PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Safety and effectiveness of dose-sparing strategies for intramuscular seasonal influenza vaccine: A rapid scoping review
AUTHORS	Lunny, Carole; Antony, Jesmin; Rios, Patricia; Williams, Chantal; Ramkissoon, Naveeta; Straus, Sharon; Tricco, Andrea

VERSION 1 – REVIEW

REVIEWER	Leite, Andreia Public Health Unit Amadora
REVIEW RETURNED	29-Apr-2021

GENERAL COMMENTS	This is a comprehensive and well-conducted scoping review regarding the safety and effectiveness of dose-sparing strategies for intramuscular seasonal influenza vaccine. The manuscript is well-written and clearly presents the main aspects of the work conducted. However, I have a few comments and suggestions to improve it. Abstract The objective in the abstract seems to have a word missing. Shouldn't it be "to identify studies"? There is no mention of the eligibility criteria in the abstract Objective Still regarding the objective itself, it seems that the focus is on studies assessing safety and effects of sparing strategies. I suggest the authors clarify that in the objective as well. Page 7 - line 136 - It is not totally clear what the authors mean by "Any of the interventions listed above". How would the interventions themselves be considered as a comparator? Discussion The discussion seems quite limited given the wealth of information. I suggest the authors to expand their discussion including the following aspects: - a more detailed reflection regarding the studies to be conducted, given the paucity of information retrieved from the literature; - clarify what future scoping reviews should be conducted; - discuss the limitations of the work conducted. PRISMA ScR checklist is incomplete - page numbers are missing.

REVIEWER	Thomas, Roger University of Calgary, Family Medicine
REVIEW RETURNED	24-May-2021

GENERAL COMMENTS	I understand that this is a commissioned review for the Canadian NACI vaccine advisory organisation to to a 6 week deadline and that they used the SR to author a report. Nevertheless: Search: The search is in English (and Canada is a bilingual country) and you mentioned this was due to the 6 week time limit. Fair enough. However, computer translations of articles other that in English have improved and some articles often have useful English abstracts and you now have the time to expand your search languages. The search ended in 2020. Since you are publishing this and it is relevant to the 2021 flu season the search should be updated to the present and if no new RCTs are found just say so. You now have the time to perform the RoB and Grade analyses. You identified two RCTs with outcome data. One reported influenza like illness (ILI). A review found that less than 25% of cases diagnosed by physicians as ILI were later laboratory proven influenza cases. Thus you have only one RCT with outcome measures and this should be further emphasised. This 2014 review would need updating to assess how many new cases of ILI are lab proven influenza. Thomas RE, Is influenza-like illness a useful concept and an appropriate test of influenza vaccine effectiveness? Vaccine 2014;32:2143-2149. PMID: 24582634ar

VERSION 1 – AUTHOR RESPONSE

#	**Editor/Peer Reviewer Comment**	**Authors response**
	Reviewer 1	
4	Abstract The objective in the abstract seems to have a word missing. Shouldn't it be "to identify studies"? -- Objective Still regarding the objective itself, it seems that the focus is on studies assessing safety and effects of sparing strategies. I suggest the authors clarify that in the	Thank you for this comment and your feedback which will help to make our manuscript stronger. We have edited the objective in the abstract to reflect your concerns: “The objective of this rapid scoping review was to assess the safety and efficacy of dose-sparing strategies for administration of intramuscular seasonal influenza vaccines in healthy individuals of all ages.” --Here we are assessing the safety and efficacy of dose-sparing interventions (low dose vs regular dose), not the individual studies.

	objective as well.	
5	There is no mention of the eligibility criteria in the abstract	Thanks for the comment. We added the following to the abstract: “We included studies in healthy humans of any age that used any dose-sparing strategy to administer intramuscular seasonal influenza vaccines.”
6	Page 7 - line 136 - It is not totally clear what the authors mean by "Any of the interventions listed above". How would the interventions themselves be considered as a comparator?	Interventions can be comparators, as intervention A can be compared with intervention B. For example, when comparing the full-dose Fluviral TIV (15µg/strain) compared with the half-dose (7.5µg/strain) and an active comparator Vaxigrip (7.5µg/strain). (lines 36-38)
7	Discussion The discussion seems quite limited given the wealth of information. I suggest the authors to expand their discussion including the following aspects: - a more detailed reflection regarding the studies to be conducted, given the paucity of information retrieved from the literature; - clarify what future scoping reviews should be conducted; - discuss the limitations of the work conducted.	Thanks for the suggestion. --We included in the limitations, that only one RCT was found with the outcome “Lab confirmed influenza” (line 362-368) --We have suggested a future scoping review examine intradermal verses intramuscular or subcutaneous fractional vaccination efficacy and safely (line 373) --We added a strengths and limitations section. (lines 355-370)
8	PRISMA ScR checklist is incomplete - page numbers are missing.	Thank you for noticing this. We have made the correction and added page numbers.
	Reviewer 2	
9	Search: The search is in English (and Canada is a bilingual country) and you	This rapid scoping review was done to inform the full systematic review with meta-analysis by National Advisory Committee on Immunization (NACI) in 2020, and thus

	mentioned this was due to the 6 week time limit. Fair enough. However, computer translations of articles other that in English have improved and some articles often have useful English abstracts and you now have the time to expand your search languages. The search ended in 2020. Since you are publishing this and it is relevant to the 2021 flu season the search should be updated to the present and if no new RCTs are found just say so.	expanding the search is beyond the scope of this study. Furthermore, the NACI did not have any further funds to update their systematic review.
10	You now have the time to perform the RoB and Grade analyses.	A risk of bias and GRADE assessment was done in the full systematic review with meta-analysis by NACI, and is beyond the scope of this rapid scoping review,[1] as per the JBI guide to scoping reviews.[2]
11	You identified two RCTs with outcome data. One reported influenza like illness (ILI). A review found that less than 25% of cases diagnosed by physicians as ILI were later laboratory proven influenza cases. Thus you have only one RCT with outcome measures and this should be further emphasised. This 2014 review would need updating to assess how many new cases of ILI are lab proven influenza: Thomas RE, Is influenza-like illness a useful concept and an appropriate test of influenza vaccine effectiveness? Vaccine 2014;32:2143-2149. PMID: 24582634ar	Thank you for this observation. We included in the limitations, that only one RCT was found with the outcome lab confirmed influenza. We note “We were also limited by the lack of studies providing sufficient outcome data. Only one study by Kramer et al. reported the outcome “lab confirmed influenza.” Twelve dose-sparing RCTs were not included because they did not provide sufficient data, and did not include vaccines that were deemed of interest to the stakeholders.

References

1. PHAC. Recommendations on fractional influenza vaccine dosing. 2021.
2. Peters MD, Godfrey C, McInerney P, et al. Chapter 11: scoping reviews (2020 version). *JBI manual for evidence synthesis, JBI*. 2020;2020.

VERSION 2 – REVIEW

REVIEWER	Leite, Andreia Public Health Unit Amadora
REVIEW RETURNED	06-Aug-2021

GENERAL COMMENTS	Many thanks for addressing the comments. I believe the replies have been satisfactory and have nothing further.

REVIEWER	Thomas, Roger University of Calgary, Family Medicine
REVIEW RETURNED	06-Aug-2021

GENERAL COMMENTS	It is important that the abstract, results and conclusions stress that there is only one RCT (Kramer 2006) which provided laboratory confirmation of influenza. The review by Thomas RE, Is influenza-like illness a useful concept and an appropriate test of influenza vaccine effectiveness? Vaccine 2014;32:2143-2149. PMID: 24582634 identified studies in which patients were assessed as having influenza-like illness but less than 20% were confirmed by laboratory tests. Thus Engler 2008 which reports ILI as the outcome as not an appropriate measure of influenza. The 2021 NACI report and its assessment of efficacy is noted in a brief paragraph and you did note the key conclusions: "report found that there is some, but still insufficient, evidence that fractional doses of influenza vaccine provided via the intramuscular route are effective and immunogenic in healthy individuals. NACI concludes that since many of those at high risk of influenza (e.g., adults 65 years of age and older, individuals with specific underlying chronic health conditions) may have a lower immune response to influenza vaccination already (due to immunosenescence in older adults or a condition that alters immune function), it is important to ensure that those at high risk continue to receive the full dose of influenza vaccine. Please provide a detailed analysis of their report and present their key data to explain their conclusions as they are a key accompaniment of your study.

VERSION 2 – AUTHOR RESPONSE

Reviewer	Comment	Authors response
1	Many thanks for addressing the comments. I believe the replies have been satisfactory and have nothing further	Thank you for your peer review which has helped make this manuscript stronger.

2	It is important that the abstract, results and conclusions stress that there is only one RCT (Kramer 2006) which provided laboratory confirmation of influenza.	Thank you for taking the time to review and comment on our paper. We agree with your comments which have enhanced this report. We have added this to the abstract: “Of the four adult studies (≥ 18 years), two studies reported on effectiveness outcomes, however only one RCT reported on laboratory confirmed influenza.” We have edited the results to read: “Only one study by Kramer et al. included lab-confirmed influenza infection, two reported influenza like illness, and one reported hospitalizations or emergency room visits after vaccination The RCT by Kramer et al. (2006) found that 3.6% of participants receiving a 15-µg/strain dose of vaccine reported influenza like illness compared to 6.8% of participants that received a 7.5-µg/strain dose. However, only one participant that received the full dose 15-µg/strain was confirmed via laboratory analysis to have influenza, and no patients in the half dose arm got lab confirmation.” In the conclusion we edited to “We found that due to the low number of studies in healthy adults, namely one study assessing laboratory confirmed influenza and two evaluating influenza-like illness in adults, there remains a need for further evaluation of the clinical effectiveness of IM dose-sparing strategies using vaccines currently available in this population.”
	The review by Thomas RE, Is influenza-like illness a useful concept and an appropriate test of influenza vaccine effectiveness? Vaccine 2014;32:2143-2149. PMID: 24582634 identified studies in which patients were assessed as having influenza-like illness but less than 20% were confirmed by laboratory tests. Thus Engler 2008 which reports ILI as the outcome as not an appropriate measure of influenza.	We have stated this in the discussion, citing your review: “Since a 2014 narrative review found that less than 25% of cases diagnosed by physicians as influenza like illness were later *laboratory proven* influenza cases [24], we are lacking RCTs examining fractional dosing of IM influenza immunization.” (lines 367-370)
	The 2021 NACI report and its assessment of efficacy is noted in a brief paragraph and you did note the key conclusions: "report found that there is some, but still insufficient, evidence that fractional doses of influenza	We have briefly summarised the NACI report but do not think it is appropriate to fully detail their results and conclusions. This rapid scoping review aims to identify studies of dose-sparing strategies for administration of ***intramuscular seasonal influenza***

	vaccine provided via the intramuscular route are effective and immunogenic in healthy individuals. NACI concludes that since many of those at high risk of influenza (e.g., adults 65 years of age and older, individuals with specific underlying chronic health conditions) may have a lower immune response to influenza vaccination already (due to immunosenescence in older adults or a condition that alters immune function), it is important to ensure that those at high risk continue to receive the full dose of influenza vaccine. Please provide a detailed analysis of their report and present their key data to explain their conclusions as they are a key accompaniment of your study.	***vaccines*** in healthy individuals of all ages, and report on their characteristics. We have reported on ***intramuscular seasonal influenza vaccines*** of the NACI report's conclusions. In our results section we describe both the Kramer and the Engler studies in terms of their effect estimates and 95% CI. We have added the data on adverse events from the NMACI report: "With regard to the safety of intramuscular seasonal fractional doses of influenza vaccines, there is fair evidence that fractional doses of influenza vaccine do not result in significant differences compared to full dose with regard to severe adverse effects post-influenza vaccination. Readers are encouraged to reference the full NACI report on the Health Canada website." (lines 356-60)