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ESTABLISHING EXPLICIT CLINICAL IMPORTANCE THRESHOLDS IS A TOOL FOR AUTHORS TO ENHANCE TRANSPARENCY IN RESULTS INTERPRETATION

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We thank Garcia-Zamora et al. for their interest in our work[1]. Below, we provide answers to the queries they raised. As many of these appear to stem from a misinterpretation of our findings, we hope our responses will help clarify these points.

In their letter, Garcia-Zamora et al. state that we concluded the "recombinant herpes zoster vaccine has a negligible impact on the general population and is ineffective in reducing postherpetic neuralgia in high-risk patients." However, this interpretation is inaccurate, in the discussion and conclusion sections of our paper, we explicitly stated that "our findings support the efficacy of the recombinant herpes zoster vaccine in reducing the incidence of both herpes zoster (HZ) and postherpetic neuralgia."

Garcia-Zamora et al. assert that because the certainty of the evidence was moderate to high, we should have unequivocally concluded that the vaccine is effective. In fact, we did conclude that the vaccine is effective. Their disagreement seems to stem from our interpretation that the estimated reduction in the incidence of HZ and postherpetic neuralgia for a population with average risk was trivial or of limited clinical significance. Interpreting the importance of the magnitude of an intervention's effects is inherently value- and context-dependent, hence disagreements are to be expected and should not be viewed as problematic[2].

When interpreting evidence, authors inevitably rely on a set of rules and thresholds, which may or may not be explicitly stated. For example, Garcia-Zamora et al., in a study evaluating the efficacy of an online course on enhancing the diagnosis of Chagas disease, concluded that the course improved participants' skills based on a 32.2% increase in correct answers[3]. Although they did not make it explicit, their conclusion implicitly reflects a threshold distinguishing an important improvement from an unimportant one. Depending on the perspective, context, and values, others might agree with their conclusion or, conversely, disagree. For example, some might expect a larger improvement (e.g., 50%) to consider the intervention significant or meaningful.

Following published guidance[4], we chose to make our interpretation rules and thresholds explicit. While Garcia-Zamora et al. did not explicitly state so in their letter, it appears they disagree with those thresholds. The purpose of setting thresholds for the magnitude of effects in the context of primary studies or systematic reviews is to ensure transparency in the interpretation process which is irrevocably performed by the authors. Therefore, Garcia-Zamora et al. are correct when they state that our study's conclusions reflect our opinions, as is always the case.

Regarding the analysis performed, Garcia-Zamora et al. argue that our data is inconsistent with the references cited and that one trial should not have been included in the pooled analysis[5]. To support this claim, without conducting a meta-analysis, they combined results on HZ outcome, from two studies that included patients older than 50 years old without specific

comorbidities associated with an increase in HZ[6,7]. The results obtained were similar to ours (NNT 32.2 in their calculation vs. NNT 35.7 in our meta-analysis). While they may not agree with our methodology –pooling data from all studies and conducting subgroup analyses to explore effect modification by risk– their conclusion that our results are inconsistent with the available data is unfounded. Furthermore, we consider one of the key strengths of our review to be the assessment of subgroup effects and their credibility based on HZ risk across populations. This analysis suggested no plausible effect modification, thereby reinforcing the robustness of our primary analytical approach.

Finally, Garcia-Zamora et al. express enthusiasm for additional potential benefits of HZ vaccination beyond those reported in the RCTs. For instance, they suggest that the baseline risk of HZ may be higher in the general population, although this claim is not supported by the reference provided. In contrast, a systematic review assessing the global ocurrence of HZ reported an incidence rate of 6 to 8 per 1000 patient-years in individuals over 60 years old-figures that align closely with the RCT estimates used in our review (9 to 10 per 1000 patient-years)[8]. They also suggest that HZ vaccination could prevent cardiovascular events. Interestingly, this claim is supported by citing non-RCT studies, which provide low-certainty evidence for causality. In contrast, the results from assessed RCTs reported 47 myocardial infarctions (MIs) in 17 360 vaccinated patients and 29 MIs in 14 645 unvaccinated patients over 50 years old, showing no signal of a potential reduction in these events (RR 1.7, 95% CI 0.46-6.22)[9,10]. Garcia-Zamora et al. also reference the United Kingdom's conclusion that HZ vaccination is cost-effective; however, this finding may not be directly applicable to Argentina. For example, Giannelos et al.[11] highlighted significant variability in incremental cost-effectiveness ratios (ICERs) across studies, driven by differences in epidemiological and healthcare settings. This suggests that in Argentina, the ICER would likely differ from those reported in high-income countries. Furthermore, in more developed nations such as the UK, the willingness to pay is typically higher due to greater resource availability.

These considerations could indeed be relevant when formulating recommendations for or against HZ vaccination, but that was not the aim of our systematic review. However, our review can serve as a foundation for those willing to construct such recommendations. To properly do so, unconflicted expert panels would need to evaluate the vaccine's desirable and undesirable effects and its certainty, while also considering the recommendation's perspective (individual level or population level), person´s values and preferences, costs, and other factors such as equity, acceptability, and feasibility[12,13].

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