-19).” (Discussion, page 14).

Please note that we constructed our study population to resemble the population targeted for vaccination with the XBB.1.5-containing vaccine during autumn and winter 2023-24 in Nordic countries. Given the high population uptake of prior covid-19 vaccination rollout, the majority within the population of those aged ≥65 years would have been recommended and received at least four covid-19 vaccine doses before the study start. This can now be appreciated from supplementary figure S2 where it is shown that 77% of our 65+-year-old populations (3,956,478 of 5,115,835 individuals) had received at least four covid-19 vaccine doses as of the study start (1 October 2023).

5) One other eligibility criteria is no prior hospital admission related to covid-19. What is the time framework of this? Since the beginning of the pandemic? In the last X months? Please add. If this is since the beginning of the pandemic also would be good to know what proportion of population exited the eligible group due to this criterion and comment on what it means for generalizability.

Response: We have modified the respective sentences in the Methods and Discussion sections and included a flow chart of the construction of the study cohort (supplementary figure S3) accordingly.

“We specified the following eligibility criteria, which were assessed at the start of the study period: age ≥65 years, having country residency (to ensure a linkable identifier), having no prior hospital admissions related to covid-19 at any time, and having previously received ≥four covid-19 vaccine doses (of AZD1222, BNT162b2, or mRNA-1273 vaccines only [AZD1222 as part of the primary vaccination course only]); to construct a cohort representative of the general population targeted for vaccination with the XBB.1.5-containing vaccine during autumn and winter 2023-2024 as per the national covid-19 vaccination strategies.” (Methods, page 5)

“Accordingly, these results may only indirectly support evaluations within populations not herein studied (e.g., individuals younger than 65 years old, having received less than 4 covid-19 vaccine doses before receiving the XBB.1.5-containing vaccine, or previously hospitalised for covid-19).” (Discussion, page 14).

6) Regarding the interpretation of results, I do think that differences in point estimates by previous number of doses and by period of predominance of XBB or BA.2.86 should be highlighted in the text, despite the wide confidence intervals. Also, in line 30 of page 12,

regarding the difference in effectiveness by variant it says "… and this potential difference was also not reflected in the absolute risk estimates". It is strange that while incidence seems lower in the BA.2.86 period and effectiveness is also lower, the absolute number of cases averted by vaccination should be also lower in the BA.2.86 period. Is there any explanation for the lack of difference in absolute terms?

Response: We thank the reviewer for this comment, and we agree that these results are also important findings. We have modified the sentence accordingly to help readers interpret these findings, stratifying the calendar period according to the sublineage prevailing.

"While our results similarly tended toward slightly higher comparative vaccine effectiveness during the XBB- rather than the BA.2.86-sublineage predominance period—more so for covid-19 related hospital admission than death—the difference in the absolute risk difference, however, was small with largely overlapping 95% confidence intervals. Differences could be explained by differences in background transmission rates during the sublineages predominance periods and/or susceptibility to developing severe disease (e.g., frailer) between individuals contributing to the earlier (XBB-sublineage period) than the later (BA.2.86-sublineage period) follow-up period. Notably, any indirect comparison of the comparative effectiveness of a covid-19 vaccine against different SARS-CoV-2 strains is inherently affected by the strong correlation with calendar time." (Discussion, page 12)

In addition, we have added the following to the first paragraph of the Discussion and modified the paragraph that discusses the importance of providing absolute measures of association.

"Absolute effects were largest for the more vulnerable subgroups defined by age ≥75 years and having received more prior covid-19 vaccine doses." (Discussion, page 10).

"In contrast to the abovementioned studies, we complement the relative effect estimates with estimates of the benefits of vaccination in absolute terms. Specifically, the comparative effectiveness estimates of our primary analysis correspond to 155 (95% confidence interval, 78 to 231) hospital admissions and 120 (111 to 130) deaths related to covid-19 prevented per 100,000 individuals vaccinated with an XBB.1.5-containing vaccine within our Nordic population. Moreover, while the relative comparative vaccine effectiveness measures were similar, we observed larger absolute benefits from vaccination with the XBB.1.5-containing vaccine for those aged ≥75 years, and among those having received more prior covid-19 vaccine doses—reflecting higher background risk for these subpopulations. Absolute measures of vaccination benefit are essential for public health messaging and policy evaluation and planning." (Discussion, pages 12-13)

Minor comments

7) Authors have decided to call their estimate "comparative" effectiveness. This is not so usual, why not "relative" effectiveness or just "effectiveness"? All estimates of effectiveness are comparative by nature.

Response: We prefer the use of comparative effectiveness as we believe this better reflects the active comparative nature of our design. This is also with the intention to clearly distinguish our comparisons from studies that use unvaccinated as comparisons, which we, in general, argue holds a higher risk of introducing bias (and fully unvaccinated are not representative of the targeted population for a booster vaccine). We appreciate that the terminologies "relative vaccine effectiveness" (compared with individuals who have received some minimum amount of prior covid-19 vaccinations) and "absolute vaccine effectiveness" (compared with fully unvaccinated individuals) have been used by other research groups. However, we believe that "relative vaccine effectiveness" is more confusing and less clearly encompasses the active comparative design, and vaccine effectiveness is, by default, a relative measure. Consequently, we have not changed the terminology used within our manuscript. However, if the editors believe differently, please let us know, and we will adapt accordingly (if so, we would prefer "vaccine effectiveness" over "relative vaccine effectiveness").

8) In the introduction, authors state "evaluations of the vaccine effectiveness with respect to the prevention of severe covid.19, however, are rare". Please explain what "rare" means in this context and give examples?

Response: We have modified the sentence accordingly.

"Evaluations of the vaccine effectiveness with respect to the prevention of severe covid-19, however, are limited and mainly reflect early-season short-term effectiveness with little follow-up.[5–8]" (Introduction, page 4)

9) In the last sentence of the introduction (line 31): "… with 12 weeks of follow-up", I think it should be, "to a maximum of 12 weeks" or "up to 12 weeks", because not all individuals had exactly 12 weeks of follow-up since it depended on the timing of vaccination.

Response: We have modified the sentence accordingly.

"Across the three Nordic countries of Denmark, Finland, and Sweden, we estimated the comparative effectiveness of the monovalent XBB.1.5-containing covid-19 mRNA vaccine against hospital admission and death related to covid-19 in nationwide cohort analysis of adults aged ≥65 years at 24 weeks of follow-up." (Introduction, page 4)

10) In the first Methods subheading: study data sources, design and cohort" is there a word missing? "cohort specification" or something like that?

Response: we have adapted the subheading accordingly.

"Data sources, study design, and cohort specification" (Methods, page 5)

11) Where there many health-care personnel in this cohort of 65+ people?

Response: 4.4% of the matched cohorts were defined as healthcare workers, as seen in Table 1 (page 20). Please note that some of these may have retired since the ascertainment date.

12) Can Sweden extend the follow-up period for the next submission, to match the study period of the other two countries? It would be relevant to rule out that differences by variants or waning is not due to different populations contributing.

Response: We thank the reviewer for this comment. We have enriched with extended data for all countries, which also allowed a longer follow-up of 24 weeks. Please note that the variant-specific analysis is restrained to a 6-week follow-up window, given this was the maximum overlap period for when XBB-sublineages prevailed, and the XBB.1.5-containing vaccine was administered across three countries.

13) Page 10 line 23 says "3-three week".

Response: We thank the reviewer for noting this typo, which has now been corrected.

"Figure 2 shows the associated comparative vaccine effectiveness stratifying follow-up by 3-week intervals and the fitted trend line, representing the per 3-week change in effectiveness during follow-up." (Results, page 10)

REVIEWER: 2

1) Review Report on "Comparative effectiveness of the monovalent XBB.1.5-containing COVID -19 mRNA vaccine across three Nordic countries"

The paper evaluates the effectiveness of the monovalent XBB.1.5-containing COVID-19 mRNA vaccine in reducing COVID-19 related hospital admissions and deaths among individuals aged 65 and older across Denmark, Finland, and Sweden. Using a target trial emulation approach, the study compares outcomes between vaccinated individuals and matched non-recipients over a 12-week period during autumn and winter 2023-2024.

This study provides useful evidence on the effectiveness of the monovalent XBB.1.5-containing COVID-19 mRNA vaccine in reducing severe outcomes among older adults across three Nordic countries. While the study's strengths include its large cohort size and the use of target trial emulation, it lacks novelty. Similar studies (Huiberts et al., Hansen et al., Lin et al.) have already published comparable findings and conclusions on this topic. My specific comments are as follows:

Strengths:

Multiple Country Study and Large Cohort:
The inclusion of data from three Nordic countries and a large cohort of 1,867,448 matched pairs enhances the generalizability and robustness of the findings. The large sample size provides substantial statistical power to detect differences in outcomes and allows for comprehensive subgroup analyses.

Target Trial Emulation:
The use of target trial emulation for the observational study design is a significant strength. This method attempts to mimic the conditions of a randomized controlled trial (RCT), thereby reducing biases typically associated with observational studies.

Response: We thank the reviewer for taking the time to review our work and for the comments and the noted strengths. With respect to the question of novelty, please see our response to editorial comment 3 (within the “Other Editors”-section) and comment 3 by the reviewer (reviewer 2).

Weaknesses:

2) Antiviral Treatment Effects:
Omission of Key Treatments: The study does not consider the effects of antiviral treatments such as Paxlovid and Lagevrio, which are crucial in preventing severe outcomes of COVID-19. Ignoring these treatments could lead to an overestimation or underestimation of the vaccine's effectiveness. It is essential to include data on the usage of these antivirals and adjust for their effects in the analysis to accurately assess the vaccine's true effectiveness.

Comparison to Existing Literature: Studies like Lin et al. (2024) have demonstrated the significant impact of antiviral treatments on severe COVID-19 outcomes. The omission of these treatments in the current study limits the comprehensiveness and accuracy of its findings.

Response: Both antiviral medications have seen very little use in the Nordic countries (see e.g. references [24,25]) Use of antivirals is not conditioned on prior covid-19 vaccination history in our three countries and thus seems unlikely to confound our analysis. If, however, the use of these drugs was associated with our exposure (receiving one additional covid-19 dose compared with not receiving an additional dose at that specific date), this variable could be a mediator or a potential collider and should generally not be adjusted for.

3) Confounding Variables:
Lack of Comprehensive Confounding Control: There is limited discussion and adjustment for potential confounding variables, such as region of residency, socio-economic factors, and variations in healthcare access. These factors can significantly influence the outcomes of COVID-19 hospitalizations and deaths.
Existing Literature Comparison: Huiberts et al. (2024) and Hansen et al. (2024) have shown the importance of adjusting for a wide range of confounders to accurately estimate vaccine effectiveness. The current study could enhance its robustness by incorporating a more comprehensive set of confounding variables.

Response: We do, in fact, adjust for region of residence and prior covid-19 vaccination course and comorbidities (i.e., healthcare utilization), amongst others. In addition, as we note in supplementary table S1: “The healthcare systems in the Nordic countries are universal and tax-financed, meaning the healthcare services are either freely available to all or subsidised so that all individuals pay only a fixed-based minimum irrespective of the actual services provided and costs”. This means that variations in healthcare access are less of a concern for observational studies in our three Nordic countries as it is essentially similar across the populations.

Please note that the study compares matched pairs that have undergone the same covid-19 vaccination schedule (both in terms of the number of doses received [at least 4 prior doses] and timing of the last common prior covid-19 vaccine dose) up until the XBB.1.5.-recipients received the additional vaccine dose. Furthermore, as seen from our results (and discussed in the limitation section), most pairs consisted of comparisons of individuals receiving the XBB.1.5.-containing vaccine earlier than later in the autumn and winter 2023-24 season.

Given that we match exact on potential key confounders, including an extensive list of covariates related to the outcome is not feasible. The exact matching was required to generate and assign index dates for the matched pairs. Lastly, we have included analyses of negative outcome controls, which may provide readers with some indirect qualitative information for interpreting our main findings. Please see our response to the editorial committee (“Other Editors”-section) comment 1 for our revised discussion on the study design, covariates included, and potential for residual confounding.

4) Lack of Novel Insights:
The conclusions of this study align with those reported in other studies, such as Huiberts et al. (2024), Hansen et al. (2024), and Lin et al. (2024). The study does not provide new insights into vaccine effectiveness beyond what has already been established.

Response: We respectfully disagree with this claim. Please also see our response to the editorial committee (“Other Editors”-section) comment 3.

First, this is by far the largest study to date. The number of XBB.1.5.-containing vaccine recipients within the 3 studies the reviewer refers to were n=12,497[26], n=442,247[4], and n=3,315[27], respectively. Second, our analysis estimates the effectiveness with respect to the entire autumn-winter 2023-2024 season on both the relative and absolute scale. As we describe in the manuscript,

most other studies (including the three referenced studies[4,26,27] by the reviewer) only assess some part of the first half of the season and only estimate relative effects. As we highlight in the discussion, estimating both relative and absolute measures of effectiveness is key to allow for a complete evaluation of the effect of vaccination (e.g., while the relative estimates were similar, we observed larger absolute benefits among older relative to younger individuals). Specifically, all three referenced studies used a Cox regression to compute hazard ratios for vaccine effectiveness estimation with short follow-up data, in particular Hansen et al. with an end date of 31 October 2023 and a median follow-up of 7 days[4], while the two other referenced studies had data until 9 January 2024 (median follow-up not reported)[26], and 31 December 2023[27], respectively. Please also note that one of the other studies the reviewer refers to examined the effectiveness against self-reported SARS-CoV-2 infection and not severe covid-19 outcomes.[26] Additionally, the last study[27] referenced by the reviewer, assessed time to hospitalisation or death since SARS-CoV-2 infection by XBB.1.5-containing vaccine vaccination status (i.e. essentially an evaluation of the mitigating effect of vaccination on infection effects and not an evaluation of vaccine effectiveness) and was limited by confounding as outlined by the authors[27]. Similar concerns of confounding effects were noted in the study by Hansen et al. given the study also found associations with the negative control outcome[4]. Note, that we have now included negative control outcomes for which we observed no associations. Third, given the length of our study period, which is now extended to 21 April 2024, our updated analyses estimate the comparative effectiveness at 24 weeks of follow-up, which, to our knowledge, is by far the longest follow-up to be reported to date. Fourth, we include evaluations of effectiveness across a range of clinically important demographic subgroups (including the status of autumn-winter 2023-2024 influenza vaccination at the time of covid-19 vaccination), fifth, we estimate effectiveness against different omicron sublineages prevailing, and sixth, we estimate waning of immunity.

To clarify the novelty of our study findings, we have modified parts of the introduction as well as parts of the discussion—please see our response to the editorial committee (“Other Editors”-section) comment 3, where these paragraphs are included in the response letter.

5) Meta-Analysis and Heterogeneity:
Potential Variations Across Countries/regions: The study combines country-specific estimates using random-effects meta-analysis but does not adequately address potential heterogeneity between countries. Reporting and discussing the heterogeneity measures (e.g., I^2 statistics) would provide more insight into the consistency of the findings across different settings.

Response: The meta-analysis is a random effects model. Thus it allows for the possibility that studies in a meta-analysis have heterogeneous effects, which will also be reflected in the precision of the 95% CIs if large differences are present. Since any study estimate includes some intrinsic error (from the *true* value), a meta-analysed estimate across several countries can be considered closer to the *true* value. To help readers appreciate the rationale for the choice of meta-analysis used, we have modified the following sentence.

“We combined country-specific estimates by random-effects meta-analyses implemented using the *mixmeta* package in R.[28] This method allows for potential heterogeneity in effect across countries when combined and this is reflected by the precision of the 95% confidence intervals from the meta-analysis.” (Methods, page 7).

In addition, we have added I^2 as requested (please see supplementary table S9).

Reviewer #2 Reference:

Huiberts, A.J., Hoeve, C.E., de Gier, B., Cremer, J., van der Veer, B., de Melker, H.E., van de

Wijgert, J.H., van den Hof, S., Eggink, D. and Knol, M.J., 2024. Effectiveness of Omicron XBB. 1.5 vaccine against infection with SARS-CoV-2 Omicron XBB and JN. 1 variants, prospective cohort study, the Netherlands, October 2023 to January 2024. Eurosurveillance, 29(10), p.2400109.

Hansen, C.H., Moustsen-Helms, I.R., Rasmussen, M., Søborg, B., Ullum, H. and Valentiner-Branth, P., 2024. Short-term effectiveness of the XBB. 1.5 updated COVID-19 vaccine against hospitalisation in Denmark: a national cohort study. The Lancet Infectious Diseases, 24(2), pp.e73-e74.

Lin, D.Y., Huang, S., Milinovich, A., Duggal, A. and Wang, X., 2024. Effectiveness of XBB. 1.5 vaccines and antiviral drugs against severe outcomes of omicron infection in the USA. The Lancet Infectious Diseases, 24(5), pp.e278-e280.

RESPONSE LETTER REFERENCES

1 Hernán MA. The C-Word: Scientific Euphemisms Do Not Improve Causal Inference From Observational Data. *Am J Public Health*. 2018;108:616–9. doi: 10.2105/AJPH.2018.304337

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VERSION 2 – REVIEW

REVIEWER NAME	Wade, Angie
REVIEWER AFFILIATION	UCL, GOS ICH
REVIEWER CONFLICT OF INTEREST	None
DATE REVIEW RETURNED	22-Sep-2024

GENERAL COMMENTS	The authors have adequately addressed most of the comments made. However, I do not think that my first comment regarding ascribing causality has been addressed properly. Whilst there has been some moderation, the abstract conclusions still state a causal inference and within the overall conclusion , “we observed that the protection afforded...” requires amendment.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1, statistical report
Comments to the Author
Comment: The authors have adequately addressed most of the comments made. However, I do not think that my first comment regarding ascribing causality has been addressed properly. Whilst there has been some moderation, the abstract conclusions still state a causal inference and within the overall conclusion, “we observed that the protection afforded...” requires amendment.

Response: We thank the statistical editor for reviewing our revised version and for this comment. The abstract and manuscript text have been revised accordingly. Specifically, the abstract conclusion now reads: “This study finds that among adults aged ≥65 years, vaccination with a monovalent XBB.1.5-containing covid-19 mRNA vaccine was associated with reduced rates of covid-19 related hospital admission and death during autumn and winter 2023-2024 across three Nordic countries.” And the mentioned main conclusion sentences now reads: “We observed that the associated reduction in risk did not differ between sex, age, number of previous covid-19 vaccine doses, and seasonal influenza vaccination co-administration subgroups, nor between periods of XBB-lineage (EG.5.1) and BA.2.86-lineage (JN.1) predominance. While the associated reduction in risk was highest during the first weeks after vaccination, it was well-preserved at end of the 24 weeks of follow-up.”