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# Postlicensure herpes zoster vaccine effectiveness: systematic review protocol

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## ABSTRACT

**Introduction** Herpes zoster (HZ) and associated complications inflict substantial morbidity and associated healthcare and socioeconomic burdens. Current treatments are not fully effective, especially among the most vulnerable populations. Two HZ vaccines are available and are part of the national immunisation programmes in many countries. This review will evaluate the effectiveness of zoster vaccines against incident HZ and postherpetic neuralgia in adults 50 years and older.

**Methods and analysis** The key information sources that will be searched include MEDLINE (Ovid), Embase (Ovid), Cochrane libraries and CINAHL. This search will consider postlicensure observational studies published in all languages between 2006 and 2020 that assessed the effectiveness of HZ/zoster vaccines in adults 50 years and older. The identification of studies will be complemented with the search of reference lists and citations, and contact with authors of papers to request missing or additional data, where required. Following the search, all identified citations will be collated, and duplicates will be removed. Titles and abstracts will then be screened by two independent reviewers for assessment against the inclusion criteria for the review. Selected studies will follow the process of critical appraisal, data extraction and data synthesis. Statistical analyses will be performed using a random-effect model.

**Ethics and dissemination** Formal ethical approval is not required, as primary data will not be collected. The review will be disseminated in peer-reviewed publications and conference presentations.

## Strengths and limitations of this study

- Systematic review of high-quality observational studies.
- The selection of studies, data extraction and a quality assessment will be conducted by two independent authors.
- The protocol has been created according to published Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines.
- We do not have any language limitations.
- Observational studies may produce evidence of possible bias and confounding.

## INTRODUCTION

Varicella-zoster virus (VZV) is the aetiological agent of varicella, a highly infectious, acute, self-limiting, viral disease with serious complications in neonates, pregnant women and immunocompromised persons.[1] It is an exclusively human neurotropic alpha herpes virus.[2] After primary infection, it becomes latent in the cranial nerve ganglia, dorsal root ganglia and autonomic ganglia along the entire neuroaxis.[2] Administration of varicella vaccine or natural infection generates VZV-specific antibody and VZV-specific T-cell-mediated immunity.[2]

The memory cell response contributes to protection following re-exposure to VZV.[3] This immunity is subsequently boosted either by endogenous re-exposure (subclinical reactivation of latent VZV) or exogenous re-exposure.[3] VZV-specific T-cell-mediated immunity is necessary to maintain latent VZV in a subclinical state in the sensory ganglia.[4] A decline in VZV - specific T cell-mediated immunity associated with ageing (immunosenescence), immune-suppressive diseases or therapies causes reactivation of latent VZV as HZ.[4]

HZ presents as a unilateral vesicular rash, characteristically restricted to a single dermatome and accompanied by radicular pain.[5] It is estimated that, each year, there are one million cases in the USA, 130 000 new cases in Canada and more than 1.7 million cases in Europe.[6–9] In New Zealand, more than 9000 zoster hospitalisations have been recorded in the past 10 years.[10] HZ incidence ranges from 3.4 to 5.0 per 1000 person-years, and from 8 to 11 per 1000 person-years over the age of 65 years. One in four people is at risk of developing HZ during their lifetime, and two-thirds of people with the disease are aged 50 years or older.[11] By the age of 85 years, >50% of the population report at least one episode of HZ.[2] Major risk factors for HZ are increasing age and a decline in cell-mediated immunity.[5]

Laboratory confirmation of HZ occurs through the detection of VZV DNA using

PCR testing or isolating VZV in cell culture from vesicular fluid, crusts, saliva, cerebrospinal fluid or other specimens.[5]

The main complications of HZ include postherpetic neuralgia (PHN, pain persisting more than 90 days after rash onset) in 22% (8%–26%) of HZ patients and herpes zoster ophthalmicus (HZO), ophthalmic division of the trigeminal nerve, in ~15% of cases (if untreated, 50%–70% develop acute ocular complications, chronic complications, reduced vision and blindness).[5]

The immune response can be boosted by the VZV vaccine developed to prevent HZ. Vaccination is, therefore, an important tool to reduce the epidemiological, clinical and economic burden of HZ, and to reduce the negative impact on the quality of life.[2] Currently, two HZ vaccines are available. The recombinant zoster vaccine (RZV), approved in 2017, and the zoster vaccine live (ZVL), licensed in 2006.[12] The effectiveness and public health impact of these vaccines have been demonstrated in many studies.[13–19] The effectiveness of ZVL against an episode of HZ decreases gradually after vaccination, from 69% to 50% during the first year to about 17% by the seventh year after vaccination.[20] RZV is also known as adjuvanted recombinant subunit zoster vaccine and consists of recombinant VZV glycoprotein E and a liposome-based $AS01_B$ adjuvant system.[12]

HZ and associated complications inflict substantial morbidity and associated healthcare and socioeconomic burdens.[19] In the USA, HZ and associated diseases result in about $1.3 billion in medical care costs and $1.7 billion in indirect costs annually, and this burden will increase in the coming years due to the ageing populations.[19] Current treatments are not fully effective, especially among the most vulnerable patients.[21] The best available option is prevention through vaccination. These vaccines have been licensed and marketed in many high-income countries[1 22] like the USA, New Zealand, Australia, Germany, Canada, France and Japan (online supplemental appendix I).

A 2019 Cochrane systematic review of 24 studies (randomised controlled trials or quasi-randomised controlled trials) involving 88 531 participants, aged 60 years and above, showed that ZVL and RZV are effective in preventing HZ disease for up to 3 years.[23] This review excluded (1) trials involving immunosuppressed persons, (2) trials in people aged <60 years and (3) observational studies.

In 2018, Tricco *et al* compared the efficacy, effectiveness and safety of the HZ live attenuated vaccine with the HZ adjuvant recombinant subunit vaccine or placebo for adults aged 50 and older. They concluded that the RZV might prevent more cases of HZ than using the ZVL, but the RZV also carries a greater risk of adverse events at injection sites.[11] Of all the 27 studies included, there were only four observational studies (one case–control and three cohort studies). For the laboratory or doctor-confirmed cases of HZ, ZVL was not statistically different from placebo. There is a need to further explore these findings in observational studies.

Another systematic review estimated the relative efficacy and safety of vaccines for the prevention of HZ using a network meta-analysis. RZV was significantly more effective in reducing HZ and PHN incidence in adults aged 60 years and above, compared with ZVL. RZV resulted in more reactogenicity following immunisation.[24] The review excluded (1) trials conducted in immunocompromised patients, (2) trials in participants less than 50 years and (3) observational studies.

In 2019, Senderovich *et al* summarised the current literature available on the efficacy of the HZ vaccines in adults aged over 60 years old, and evaluated the cost-effectiveness of the HZ vaccines. Ten studies that met the inclusion criteria highlighted the efficacy of the HZ vaccines.[6] The review focused on adults over 60 years old residing in long-term care facilities and was limited to a 5-year period (January 2013–April 2018).

There is a need for a systematic review that will summarise real-world evidence[25] of the effectiveness of HZ vaccines from postlicensure studies with different designs, conducted in different populations. Vaccine performance has been shown to vary in routine public health practice (under real-world conditions).[26] Vaccine effectiveness (may be different from efficacy observed in trials) is influenced by host factors (age, comorbidity, previous exposure, coadministered vaccines and drugs and time since vaccination), vaccine characteristics (mode of administration, vaccine type and composition) and epidemiological factors (circulating strains, force of infection and herd immunity). Vaccine effectiveness (protection attributable to a vaccine administered under field conditions to a given population) measured by observational postlicensure studies[27] is important to inform public health programmes and policies. The evidence will be obtained by searching, critically appraising and synthesising the evidence from observational studies of published and unpublished literature.

This study will be the only review that will evaluate and summarise the postlicensure effectiveness of HZ vaccines from 2006 to 2020 in adults aged 50 years and above.

A preliminary search of PROSPERO, MEDLINE, the Cochrane Database of Systematic Reviews and the JBI Database of Systematic Reviews and Implementation Reports was conducted, and no current or underway systematic reviews on the topic were identified.

### Objectives

We seek to evaluate the effectiveness of zoster vaccines in adults 50 years and older. This includes incidence of HZ, postherpetic neuralgia and HZO (primary outcomes), and HZ-related hospitalisations and quality of life (secondary outcomes).

## METHODS

The proposed systematic review will be conducted in accordance with the Joanna Briggs Institute methodology for systematic reviews of effectiveness evidence.[28 29]

## Design

We will conduct a systematic review of published and unpublished studies.

## Eligibility criteria

### Types of studies

This review will consider analytical observational studies, including prospective and retrospective (historical) cohort studies, and case–control studies. Studies published in all languages will be included. Studies published from 2006 to 2020 will be included as the first HZ vaccine was licensed in 2006. Systematic reviews and meta-analyses will be used only for identifying additional studies; these will not be included in this review.

### Types of participants

The review will consider studies that include adults aged 50 years and older (studies can be included when adults younger than 50 years are included, so long as this is not the majority).

### Types of interventions

This review will consider studies that evaluate the effectiveness of HZ vaccines. The intervention is being vaccinated (live attenuated injectable HZ vaccine and adjuvant recombinant subunit HZ vaccine), that is, any licensed HZ vaccine (including all preparations, schedules, dosing and routes of administration). Incomplete vaccination (failure to get the second dose of recombinant vaccine) will be considered unvaccinated.

### Types of comparators

This review will consider studies that compare the intervention to no vaccination, placebo or other vaccine.

### Types of outcome measures

This review will consider studies that include the following outcomes: the outcome measures are defined in online supplemental appendix II.

#### *Primary outcomes*

1. Incidence of HZ (entire duration of follow-up or repeated measures).
   - Number of cases and person-years.
   - Incidence rate per arm.
2. Incidence of postherpetic neuralgia (entire duration of follow-up).
   - Ninety days.
   - Number of cases and person-years.
   - Incidence rate per arm,
3. Incidence of other HZ complications (HZO).
   - Number/proportion of events or number/proportion of patients with the event.
   - Incidence rate.

#### *Secondary outcomes*

- HZ-related hospitalisations
- Quality of life.

These outcomes will be measured by vaccine effectiveness.

## Search methods

The search strategy will aim to locate both published and unpublished studies. An initial limited search of MEDLINE was undertaken to identify articles on the topic. The text words contained in the titles and abstracts of relevant articles and the index terms used to describe the articles were used to develop a full search strategy for MEDLINE (Ovid) (online supplemental appendix III). The search strategy, including all identified keywords and index terms, will be adapted for each included information source. The reference list of all studies selected for critical appraisal will be screened for additional studies.

The databases to be searched include MEDLINE (Ovid), Embase (Ovid), Cochrane libraries, Cumulative Index to Nursing and Allied Health Literature (CINAHL), ProQuest Central and Dimensions. Sources of unpublished studies and grey literature to be searched include CareSearch, Grey Literature Report, Google and WHO.

## Study selection

Following the search, all identified citations will be collated and uploaded into EndNote X9 (Clarivate Analytics, Pennsylvania, USA), and duplicates will be removed. Titles and abstracts will then be screened by two independent reviewers for assessment against the inclusion criteria for the review using Covidence. Potentially relevant studies will be retrieved in full and their citation details will be imported into the Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information (JBI SUMARI) (Joanna Briggs Institute, Adelaide, Australia).[29]

The full text of selected citations will be assessed in detail against the inclusion criteria by two independent reviewers. Reasons for exclusion of full-text studies that do not meet the inclusion criteria will be recorded and reported in the systematic review. Any disagreements that arise between the reviewers at each stage of the study selection process will be resolved through discussion or with a third reviewer. The results of the search will be reported in full in the final systematic review and presented in Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.[30]

## Assessment of methodological quality

Eligible studies will be critically appraised by two independent reviewers at the study level for methodological quality in the review using standardised critical appraisal instruments from the Joanna Briggs Institute for Cohort and case–control studies (online supplemental appendix IV).[28 29] This will help us assess how each study has addressed bias in its design, conduct and analysis. Authors of papers will be contacted to request missing or additional data for clarification, where required. Any disagreements that arise will be resolved through discussion, or

with a third reviewer. The results of the critical appraisal will be reported in narrative form and in a table.

Most observational studies are carried out using population-based databases that reflect daily medical practice. Potential confounding is common in studies of associations between vaccination and zoster using large databases.[31] Predetermined data collection, absence of researcher control, completeness of recorded information and misclassification can potentially affect the interpretation of any observed associations.[31 32]

All studies, regardless of the results of their methodological quality, will undergo data extraction and synthesis (where possible).

## Data extraction

Data will be extracted from studies included in the review by two independent reviewers using the standardised data extraction tool.

The data extracted will include specific details about the populations, study methods, interventions and outcomes of significance to the review objective (HZ, HZO, postherpetic neuralgia, HZ-related hospitalisations and quality of life). Information on immunosuppression will also be extracted and stratified if appropriate.

Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer. Authors of papers will be contacted to request missing or additional data, where required.

## Data analysis

Studies will, where possible, be pooled in a statistical meta-analysis using JBI SUMARI.[29] Effect sizes will be expressed as either odds ratios (OR) or relative risks (RR) (for dichotomous data) and weighted (or standardised) final postintervention mean differences (for continuous data), and their 95% CIs will be calculated.

Heterogeneity will be assessed statistically using the standard $\chi^2$ and $I^2$ tests. Statistical analyses will be performed using a random-effect model.[33] We will be reviewing studies that compare the proportion of people developing zoster in vaccinated and unvaccinated groups. We expect the effect sizes (OR and RR) to be similar but not the same. The effect size may vary, depending on age and mix of participants, health status and programme implementation.[34] Hence, the random-effect model (rather than the fixed-effect model) is more appropriate. We will assess pooled vaccine effectiveness by vaccine, time since vaccination, disease (zoster, PHN and HZO), immune status and study design.

Sensitivity analyses will be conducted to test decisions made regarding the impact of excluding or including studies in a meta-analysis based on sample size or methodological quality. If results remain consistent across the different analyses, the results can be considered robust as, even with different decisions, they remain the same/similar. If the results differ across sensitivity analyses, this is an indication that the result may need to be interpreted with caution.[28]

Where statistical pooling is not possible, the findings will be presented in narrative form, including tables and figures, to aid in data presentation where appropriate. A funnel plot will be generated to assess publication bias if there are 10 or more studies included in a meta-analysis. Statistical tests for funnel plot asymmetry (Egger test, Begg test and Harbord test) will be performed where appropriate.

## Assessing certainty in the findings

The Grading of Recommendations, Assessment, Development and Evaluation approach for grading the certainty of evidence will be followed,[28 35] and a summary of findings (SoF) will be created using GRADEPro GDT (McMaster University, Ontario, Canada). The SoF will present the following information where appropriate: absolute risks for the treatment and control, estimates of relative risk, and a ranking of the quality of the evidence-based on the risk of bias, directness, heterogeneity, precision and risk of publication bias of the review results. The outcomes reported in the SoF will be HZ, HZO, postherpetic neuralgia, HZ-related hospitalisations and quality of life.

## Patient and public involvement statement

No patient was involved in this study.

## Ethics and dissemination

Formal ethical approval is not required, as primary data will not be collected. The findings will be disseminated in peer-reviewed journals and conference presentations.

## Registration and publishing statement

The systematic review protocol will be registered with the PROSPERO International Prospective Register of Systematic Reviews and reported using Preferred Reporting Items for Systematic Reviews and Meta-analysis checklist to guide the reporting of the review.

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**Contributors** JFM wrote this review. CRS and BPN contributed to conceiving this review, defining the study question and planning the review, and commented critically on several drafts of the protocol. PMAA and PEE contributed on a draft of this review with critical comments.

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**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.

terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.



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