ISSN 1669-9106 MEDICINA (Buenos Aires) 2025: 85: 473-475

PERSPECTIVES ON THE EFFICACY AND EFFECTIVENESS OF THE RECOMBINANT HERPES ZOSTER VACCINE

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We read with great interest the manuscript by Bengolea et al., which evaluates the effectiveness and safety of the recombinant herpes zoster vaccine[1]. We commend the authors for their efforts in highlighting the utility of this new vaccine. However, we believe that certain aspects of their analysis merit further discussion.

The authors conclude that 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, these conclusions are not supported by the data they presented. For instance, Table 2 indicates that, in the general population, the recombinant herpes zoster vaccine reduced the risk of developing the disease (RR 0.12; 95% CI 0.04-0.38), lowering the incidence of zoster by 28 cases per 1000 treated individuals (95% CI 20 to 31 fewer cases per 1000 individuals receiving the intervention), with a low risk of bias. We observed no imprecision in these results and, in the absence of a high risk of bias, we believe the data presented actually reinforces the vaccine's efficacy. Furthermore, the authors stratified participants into healthy individuals and high-risk groups, stating that the data were derived from three randomized clinical trials. However, the data provided are inconsistent with the references cited. The pivotal phase III studies of the vaccine in the general population were two: ZOE-50 and ZOE-70[2,3]. These studies excluded immunosuppressed patients (due to disease or pharmacological causes) and individuals with comorbidities that reduced life expectancy. Analysis of these studies, with mean follow-ups of 3.2 and 3.7 years, revealed 25 zoster cases among 8250 vaccinated individuals compared to 284 cases among 8346 unvaccinated individuals[2,3]. This equates to a number needed to treat (NNT) of 32.3 to prevent one zoster in the general population.

Regarding postherpetic neuralgia in the general population, Bengolea et al. reported that the recombinant herpes zoster vaccine reduced the risk by 0.16 (95% CI 0.07-0.37), preventing 3 cases per 1000 treated individuals (95% CI 3 to 4 fewer cases per 1000 individuals receiving the intervention). Despite acknowledging a low risk of bias, the authors conclude that the vaccine is ineffective, which seems contradictory to the presented evidence. Once again, the analyzed data differ from those published in the pivotal trials in the general population[2,3]. These trials observed 4 cases of postherpetic neuralgia among 8250 vaccinated individuals and 36 cases among 8346 unvaccinated participants, corresponding to an NNT of 263 to prevent one postherpetic neuralgia in the general population. It is important to note that the relatively short follow-up period of these studies may not fully capture the lifetime risk of developing complications such as postherpetic neuralgia. This is especially relevant given that available data suggest the vaccine's efficacy persists for at least 10 years[4]. Additionally, since clinical trial participants are typically younger and healthier than the general population, the participants in ZOE-50 and ZOE-

70 likely had a lower baseline risk of zoster and its complications than the general population[5]. Given that the vaccine is consistently effective in preventing the development of herpes zoster and postherpetic neuralgia, its real-world impact likely exceeds what has been observed in clinical trials.

The authors assessed their findings using the minimally contextualized approach, establishing cut-off points based on internal consensus. However, we found no mention of study registration, as recommended by PRISMA guidelines. Therefore, we consider these conclusions to reflect the authors' opinions, which should be interpreted accordingly.

In their discussion, the authors suggest that their study is useful in formulating recommendations for vaccination in healthy individuals or those with risk factors. For an effective and safe intervention like the recombinant herpes zoster vaccine, cost-effectiveness varies significantly depending on the economic context. For example, the UK's Office of Health Economics published a report on the Socioeconomic Value of Adult Immunization Programs, which includes zoster vaccination among cost-effective immunizations for their population[6]. Given the economic crisis in our country, these findings may not be directly applicable. Nevertheless, particularly in the context of vaccines, it is essential to clarify whether a decision is based on economic or scientific considerations. Following the COVID-19 pandemic, there has been a decline in vaccination rates for vaccines available at no cost to vulnerable populations in our country, such as influenza and pneumococcal vaccines[7]. This trend poses significant risks to the population and may increase healthcare costs for society.

Finally, it should be noted that the prevention of herpes zoster may provide benefits that extend beyond the infectious disease field. A case-control study using the Veterans Affairs' Corporate Data Warehouse found that herpes zoster reactivation was associated with an increased risk of stroke (odds ratio [OR] 1.93, CI95% 1.57–2.4, p<0.001) and that both the live attenuated vaccine (OR 0.77, CI95% 0.65–0.91, p=0.002) and recombinant vaccine (OR 0.57, CI95% 0.46–0.72, p<0.001) reduced stroke occurrence[8]. Similarly, a propensity-score-matched study using the TriNetX database found that adults who received two doses of the recombinant herpes vaccine had a lower risk of myocardial infarction (adjusted relative risk 0.73, CI 0.55–0.96) over a 3-year follow-up[9]. These observational studies suggest that the recombinant herpes zoster vaccine may be an effective and safe intervention to reduce cardiovascular events.

These findings align with longstanding evidence that infectious processes can trigger cardiovascular events[10,11]. In this context, it has been shown that various vaccines, including influenza, pneumococcal, and COVID-19 vaccines, contribute to reducing cardiovascular events[10].

In conclusion, we agree with the authors that the greatest benefit of the recombinant herpes zoster vaccine is likely to be observed in individuals with comorbidities and higher risk profiles. However, based on the current evidence, we believe the vaccine also demonstrates both efficacy and safety in the general adult population, even in the absence of additional risk factors.

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