Decision Letter (JCQ-2026-0008)

From: [redacted]
To:
CC:
BCC:

Subject: Journal of Clinical Question - Decision on Manuscript ID JCQ-2026-0008

Body: 08-Mar-2026

Dear Dr Yumoto:

Manuscript ID JCQ-2026-0008 entitled "Clinical Effectiveness of High-Dose versus Standard-Dose Influenza Vaccines in Older Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials" which you submitted to the Journal of Clinical Question, has been reviewed. The comments of the reviewer(s) are included at the bottom of this letter.

The reviewer(s) have recommended publication, but also suggest some revisions to your manuscript. Therefore, I invite you to respond to the reviewer(s)' comments and revise your manuscript.

To submit your revised manuscript, follow the below steps.
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5. The system creates your revision manuscript form. Provide your comments about the revised points at the response field, fill in on each field step by step as same as you did for the original submission, and submit your revised manuscript.
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When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) in the space provided. You can use this space to document any changes you make to the original manuscript. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s).

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

Because we are trying to facilitate timely publication of manuscripts submitted to the Journal of Clinical Question, your revised manuscript should be uploaded as soon as possible. If it is not possible for you to submit your revision in a reasonable amount of time, we may have to consider your paper as a new submission.

Once again, thank you for submitting your manuscript to the Journal of Clinical Question and I look forward to receiving your revision.

Sincerely,
Richard S. Isaacs
Editor in Chief
Journal of Clinical Question

[Editor's Comments]
Associate Editor
Comments to the Author:
(There are no comments.)

[Reviewer(s)' Comments]

Reviewer: 1

Comments to the Author
Comments
This manuscript presents a systematic review and meta-analysis comparing high-dose versus standard-dose influenza vaccines in adults aged ≥65 years. The topic is clinically important and highly relevant to geriatric medicine and public health, particularly given aging populations and influenza-related morbidity. The study is generally well structured, follows PRISMA reporting standards, and focuses on clinically meaningful outcomes rather than immunogenicity alone a clear strength. However, several methodological, analytical, and interpretative issues require clarification or improvement before publication.
1. Although databases are listed, the manuscript lacks sufficient reproducibility details, Full search strings are not presented in the main manuscript. Keywords appear overly implified ("influenza," "senior," "old"). No mention of MeSH terms structure, Boolean operators, language restrictions, grey literature search clinical trial registry screening. Raises concern about study identification completeness and potential selection bias. Provide complete search strategies for all databases. Include PROSPERO registration number (if available);
2. No statement about protocol registration (PROSPERO). Prevents outcome switching. Required by many journals for meta-analyses. Clarify whether protocol was preregistered. If not, justify retrospectively.
3. The authors state RoB 2 was used, but reporting is insufficient. Domain-level judgments not summarized in text. No explanation of allocation concealment blinding differences, cluster RCT adjustments, Claim "no apparent risk of bias" appears overly strong. Large pragmatic trials often carry performance bias. Provide summary table in main manuscript. Discuss bias influence on results.
4. Authors emphasize statistical significance but absolute risk reductions are very small. ARR ≈ 0.07–0.08%, NNT ≈ 1200–1450. Clinical significance should be discussed more critically. Current discussion may overstate practical benefit.
5. Minor comments: Minor repetition in Introduction., Some references overly narrative rather than primary evidence., Minor grammatical inconsistencies, Figures should include clearer legends.

Reviewer: 2

Comments to the Author
General Comments
This manuscript addresses an important clinical question: whether high-dose influenza vaccination provides superior protection compared with standard-dose vaccination in adults aged ≥65 years. The inclusion of randomized controlled trials and the focus on clinically meaningful outcomes represent strengths.
However, several methodological and interpretative issues limit the robustness of the conclusions. Clarification and revision are required to improve transparency, reproducibility, and clinical interpretation.

Major Issues
1. Search Strategy Is Not Sufficiently Comprehensive
The search terms presented in Table S1 appear overly narrow and may miss relevant trials.
For example, the strategy mainly uses "influenza," "high-dose," "standard-dose," and "senior/elderly." This approach omits many relevant synonyms, such as influenza vaccine; inactivated influenza vaccine; HD-IIV; IIV-HD; dose-escalated influenza vaccine, and Fluzone High-Dose
A more comprehensive search string should be provided to ensure adequate sensitivity.

2. Clarification Needed Regarding Included Trials
The manuscript reports eight RCTs, including 610,266 participants.
However:
• Several trials listed (e.g., DANFLU-2 or GALFLU) are large pragmatic registry-based randomized trials.
• The methods section must explicitly state whether the meta-analysis treated cluster randomization and pragmatic registry-based trials differently.
Additionally, it is unclear whether cluster trials were adjusted for design effect, which is crucial for ensuring the validity of the results in the context of the meta-analysis.
3. Outcome Definitions Require Standardization
The manuscript pools heterogeneous endpoints, such as laboratory-confirmed influenza, influenza-like illness, influenza-related hospitalization, and pneumonia hospitalization
Pooling ILI and laboratory-confirmed influenza may introduce clinical heterogeneity.
The authors should clarify how each outcome was defined and whether subgroup analyses were conducted by outcome definition.

4. Interpretation of Absolute Effects
The manuscript reports 185 fewer influenza cases, 235 fewer hospitalizations, and NNT ≈ 1,200–1,450. These absolute effects are very small, suggesting a modest clinical impact. The discussion should give a fairer view of these results, especially about costs, how available the vaccine is, and other better vaccines (like those with adjuvants).
5. Heterogeneity in Hospitalization Outcomes
The pooled analysis shows:
• I^2 = 62.6% for influenza-related hospitalization
• I^2 = 80.5% for all-cause hospitalization.
Such high heterogeneity suggests important differences between studies.
The manuscript would be improved by looking at different groups based on vaccine type (TIV vs QIV) and setting (community vs nursing homes), and by doing a sensitivity analysis that leaves out cluster trials.

6. Comparison With Recent Evidence
The discussion should better contextualize the results relative to recent publications, such as
• large pragmatic influenza vaccine trials (2023–2025)
• recent network meta-analyses of enhanced vaccines.
Such studies would help clarify whether high-dose vaccines are superior to adjuvanted or recombinant vaccines, a clinically relevant question.

Minor Issues
1. Title
The title is clear but could be slightly more precise:
2. PRISMA Reporting
The authors state that the study followed PRISMA 2020 guidelines, but the manuscript does not indicate whether a protocol was registered (e.g., PROSPERO) or whether screening was conducted using a systematic platform. This issue should be clarified.
3. Risk-of-Bias Figures
The RoB-2 figures are clear (Supplementary Figures S9–S13), but the text states that no apparent bias was identified, which is inaccurate because several domains show "some concerns."
The wording should be revised.

Date Sent: 08-Mar-2026

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Author's Response to Decision Letter for (JCQ-2026-0008)

Clinical Effectiveness of High-Dose versus Standard-Dose Influenza Vaccines in Older Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Response to Reviewers

We sincerely thank the Editor and the Reviewers for their careful evaluation of our manuscript and for the constructive comments that have helped us substantially improve the quality, clarity, and transparency of the paper. We have revised the manuscript accordingly. All changes are highlighted in the revised manuscript.Below we provide a point-by-point response to each comment.

Reviewer 1
We appreciate the reviewer's positive assessment of the clinical relevance and structure of our systematic review and meta-analysis. We have addressed all methodological and reporting concerns as detailed below.
Major Comment
1. Although databases are listed, the manuscript lacks sufficient reproducibility details, Full search strings are not presented in the main manuscript. Keywords appear overly implified ("influenza," "senior," "old"). No mention of MeSH terms structure, Boolean operators, language restrictions, grey literature search clinical trial registry screening. Raises concern about study identification completeness and potential selection bias. Provide complete search strategies for all databases.
Response: We thank the reviewer for emphasizing the importance of transparency and reproducibility in the search strategy. In response, we have clarified and expanded the description of our search methods. Specifically, we have added the detailed PubMed search formula in the Methods section and provided the complete search strategies for all databases in Supplementary Table S1. The manuscript has been revised accordingly as follows: "In PubMed, the search strategy was defined as: '(influenza[MeSH Terms] OR influenza[Title/Abstract]) AND ("standard-dose"[Title/Abstract] OR "high-dose"[Title/Abstract]) AND (elderly[MeSH Terms] OR senior[Title/Abstract] OR "older adults"[Title/Abstract])'. The detailed search strategies for each database are presented in Table S1."

2 No statement about protocol registration (PROSPERO). Prevents outcome switching. Required by many journals for meta-analyses. Clarify whether protocol was preregistered. If not, justify retrospectively.
Response: We thank the reviewer for this important comment. To enhance transparency and minimize the risk of outcome switching, the protocol for this systematic review was prospectively registered in the Open Science Framework (OSF). The registration number and corresponding URL have now been added to the Methods section of the revised manuscript.

3. The authors state RoB 2 was used, but reporting is insufficient. Domain-level judgments not summarized in text. No explanation of allocation concealment blinding differences, cluster RCT adjustments, Claim "no apparent risk of bias" appears overly strong. Large pragmatic trials often carry performance bias. Provide summary table in main manuscript. Discuss bias influence on results.
Response: We thank the reviewer for this valuable comment. We have reappraised the risk of bias using the RoB 2 tool and revised the reporting accordingly. As noted by the reviewer, individual studies ranged from some concerns to high risk across specific domains. Considering these assessments, the overall risk of bias for the included outcomes was judged as some concerns. We have clarified this in the revised manuscript and added a summary of the domain-level assessments.
Detailed risk-of-bias assessments are presented in the Supplementary Material (Figures S9–S13). Because the overall certainty ratings were consistent across outcomes, a separate summary table in the main manuscript was not included. We also revised the description to avoid overstating the absence of bias and to better reflect the potential influence of bias on the findings.
The revised text in the manuscript now reads as follows:
"The summary of the risk of bias for each study across the included outcomes is presented in Figures S9–S13. The overall risk of bias was appraised as 'some concerns' for all included outcomes. The certainty of evidence was rated as moderate for laboratory-confirmed influenza and safety outcomes, downgraded due to risk of bias. The certainty of evidence was rated as low for influenza- or pneumonia-related hospitalization, all-cause hospitalization, and all-cause mortality due to moderate heterogeneity and risk of bias."

4. Authors emphasize statistical significance but absolute risk reductions are very small. ARR ≈ 0.07–0.08%, NNT ≈ 1200–1450. Clinical significance should be discussed more critically. Current discussion may overstate practical benefit.
Response: Thank you for this important comment. We agree that the absolute risk reductions observed in our analysis are small and that statistical significance should be interpreted cautiously when considering clinical relevance.
In the revised manuscript, we have updated the outcome definitions from influenza occurrence to

hospitalization due to influenza and hospitalization due to respiratory infection, which represent more clinically meaningful endpoints. Influenza frequently precipitates complications in older adults, including secondary bacterial infections, exacerbations of chronic cardiopulmonary disease, and cardiovascular events. Therefore, preventing influenza- or respiratory infection–related hospitalizations is clinically relevant in this population.
In our analysis, high-dose vaccination was associated with fewer influenza- and respiratory infection–related hospitalizations compared with standard-dose vaccination. Although the absolute reductions were modest at the individual level (ARR ≈ 0.05–0.09%, corresponding to an NNT of approximately 1110–1965), even small reductions may translate into meaningful population-level benefits when applied to large vaccination programs targeting older adults. This is particularly relevant because respiratory infection–related hospitalizations are associated with substantial morbidity, healthcare utilization, and costs.
We have also revised the Discussion to more critically acknowledge the modest magnitude of the absolute effect and to avoid overstating the practical benefit. Furthermore, we note that high-dose vaccination did not significantly reduce all-cause hospitalization or mortality. These findings likely reflect the multifactorial causes of hospitalization and death in older adults, potential heterogeneity across study populations and outcome definitions, and limited statistical power for rare outcomes. In addition, a formal cost-effectiveness analysis was not conducted in the present study; therefore, the optimal use of high-dose vaccination should be interpreted cautiously and may depend on local epidemiological conditions, healthcare resources, and policy priorities. The manuscript has been revised accordingly to provide a more balanced interpretation of the clinical significance of the findings.
"The reduction in influenza- or respiratory infection–related hospitalizations is clinically significant because influenza frequently precipitates complications in older adults, including secondary bacterial infections, exacerbations of chronic cardiopulmonary disease, and cardiovascular events. In the present analysis, high-dose vaccination was associated with fewer influenza and respiratory infection–related hospitalizations compared with standard-dose vaccination. Although the absolute reductions were modest at the individual level, even small improvements may yield meaningful population-level benefits given the large number of individuals targeted by influenza vaccination programs. This consideration is particularly relevant for respiratory infection–related hospitalizations, which are associated with substantial clinical burden and healthcare costs. Despite these benefits, high-dose vaccination did not significantly reduce all-cause hospitalization or mortality. These findings likely reflect the multifactorial causes of hospitalization and death in older adults, the limited statistical power to detect rare outcomes, and heterogeneity across study populations and outcome definitions. In addition, a formal cost-effectiveness analysis was not conducted in the present study; therefore, the optimal use of high-dose vaccination should be interpreted cautiously and may depend on local epidemiological conditions, healthcare resources, and policy priorities. Nevertheless, the consistent direction of effect favoring high-dose vaccination suggests potential benefit that warrants further."
Minor comments
1. Minor repetition in Introduction.
Response: Thank you for these helpful suggestions. Repetitive statements in the Introduction have been removed or consolidated to improve clarity and flow.

2. Some references overly narrative rather than primary evidence
Response: Thank you for these helpful suggestions. Where appropriate, several references that were previously narrative in nature have been replaced with primary evidence sources.

3. Minor grammatical inconsistencies
Response: Thank you for these helpful suggestions. Minor grammatical inconsistencies have been corrected through careful proofreading and professional language editing.

4.Figures should include clearer legends.
Response: Thank you for these helpful suggestions. Figure legends have been expanded to improve clarity, including clearer descriptions of outcome definitions and the statistical measures presented.

Reviewer 2
We thank the reviewer for recognizing the importance of the research question and for the detailed suggestions to improve methodological transparency and interpretation.
1. The search terms presented in Table S1 appear overly narrow and may miss relevant trials. For example, the strategy mainly uses "influenza," "high-dose," "standard-dose," and "senior/elderly." This approach omits many relevant synonyms, such as influenza vaccine; inactivated influenza vaccine; HD-IIV; IIV-HD; dose-escalated influenza vaccine, and Fluzone High-Dose A more comprehensive search string should be provided to ensure adequate sensitivity.
Response: We appreciate this important observation. As Reviewer 1 pointed out, we rechecked our search strategy and expanded the keywords as suggested. In PubMed, the revised search strategy was as follows:
"(((((((((influenza vaccine[Title/Abstract]) OR (inactivated influenza vaccine[Title/Abstract])) OR (HD-IIV[Title/Abstract])) OR (IIV-HD[Title/Abstract])) OR (dose-escalated influenza vaccine[Title/Abstract])) OR (Fluzone High-Dose[Title/Abstract])) OR (standard-dose[Title/Abstract])) OR (high-dose[Title/Abstract])) AND (influenza[Title/Abstract])) AND ((senior[Title/Abstract]) OR (older adults[Title/Abstract]))".
This search yielded 766 records in PubMed, 1,000 records in the Cochrane Library, 943 records in Embase, and 2,978 records in Web of Science, for a total of 5,787 records—approximately five times the number identified in our original search (1,203 records). To assess whether any important studies had been omitted, we conducted a second round of screening. No additional eligible records were identified; therefore, we retained the original search strategy.

2. The manuscript reports eight RCTs, including 610,266 participants. However: Several trials listed (e.g., DANFLU-2 or GALFLU) are large pragmatic registry-based randomized trials. The methods section must explicitly state whether the meta-analysis treated cluster randomization and pragmatic registry-based trials differently. Additionally, it is unclear whether cluster trials were adjusted for design effect, which is crucial for ensuring the validity of the results in the context of the meta-analysis.
Response: We thank the reviewer for raising this methodological point. The Methods section has been revised to clarify that both individually randomized trials and large pragmatic registry-based randomized trials were included. For cluster trials, we used the effect estimates reported in the original studies when available and did not perform additional design-effect adjustments. We have also added the contents in Method section.

3.The manuscript pools heterogeneous endpoints, such as laboratory-confirmed influenza, influenza-like illness, influenza-related hospitalization, and pneumonia hospitalization Pooling ILI and laboratory-confirmed influenza may introduce clinical heterogeneity. The authors should clarify how each outcome was defined and whether subgroup analyses were conducted by outcome definition.
Response: Thank you for this insightful comment. We agree that pooling heterogeneous endpoints, such as laboratory-confirmed influenza, influenza-like illness (ILI), influenza-related hospitalization, and pneumonia hospitalization, may introduce clinical heterogeneity. In the revised manuscript, we have clarified the definitions of the outcomes. Specifically, data on laboratory-confirmed influenza and influenza-like illness have been updated and reorganized into a new outcome category, hospitalization due to influenza, in order to reduce heterogeneity. Meanwhile, influenza-related hospitalization and pneumonia hospitalization have been categorized as hospitalization due to respiratory infection. The manuscript has been revised accordingly to provide clearer and more consistent outcome definitions.

4. The manuscript reports 185 fewer influenza cases, 235 fewer hospitalizations, and NNT ≈ 1,200–1,450. These absolute effects are very small, suggesting a modest clinical impact. The discussion should give a fairer view of these results, especially about costs, how available the vaccine is, and other better vaccines (like those with adjuvants).
Response: Thank you for this important comment. We agree that the absolute effects observed in our analysis are relatively small and that the clinical significance should be interpreted cautiously.
As also noted by the reviewer 1, we have revised the manuscript to present a more balanced interpretation of the findings. In particular, we updated the outcome definitions from influenza occurrence to the more clinically meaningful endpoints of hospitalization due to influenza and hospitalization due to respiratory infection. Influenza frequently precipitates serious complications in older adults, including secondary bacterial infections, exacerbations of chronic cardiopulmonary disease, and cardiovascular events. Therefore, reductions in influenza- or respiratory infection–related hospitalizations may still be clinically relevant in this high-risk population.
At the same time, we acknowledge that the absolute reductions are modest (approximately 185 fewer influenza-related events and 235 fewer hospitalizations, corresponding to an NNT of approximately 1,200–1,450). Although the benefit at the individual level is small, even modest improvements may translate into meaningful public health benefits when applied to large vaccination programs targeting older adults.
We have also expanded the Discussion to better contextualize these findings. Specifically, we now acknowledge that the practical value of high-dose vaccines should be considered alongside factors such as cost, vaccine availability, and alternative enhanced vaccines, including adjuvanted influenza vaccines, which may offer comparable or complementary benefits in some settings. In addition, we note that a formal cost-effectiveness analysis was not conducted in the present study due to limited available data on costs and economic outcomes. Therefore, conclusions regarding the optimal use of high-dose vaccination should be interpreted cautiously and may depend on local epidemiology, healthcare resources, and vaccination policies. The manuscript has been revised accordingly to provide a more balanced and comprehensive discussion of the clinical and policy implications of these results.

5 The pooled analysis shows: I^2 = 62.6% for influenza-related hospitalization; I^2 = 80.5% for all-cause hospitalization. Such high heterogeneity suggests important differences between studies. The manuscript would be improved by looking at different groups based on vaccine type (TIV vs QIV) and setting (community vs nursing homes), and by doing a sensitivity analysis that leaves out cluster trials.
Response Thank you for this helpful suggestion. We agree that the relatively high heterogeneity observed in the pooled analyses (I^2 = 62.6% for influenza-related hospitalization and I^2 = 80.5% for all-cause hospitalization) suggests potential differences across studies and warrants further exploration.
To address this issue, we conducted additional subgroup analyses by vaccine type (TIV vs QIV). The results showed that, for all-cause mortality, neither TIV nor QIV demonstrated a significant reduction. For all-cause hospitalization, however, studies evaluating QIV showed a modest reduction in risk (OR = 0.97, 95% CI: 0.95–0.99), whereas the results for TIV were not statistically significant. We also considered performing subgroup analyses by study setting (community vs long-term care facilities). However, this analysis was not feasible because only one included study was conducted in a long-term care facility, which limited meaningful comparison across settings.

6. The discussion should better contextualize the results relative to recent publications, such as large pragmatic influenza vaccine trials (2023–2025); recent network meta-analyses of enhanced vaccines. Such studies would help clarify whether high-dose vaccines are superior to adjuvanted or recombinant vaccines, a clinically relevant question.
Response: Thank you for this helpful comment. We have revised the Discussion to better contextualize our findings with recent network meta-analyses comparing enhanced influenza vaccines. The following sentence has been added to the manuscript: "Recent comparative studies and network meta-analyses indicate that enhanced influenza vaccines provide greater protection than standard-dose vaccines in older

adults, while the relative effectiveness of high-dose vaccines compared with adjuvanted and recombinant influenza vaccines remains uncertain."
Minor Comments
1. The title is clear but could be slightly more precise:
Response Thank you for this helpful suggestion. The title has been slightly revised to improve clarity and specificity. "Clinical Effectiveness of High-Dose versus Standard-Dose Influenza Vaccines in Older Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials"

2. The authors state that the study followed PRISMA 2020 guidelines, but the manuscript does not indicate whether a protocol was registered (e.g., PROSPERO) or whether screening was conducted using a systematic platform. This issue should be clarified.
Response Thank you for this helpful suggestion. The Methods section now explicitly as it was previously registed in Open Science Framework

3. The RoB-2 figures are clear (Supplementary Figures S9–S13), but the text states that no apparent bias was identified, which is inaccurate because several domains show "some concerns." The wording should be revised.
Response Thank you for this helpful suggestion. As Reviewer 1 pointed out, we have updated the assessment of risk of bias and certainty of evidence in the revised manuscript as follows:
"The summary of the risk of bias for each study across the included outcomes is presented in Figures S9–S13. The overall risk of bias was judged as 'some concerns' for all included outcomes. The certainty of evidence was rated as moderate for laboratory-confirmed influenza and safety outcomes, downgraded due to risk of bias. The certainty of evidence was rated as low for influenza- or pneumonia-related hospitalization, all-cause hospitalization, and all-cause mortality due to moderate heterogeneity and imprecision."

We are grateful to the reviewers for their insightful comments, which significantly improved the methodological rigor and clarity of our manuscript. We believe that the revisions have strengthened the transparency, reproducibility, and clinical interpretation of our findings. We hope that the revised manuscript meets the journal's standards and we appreciate the opportunity to resubmit our work.

Thanks again
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