An Advisory Committee Review (ACR) National Advisory Committee on Immunization (NACI)

Literature Review on the Immunogenicity of Herpes Zoster Vaccines

PROTECTING AND EMPOWERING CANADIANS TO IMPROVE THEIR HEALTH

Public Health Agency of Canada | Agence de la santé publique du Canada

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PREAMBLE

The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada (PHAC) with ongoing and timely medical, scientific, and public health advice relating to immunization.

In addition to burden of disease and vaccine characteristics, PHAC has expanded the mandate of NACI to include the systematic consideration of programmatic factors in developing evidence-based recommendations to facilitate timely decision-making for publicly funded vaccine programs at provincial and territorial levels.

The additional factors to be systematically considered by NACI include: economics, ethics, equity, feasibility, and acceptability. Over the coming years NACI will be refining methodological approaches to include these factors. Not all NACI Statements will require in-depth analyses of all programmatic factors. As NACI works towards full implementation of the expanded mandate, select Statements will include varying degrees of programmatic analyses for public health programs.

PHAC acknowledges that the advice and recommendations set out in this statement are based upon the best current available scientific knowledge and is disseminating this document for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph(s). Recommendations for use and other information set out herein may differ from that set out in the product monograph(s) of the Canadian manufacturer(s) of the vaccine(s). Manufacturer(s) have sought approval of the vaccine(s) and provided evidence as to its safety and efficacy only when it is used in accordance with the product monographs. NACI members and liaison members conduct themselves within the context of PHAC's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

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EXECUTIVE SUMMARY

Herpes zoster is an acute viral infection caused by reactivation of varicella-zoster virus (VZV). LZV, a live, attenuated vaccine for zoster has been available in Canada for many years. A new subunit recombinant zoster vaccine (RZV) named Shingrix was approved in Canada in October 2017. This zoster vaccine immunogenicity review was done to have a comprehensive understanding of the immunogenicity of both live and subunit vaccines. This immunogenicity review was done in conjunction with a larger review of the clinical efficacy and safety of zoster vaccines that supported recommendations in the NACI Statement titled "Updated Recommendations on the Use of Herpes Zoster Vaccines" published August 30, 2018 .

A search strategy was developed with a federal Reference Librarian (Health Library) and was verified by the NACI Zoster Working Group. Four databases (MEDLINE, EMBASE, Cochrane Central, and PsychInfo) were queried on June 5, 2017 (updated October 12, 2017). Through this literature review, 52 relevant studies were included in the evidence synthesis. In addition to this search, a review of herpes zoster vaccine related posters from IDWeek 2017 as done to obtain the most current information. These studies assessed the immunogenicity of live vaccine in general and special populations, the immunogenicity of RZV in general and special populations, and concomitant administration with other vaccines. The type of evidence retrieved on the topic was diverse and included randomized controlled trials and cohort studies with quality of evidence ranging from good to poor.

The humoral and cellular correlates of protection from zoster among patients who have had VZV are not clear and none have been clearly established as markers of protection[1, 2]. It does appear that CD4+ and CD8+ cells play a central role in preventing VZV reactivation[3]. Furthermore, commercially available laboratory tests for assessing immunity from natural VZV infection are not accurate for diagnosing immunity from prior vaccination[4]. Therefore, studies evaluating the immunogenicity of zoster vaccination should be interpreted with caution.

LZV was found to be immunogenic in all studies in the general population. Among live vaccine studies, humoral immunity was generally measured in levels of Anti-VZV antibodies while cell-mediated immunity was measured through VZV-specific IFN-gamma spot-forming cells with ELISPOT or though a responder cell frequency assay of CD4+ memory cells. The duration of follow-up was up to 3 years[5], suggesting protection extends at least that long. It appears that cell-mediated immunity and the rate of rise in anti-VZV titres were most correlated with clinical protection, rather than absolute levels of anti-VZV antibodies[6, 7]. The immune response among those aged 50-59 appears more robust than those over the age of 60[8, 9, 10]. LZV was also generally immunogenic among immunocompromised populations, whether through a disease or through immunosuppressive therapies[11, 12]. Among patients with hematologic malignancies[13, 14, 15], solid tumor malignancies[13], rheumatoid arthritis on immunosuppressive treatments[16], inflammatory bowel disease patients on immunomodulators[17, 18], and HIV patients with CD4 count <200[13], live attenuated vaccine was found to be immunogenic. It was only among certain groups of patients with hematopoietic stem cell transplants where immune responses were not elicited. Concurrent administration of LZV with other vaccines like pneumococcal or influenza vaccine does not appear to affect immunogenicity compared to non-concurrent vaccination[19, 20].

Similarly, the RZV vaccine was immunogenic in all studies in the general population. Among subunit vaccine studies, humoral immunity was generally measured by levels of Anti-gE antibodies while cell-mediated immunity was measured through levels of CD4+ cells with at

least two activation markers (including expression of IFN-gamma, IL-2, TNF-a, or CD40 ligand). The longest follow-up was for 9 years and demonstrated immune markers elevated from baseline[21]. Unlike the live vaccine, RZV appears to be similarly immunogenic across all adults over 50 years of age[22, 23]. There appear to be no changes in immunogenicity when it is given with or without a live vaccine[24] such as the live varicella zoster vaccine Varilrix. One abstract also suggested that RZV is immunogenic for patients who have been previously vaccinated with the live vaccine at least 5 years prior to RZV administration (mean duration 6.7 years), with no differences in immunogenicity among those with and without prior live vaccine[25]. RZV also appears to be immunogenic among immunocompromised populations. One study demonstrated robust CMI and humoral immunity for HIV patients, even with CD4 counts <200 if on ART[26]. Another study suggested that for patients with autologous hematopoietic stem cell transplant, RZV was able to elicit a significant humoral and CMI response[27]. Three abstracts suggested that RZV was at least partially immunogenic among patients with hematologic malignancy[28], solid tumor malignancy[29], and among renal transplant patients with chronic immunosuppressive therapy[30]. One study suggested that concurrent administration of RZV with influenza vaccine was not associated with diminished immunogenicity[31].

One head-to-head study currently only available in abstract format suggested that RZV may be better at eliciting a memory T-cell response than LZV[32].

Ultimately, there is a large body of data suggesting that both LZV and RZV are immunogenic in both the general and special populations. It also appears plausible, through one head-to-head study, that RZV is potentially more immunogenic than LZV based on a superior memory T-cell response.

I. INTRODUCTION

Herpes zoster, or shingles, is an acute viral infection caused by reactivation of varicella-zoster virus (VZV). It is associated with a significant burden of disease that is reviewed in the NACI Statement titled “Updated Recommendations on the Use of Herpes Zoster Vaccines” published August 30, 2018.

LZV, a live attenuated vaccine for zoster, has been available in Canada since 2008 (with the new refrigerator-stable product, Zostavax II, authorized in Canada in 2011). A new adjuvanted subunit vaccine (i.e. Shingrix) has recently been authorized for use in Canada in October 2017. This literature review was conducted to determine the immunogenicity of live versus subunit zoster vaccines as part of a larger NACI update on all zoster vaccines. 52 studies were identified for evidence synthesis for this review.

The primary objectives of this literature review were:

1) To assess the immunogenicity of different live and subunit herpes zoster vaccines in the general population for which they are indicated.
2) To assess the immunogenicity of different live and subunit herpes zoster vaccines in specific sub-populations, such as: immunocompromised populations (including people with hematologic and solid malignancies, hematopoietic stem cell transplants, immunosuppressive therapies for auto-immune conditions such as rheumatoid arthritis and inflammatory bowel disease, and people with HIV), those who have previously had herpes zoster, and those who have previously had zoster vaccine.

II. METHODS

This Literature review was completed to inform NACI's evidence-based recommendations on herpes zoster vaccines, which are presented in the NACI Statement titled "Updated Recommendations on the Use of Herpes Zoster Vaccines" published August 30, 2018 .

II.1 Research question

What is the humoral and cell-mediated immunogenicity of live and subunit herpes zoster vaccines?

A search strategy was developed with a federal Reference Librarian (Health Library) and was verified by the NACI Zoster Working Group. Four databases (OvidMEDLINE, EMBASE, PsycINFO, and Cochrane) were queried on June 5, 2017 and updated October 12, 2017 Language was restricted to English and French. Full search terms and results flow diagram can be found in Appendix A and B respectively.

Databases consulted June 5, 2017: MEDLINE (672 results), Embase (895 results) Cochrane (164 results)
Databases re-consulted October 12, 2017: MEDLINE, Embase, and Cochrane (34 results added)

Inclusion criteria:

- Studies of herpes zoster vaccine with immunogenicity data

Exclusion criteria:

- Studies of varicella-zoster vaccine
- Non-primary studies (including systematic reviews, meta-analyses, etc.)
- Modelling studies

Both reviewers screened (JH, MT) screened the results for relevant studies. One reviewer (JH) assessed all studies for quality as per NACI methodology (Appendix C) and assigned the level of evidence as per NACI methodology. The other reviewer (MT) reviewed a sample of studies for quality and level of evidence to ensure consistency. Any discrepancies with screening or quality appraisal were resolved through consensus. One reviewer (JH) extracted data into an evidence table and synthesized evidence into a summary document. All work was reviewed by the NACI Zoster Working Group chair.

III. RESULTS

III.1 Overview

Through a comprehensive literature review, 52 studies were identified for evidence synthesis (See Appendix D). The relevant studies were grouped as follows:

1) Live vaccines in the general population
2) Live vaccines in immunocompromised populations
3) Subunit vaccines in the general population

4) Subunit vaccines in immunocompromised populations
5) Head-to-head comparisons of live and subunit vaccines
6) Concomitant administration of herpes zoster and other vaccines

III.2 Live vaccines in the general population

Summary: *There were 22 studies assessing live vaccine immunogenicity in the general population. Of these 5 were good quality studies, 6 were fair quality studies, 9 were poor quality studies, and the remaining could not be assessed (usually because they are abstracts). All studies used Zostavax (there were no other live vaccines in this population group). Studies generally assessed humoral immunity (through anti-VZV antibody levels) and many also assessed cell-mediated immunity (CMI) (usually through VZV-specific IFN-gamma spot-forming cells with ELISPOT or through a responder cell frequency assays measuring counts per minute of H^3-thymidine incorporation in peripheral blood mononuclear cells stimulated with VZV). LZV was found to immunogenic (i.e. there were significant increases in antibody or T-cell levels) in all studies. Key takeaways from the studies include:*

- ***Duration of protection:*** *The duration of follow-up ranged from 4 weeks to up to 3 years (except for studies looking at those who were receiving a booster shot). In general, immunity as measured by antibody levels and cell counts peaked at 6 weeks and declined afterwards.*
- ***Humoral immunity versus CMI:*** *One good quality study[7] suggested that CMI (as measured by IFN-gamma T-cells) at the time of zoster onset were associated with reduced disease severity and likelihood of post-herpetic neuralgia, whereas humoral immunity (as measured by Anti-VZV antibodies) was not. Another good quality study suggested that the rise in antibody titres up to 6 weeks post-vaccination was correlated with vaccine efficacy whereas antibodies levels after 6 weeks was not[6].*
- ***Age of vaccine recipient and immunogenicity:*** *One study[8] suggested that the humoral response among those 50-59 years old was slightly higher than among those 60 years and older. Another study suggested that the CMI response was lower in those over 70 compared to those ages 60-69[10]. These results were corroborated by another study which showed generally more robust responses in terms of CMI and humoral immunity in younger populations[9].*
- ***Mechanism of administration:*** *One fair-quality study suggested that intradermal administration was associated with higher and more persistent increases in humoral immunity than traditional subcutaneous administration[33]. Another fair-quality study did not find any differences in intramuscular versus subcutaneous administration[34].*
- ***Number of doses:*** *Two studies suggested there were no differences in immunogenicity between 1 and 2-dose administrations of LZV[35, 36]. This was the case for both humoral immunity and CMI.*
- ***Booster doses:*** *One fair quality and one poor quality study assessed the effect of a booster dose among those older than 70 compared to those who were being vaccinated for the first time. For those receiving boosters, there appeared to be a greater CMI response but no differences in humoral response[10, 37].*

Levin et al. (2013)[38] was a good quality study with large sample size (n=2269) that assessed anti-VZV antibodies at baseline and 6 weeks. The study demonstrated a geometric mean fold rise (GMFR) of 2.31 in the vaccine group compared to no change in the placebo group. Levin et al. (2008)[5] was another good quality study with a large sample size (n=1395) that assessed both CMI and humoral immunity in patients older than 60 years up to three years from baseline.

In this study, both measures of CMI and humoral immunity were higher among the vaccine group up to three years, but levels peaked at 6 weeks and declined afterwards.

Vermeulen et al. (2012)[35] was a good quality study that assessed differences between one versus two doses of LZV. There were no differences in CMI or humoral immunity between the one and two dose groups at up to 6 months post-vaccination. Similarly, Vesikari at al. (2013)[36] was a fair quality study that found the humoral response between one and two doses of LZV (administer at 0 and 1 and 0 and 3 months) were no different at up to 12 months post-vaccinations.

Weinberg et al. (2009)[7] was a good quality study that assessed the association between CMI and humoral immunity and protection against zoster. It found that levels of IFN-y producing peripheral blood mononuclear cells (PBMCs, a measure of CMI) at the time of disease onset was correlated with severity of zoster and likelihood of post-herpetic neuralgia whereas levels of Anti-VZV antibodies (a measure of humoral immunity) were not. Gilbert et al. (2014)[6] was a good quality study that found that the fold-rise in Anti-VZV antibodies from baseline to 6 weeks post-vaccination was associated with protection against zoster as measured by vaccine efficacy whereas levels more than 6 weeks post-vaccination were not. Thus, it is the rate of increase in antibodies in the first 6 weeks that is the best predictor of actual vaccine efficacy.

Beals et al. (2016)[33] was a fair quality study that assessed differences in immunogenicity between intradermal and subcutaneous administration. The study found a higher GMFR for intradermal (3.25) than subcutaneous (1.74) administration. Increases in Anti-VZV antibodies persisted up to 18 months in the intradermal group but not the subcutaneous group. Diez-Domingo et al. (2015)[39] was a fair quality study that assessed CMI and humoral immunity between subcutaneous and intramuscular administration. At four weeks post-vaccination, there were no differences between these two routes. Gilderman et al. (2008)[40] was a fair quality study that assessed differences between refrigerator-stable versus frozen formulation of LZV. Both formulations were found to elicit similar responses in Anti-VZV antibody levels at four weeks post-vaccination.

Sutradhar et al. (2009)[8] was a fair quality study that assessed differences in humoral response between those 50-59 years old and those older than 60. While GMFRs in the two groups were higher than baseline (2.6 and 2.3 for 50-59 and 60+ respectively), the GMFR ratio was significantly higher among those 50-59 years old at 1.13 (95% CI 1.02, 1.25).

Levin et al. (2016)[10] was a fair quality study that assessed CMI and humoral immunity of a booster dose among those 70 years and older who had received vaccine at least 10 years prior versus first-time vaccine recipients between 50-59, 60-69 and older than 70 years of age. In general, CMI/humoral responses were more robust among the younger age groups. Markers of CMI (IFN-gamma and IL-2) were higher among those 70 years and older receiving a booster dose versus a first dose, suggesting a possible role for LZV booster. The study also demonstrated a decrease in CMI response 6-weeks post-vaccination for those over 70 years of age compared to those between 60 and 69 years of age; such a difference was not observed for the humoral response. Similarly, Weinberg et al. (2015)[37] was a study that compared humoral/CMI response among those 70 years and older receiving a first dose and those who had been vaccinated at least 10 years prior. While antibody responses were similar in both groups, IFN-gamma cell counts were higher in the previously vaccinated group at peak response and at 1 year of follow-up. Weinberg et al. (2017)[32] was a poor quality cohort study that assessed differences in the immune response between younger and older adults. It found

that older adults appear to have a higher proportion of senescent and exhausted VZV-specific T-cells.

Arnou et al. (2011)[41] was a poor quality study using vaccine near its expiration date that demonstrated an acceptable rise in anti-VZV antibodies in all age groups 28-35 days post vaccination, but with a more robust response among those 50-59 versus those over 60. Choi et al. (2016)[42] was a poor-quality study among Korean adults that demonstrated acceptable antibody increases 6 weeks post-vaccination. Yao et al. (2015)[43] was a poor-quality study among Taiwanese adults that demonstrated a GMFR of 3.05 four weeks post-vaccination.

Laing et al. (2015)[44] was a small (n=12) poor quality study that assessed magnitude and breadth the CD4+ T-cell response post-vaccination. The magnitude and breadth increased by 2.3 and 4.2 times respectively at one-month, although levels declined by 6 months. Patterson-Bartlett et al. (2007)[45] was a poor quality study aimed at phenotypic and functional characterization of T-cells, and demonstrated a significant increase in VZV-specific TH1, memory, early effector, and cutaneous homing receptor-bearing T-cells. Qi et al. (2016)[46] was a poor quality study that assessed defective T-memory cell differentiation. It showed that IFN-gamma T-cells peaked at 7-14 days post-vaccinations and declined afterwards and also demonstrated that antibody levels and T-cell frequencies were not correlated. Sei et al. (2015)[47] was a poor-quality study that demonstrated that an increase in polyfunctional CD4+ and ORF9-specific CD8+ cells contribute to vaccine efficacy. Sullivan et al. (2013)[48] was a study that compared B and T-cell response in adults 25-40 years versus 60-79 years. It demonstrated an increase in B-cell proliferation in both groups but a more rapid decline among the elderly; for the T-cell response there was no difference across age groups.

Macaladad et al. (2007)[49] was a poor quality study that assessed LZV among adults over 30 who were seronegative or low low-seropositive. It found that the vaccine elicited a robust anti-VZV antibody response among all patients, regardless of initial serostatus.

III.3 Live vaccines in immunocompromised populations

Summary

Studies assessed people who were immunocompromised from their disease and through immunosuppressive therapies. There were 12 studies in this group, of which 2 were good quality, 2 were fair quality, 3 were poor quality, and the remainder could not be assessed as they were abstracts only. Study interventions for this population group included LZV, heat-treated zoster vaccine (ZV_{HT} – generally administered four times 30 days apart) and inactivated Zoster vaccine (ZV_{in} – generally administered four times 30 days apart). Studies generally assessed humoral immunity (through anti-VZV antibody levels) and many also assessed CMI (usually through VZV-specific IFN-gamma spot-forming cells with ELISPOT). Key takeaways from the studies include:

- ***Hematologic malignancies:*** *Three studies[13, 14, 15] showed that patients with hematologic malignancies demonstrated both CMI and humoral immunity responses following immunization.*
- ***Solid tumor malignancy:*** *One study showed robust CMI and humoral immunity responses in this group[13].*
- ***Hematopoietic stem cell transplant (HSCT) patients:*** *Among allogenic HSCT patients, one study[13] showed a decline in IFN-gamma GFMR while another showed no increase[50]. There was a significant IFN-gamma response among autologous HSCT*

patients in both studies. Both studies also showed no humoral response among allogenic or autologous HSCT patients.

- ***Chronic/maintenance corticosteroids:*** *One good quality study demonstrated significant humoral response on patients on steroids who received vaccine compared to the non-vaccine placebo group*[11].
- ***Rheumatoid arthritis (RA) patients:*** *One study demonstrated a robust humoral response comparable to the general population for RA patients on methotrexate +/- tofacitinib. The CMI response was significant, but of slightly lower magnitude than healthy individuals without RA*[16].
- ***Inflammatory bowel disease (IBD):*** *Two studies*[17, 18] *demonstrated that IBD patients on immunomodulators had a blunted (but still significant) CMI and humoral immunity response compared to IBD patients not on such treatment.*
- ***Autoimmune conditions not on biologics:*** *One study found significant increases in CMI and humoral immunity response in autoimmune patients not on biologics (note it did not specify which type of autoimmune conditions)*[12].
- ***HIV+ with CD4<200****: One study showed robust CMI and humoral immunity responses in this group*[13].
- ***Other chronic diseases:*** *One study found no difference in response between diabetic patients and healthy controls*[51]*; another found no difference in response between those with end-stage renal diseases and healthy donor controls*[52]*. One study among patients with major depressive disorder found no differences in IFN-gamma and anti-VZV antibody response between depressed (treated), depressed (untreated), and not depressed but did find a lower response in VZV-RCF (responder cell frequency), another marker of CMI, among those with untreated depression compared to the other group*[53].

Mullane et al. (2013)[13] was a good quality study of ZVHT among five different types of immunocompromised populations (solid tumor malignancy, hematologic malignancy, HIV-infected, autologous HSCT, allogenic HSCT). At four weeks post-vaccination, all groups had increases in GMFR for both Anti-VZV antibodies and IFN-gamma ELISPOT counts with two exceptions. Allogenic HSCT patients had a significant decline in IFN-gamma GMFR while neither allogenic not autologous HSCT patients had a significant rise in anti-VZV antibody GMFR (note autologous HSCT patients did have an increase in IFN-gamma response). Winston et al. (2011)[50], a study of ZV_{HT} demonstrated similar results: There was a slight decrease in anti-VZV antibodies among both autologous and allogenic HSCT patients while for IFN-gamma response there was an increase among autologous HSCT patients (GMFR 7.6 at post-dose 4) but not allogenic HSCT patients (GMFR 0.2 at post-dose 2)

Russell et al. (2015)[11] was a good quality study of LZV that assessed humoral response among patients on chronic/maintenance corticosteroids. It found a significantly higher GMFR among the vaccine group (2.3) versus the placebo group (1.1).

Camacho et al. (2010)[14] was a ZV_{HT} study among patients with hematologic malignancy that demonstrated increases in GMFR for both anti-VZV antibodies (1.3) and IFN-gamma ELISPOT counts (2.2). Parrino et al. (2017)[15] used ZV_{in} for patients with hematologic malignancies on anti-CD20 monoclonal antibodies. CMI was assessed through IFN-gamma ELISPOT and was found to have a GMFR of 4.34 at 28 to 35 days post-vaccination.

McAdam et al. (2013)[12] was a study of ZV_{in} among patients with autoimmune conditions not on biologics that found significant increases in GMFR for both anti-VZV antibodies (1.57) and IFN-gamma ELISPOT (2.01) 4-weeks post-vaccination. Winthrop et al. 2017[16] was a fair quality study of LZV among methotrexate-treated rheumatoid arthritis patients with and without

tofacitinib. Both CMI and humoral immunity response was similar in these two groups; results were comparable to the expected response in healthy individuals for the humoral response and slightly lower for the CMI response.

Wasan et al. (2016)[17] was a fair quality study with 39 participants that used LZV in inflammatory bowel disease patients on low-dose immunomodulators (immunosuppressed) or 5-ASA or no therapy (not immunosuppressed). The former group had a reduced humoral and CMI response compared to the latter but still had a significant response. These results build on an earlier Wasan et al. (2012)[18] study with 17 participants that also used LZV in inflammatory bowel disease patients with and without immunosuppression. The immunosuppressed group did manage to mount a significant immune response but one that was lower than the immunocompetent group.

Hata et al. (2013)[51] was a poor quality study that assessed LZV among diabetic patients and healthy volunteers. Both CMI and humoral immunity at 6 months post-vaccination were similar across these two groups. Kho et al. (2016)[52] assessed LZV among patients with end-stage renal disease awaiting transplant. VZV-specific IgG titers at 1, 3, and 12 months post-vaccination were comparable to healthy controls post-vaccination. Irwin et al. (2013)[53] was a poor quality study that assessed LZV among patients with and without major depressive disorder (and among those with MDD people on and not on treatment). CMI was assessed through VZV-RCF (responder cell frequency) and IFN-gamma ELISPOT while humoral immunity was assessed through anti-VZV antibodies at 6, 52, and 104 weeks. There were no differences in IFN-gamma or antibody response but there was reduced VZV-RCF response among those with untreated depression compared to the treated and healthy cohort.

III.4 Subunit vaccines in the general population

Summary: *There were 9 studies assessing RZV immunogenicity in the general population. Of these 1 was a good quality studies, 2 were fair quality studies, 3 were poor quality studies, and the remaining could not be assessed as they were abstracts. All studies used RSV (2 doses administered two months apart). Studies generally all assessed humoral immunity (through anti-gE antibody levels) and many also assessed CMI, usually through CD4+ T-cells with at least two activation markers (including expression of IFN-gamma, IL-2, TNF-alpha, or CD40 ligand). The RSV vaccine contains a new adjuvant, AS01$_B$ that has been explored in candidate malaria vaccines but has not been previously authorized for use in Canada. RZV was found to be immunogenic in all studies. Key takeaways from the studies include:*

- ***Duration of protection:*** *One study found that while humoral and cell-mediated immunity peak at month 3, anti-gE and CD4+ T-cells were elevated from baseline at 72 months post-vaccination[22]. Another study available only as an abstract found that levels were still elevated from baseline at 9 years post-vaccination, with anti-gE And T-cell levels plateauing between years 4 and 9 post-vaccination[21].*
- ***Age of vaccine recipient and immunogenicity:*** *One study found that similar levels of CMI and humoral immunity were elicited across those aged 50-59, 60-69, and over 70 years of age[54]. Among patients with prior zoster infection, the subunit vaccine was found to generate a robust humoral response that was similar for all age groups over 50[23].*
- ***Vaccine formulation:*** *One study found that the highest vaccine response was elicited using AS01B adjuvant[54] versus AS01E adjuvant or no adjuvant.*

- ***Concurrent vaccination with live vaccination:*** *One study showed that there was no difference in immune response between receiving RZV or RZV and Varilrix (a live vaccine[24]).*
- ***Mechanism of administration:*** *One study found that there was no difference in the production of anti-gE antibodies between intramuscular or subcutaneous vaccine administration[55].*
- ***Prior zoster or zoster vaccine:*** *One study showed that measures of immunity were similar among those given RZV with and without a prior history of live zoster vaccine[25]. Similarly, one study demonstrated that among patients with a history of zoster, RZV elicited a robust humoral immune response that was similar for all age groups over 50 [23].*

Chlibek et al. (2016)[22] was a poor quality study of RZV that assessed long-term immunogenicity (follow-up to 72 months). Anti-gE and CD4 T-cell counts peaked at month 3 and declined but were still higher than baseline at 72 months. Pauksens et al. (2017)[21] was a long-term cohort study that assessed CMI and humoral immunity 9 years post-vaccination. Both CMI (3.4 times) and humoral immunity (7.4 times) were higher at 9 years than at baseline. Responses peaked at 3 months but persisted up to 9 years with a plateauing between 4 and 9 years.

Diez-Domingo et al. (2016)[34] assessed a large population of European adults (n=23,289) over 50 years for receiving RZV with anti-gE geometric mean concentration (GMC) and CD42+ T-cell-frequencies. There was a 38.0 and 21.2 times fold rise from baseline to 1-month post vaccination respectively for anti-gE and CD42+ T-cells.

Chlibek et al. (2013)[54] was a good quality study that assessed differences in CMI (CD4+ T-cells with at least two activation markers) and humoral immunity (anti-gE and anti-VZV antibodies) response among different adjuvant combinations with RZV. It found that AS01B was superior to AS01E and saline in eliciting both responses. Patients immunized with AS01B had similar CMI and humoral immunity responses at all ages. Leroux-Roels et al. (2012)[24] was a fair quality study that assessed CMI and humoral immunity among patients receiving RZV, Varilrix (a live vaccine), and RZV and Varilrix. Up to 12 months, the immune response was higher among RZV and RZV + Varilrix groups versus the Varilrix only group; adding Varilrix to RZV did not enhance immunogenicity. A subset of the study population was followed to 42 months post vaccination – immune response had decreased by then but were still above baseline.

Vink et al. (2017)[55] was a fair quality study that assessed subcutaneous versus intramuscular administration of RZV among Japanese adults. It found a decline in anti-gE antibodies between 1 and 12 months post-vaccination but no differences between the two modes of administration.

Grupping et al. (2017)[25] assessed the use of RZV in patients previously immunized with live vaccine at least 5 years prior. It found that measures of CMI and humoral immunity (CD4+ cells with at least 2 activation markers, anti-gE antibodies) were similar at baseline among immunized and non-immunized groups and post-vaccination were equally higher among both groups. Godeaux et al. (2017)[23] was a poor quality study of RZV among patients with a previous history of zoster. It found that anti-gE levels increased significantly and similarly across all age groups (50-59, 60-69, and 70+) from baseline to 1 month post-vaccination.

Lal et al. (2013)[56] was a poor quality study of RZV in ethnically Japanese patients. It found significant increases in anti-gE and anti-VZV antibody levels up to month 3 (31-fold and 11-fold

increase respectively among those aged 50-69). Response was higher among those aged 18-30 versus those aged 50-69.

III.5 Subunit vaccines in immunocompromised populations

Summary: *Five studies assessed the use of RZV in immunocompromised populations, including patients with HIV, autologous HSCT, hematologic malignancies, solid tumors, and renal transplants. Studies assessed humoral immunity (through anti-gE antibody levels) and CMI (generally through CD4+ T-cells with at least two activation markers). In some of the abstracts, only vaccine response rate (VRR) was reported. In general, these studies demonstrated that RZV elicited significant humoral and CMI responses among these populations. It is important to note that three of the five studies in this section were posters from the IDWeek 2017 conference and not full manuscripts.*

Berkowitz et al. (2015)[26] was a good quality study that assessed a three-dose course of RZV among HIV positive patients (on ART with CD4≥200, on ART with CD4 between 50-199, and ART-naïve with CD4≥500). The study found that up to 18 months, both CMI and humoral immunity levels were higher than baseline among all three groups, with geometric mean ratios of 21.95 and 46.22 compared to placebo respectively. The third dose did not improve immunogenicity from the first two.

Stadtmauer et al. (2014)[27] was a fair quality study that suggested a third-dose was helpful among patients with autologous HSCT. This was a fair quality study that assessed two versus three dose regimes of RZV+AS01B and a three-dose regimen of RZV+AS01E among autologous HSCT transplant patients. The three-dose regime with AS01B was superior to the three dose AS01E and the two dose AS01B regimes.

Oostvogels (2017)[28], Vink (2017)[29], and Vink (2) (2017)[30] assessed immunogenicity in patients with hematologic malignancies, solid tumors before and after immunosuppressive therapy, and renal transplant patients respectively. Oostvogels (2017 – ID week poster) demonstrated a CMI VRR of 80% compared to <10% in vaccine and placebo groups respectively at 1 month post-vaccination. Vink (2017 – ID week poster) demonstrated an adjusted humoral GMC of 23.2 and an adjusted CMI GMC of 9.9. Vink et al. (2) (2017 – ID week poster) demonstrated an adjusted humoral GMC of 17.0 and an adjusted CMI GMC of 14.0.

III.6 Head-to-head comparisons of live versus subunit vaccines

Weinberg et al. (2017)[32] was the only study that compared immunogenicity in a head-to-head fashion. It suggests that there is a higher memory CD4+ and CD8+ response among those receiving RZV than those receiving the live vaccine.

III.7 Concomitant administration of herpes zoster and other vaccines

Two studies[19, 20] assessed the immunogenicity of concomitantly administering LZV with other vaccines and one study assessed the immunogenicity of concomitant administration of RZV with the influenza vaccine[31].

MacIntyre et al. (2010)[19] was a good quality study that assessed concomitant administration of LZV with Pneumovax 23. It found a geometric mean titre (GMT) ratio of 0.70 (95% CI 0.60, 0.80) for concomitant versus non-concomitant (LZV delayed for 28 days), suggesting a lower

response. However, the GMFR for concomitant administration did meet acceptable anti-VZV antibody response thresholds. Levin et al. (2018)[20] was a good quality study that assessed concomitant administration of LZV with quadrivalent influenza vaccine. Concomitant administration was found to be non-inferior according to pre-specified criteria (GMT ratio 0.87) to non-concomitant administration and led to an anti-VZV antibody GMFR of 1.9. Schwarz et al. (2017)[31] was a fair quality study that assessed concomitant administration of RZV with quadrivalent influenza vaccine. Concomitant administration was found to be non-inferior (GMC ratio control to concomitant was 1.08) for both RZV and the influenza vaccine as measured by GMC ratios at 1 month post-vaccination.

IV. EVIDENCE GAPS

Limited evidence is available on head-to-head comparisons of LZV and RZV immunogenicity. Another area where evidence is relatively sparse is in the use of RZV in special populations including those with immunosuppression. Three of the five studies included in the review for RZV in this group come from ID Week 2017 posters and have not been peer-reviewed at the time of publication of this literature review.

V. DISCUSSION/SUMMARY

In general, most papers suggest that both LZV and RZV are immunogenic in the general population. The duration of immunogenicity appears to be at least for 3 years for LZV and at least 9 years for RZV. Among immunosuppressed populations, LZV appears broadly immunogenic except for patients receiving allogenic or autologous hematopoietic stem cell transplants. RZV also appears immunogenic in immunosuppressed populations, but this conclusion is based on a small number of studies which are mostly non-peer reviewed. In one non-peer reviewed head-to-head study of live versus subunit vaccine, the latter appears to generate a more robust memory T-cell response, which suggests it ay be more immunogenic.

Unfortunately, there is a relative dearth of studies directly comparing the immunogenicity of LZV and RZV. There is also a deficit of peer-reviewed studies on RZV in immunocompromised populations. From a data quality perspective, a large proportion of the included studies were abstracts, making assessment of study quality challenging.

VI. CONCLUSIONS

While there are no proven immunologic correlates of protection for zoster, some evidence suggests that memory T-cells play an important role in protection. Among studies that assessed the live vaccine, the most commonly used measure of humoral immunity were levels of Anti-VZV antibodies while the most commonly used measures of cell-mediated immunity it were VZV-specific IFN-gamma spot-forming cells with ELISPOT or responder cell frequency assay of CD4+ memory cells. Among studies that assessed the subunit vaccine, the most commonly used measure of humoral immunity were levels of Anti-gE antibodies while the most commonly used measures of cell-mediated immunity was CD4+ cells with at least two activation markers.

The evidence reviewed suggests that both LZV and RZV are immunogenic in the general and immunocompromised populations. For LZV, duration of protection extended up to 3 years (based on the longest follow-up study). Immunogenicity from LZV appears to wane based on

age of the recipient, with the highest response among those aged 50 to 59 and a diminished response for those 70 and older. Finally, there was no difference in humoral or CMI response between one or two dose regimens. Concomitant administration of LZV with pneumococcal or influenza vaccine was non-inferior to non-concomitant administration. Among immunocompromised populations, an altered formulation of live vaccine (usually heat-treated or inactivated with a four-dose schedule) was found to be immunogenic in all groups except for allogenic and autologous HSCT patients.

For RZV, the duration of protection extended up to 9 years (based on the longest follow-up study. Immunogenicity from RZV does not appear to decrease with age of the vaccine recipient. The AS01B adjuvant was found to be most immunogenic and there were no benefits to administering RZV with a live zoster vaccine. Concomitant administration of RZV with influenza vaccine was non-inferior to non-concomitant administration. Among immunocompromised populations, two peer-reviewed publications demonstrated that RZV was immunogenic among HIV+ patients and those receiving autologous HSCT. Three non-peer reviewed publications demonstrated immunogenicity in other immunocompromised patient groups.

There is limited evidence of head-to-head to comparisons between these two vaccines: One non-peer reviewed study that assessed this found a higher memory CD4+ and CD8+ response for RZV recipients versus live vaccine recipients. Ultimately, it appears that while both vaccines are immunogenic, RZV is at least comparable if not superior to LZV in eliciting an immune response based on the duration of protection and a stronger memory T-cell response.

VII. LIST OF ABBREVIATIONS

Abbreviation	***Term***
AE	Adverse Effect
AS	Adjuvant System
BGTD	Biologics and Genetic Therapies Directorate
BOI	Burden of Illness
CUA	Cost Utility Analysis
CIHR	Canadian Institutes of Health Research
CMI	Cell-Mediated Immunity
CI	Confidence Interval
CKD	Chronic Kidney Disease
DSEN	Drug Safety and Effectiveness Network
GM	Geometric Mean
GMC	Geometric Mean Concentration
GMFR	Geometric Mean Fold Rise
GMR	Geometric Mean Ratio
GMRI	Geometric Mean Ratio Increase
GMT	Geometric Mean Titre
GP	General Practitioner
HR	Hazard Ratio
HSCT	Hematopoietic Stem Cell Transplantation
HZ	Herpes Zoster
HZWG	Herpes Zoster Working Group
HZO	Herpes Zoster Ophthalmicus
ICER	Incremental Cost-Effectivness Ratio
IM	Intramuscular Administration
IR	Incidence Rate
LZV	Live Zoster Vaccine
MAGIC	Methods and Applications Group for Indirect Comparisons
NACI	National Advisory Committee on Immunization
NNV	Number Needed to Vaccinate
PHN	Post-Herpetic Neuralgia
PICOS	Population, Intervention, Comparator, Outcomes and Study design
Pneu-P-23	Pneumococcal polysaccharide 23-valent vaccine
PY	Person Years
QALY	Quality Adjusted Life Years
RAMQ	Regie de l'Assurance Maladie du Quebec
RCF	Responder Cell Frequency
RR	Relative Risk
RZV	Recombinant Zoster Vaccine
SAE	Serious Adverse Effect
SAAE	Serous Autoimmune Adverse Event
SC	Subcutaneous Administration

SFC	Spot Forming Cells
SPS	Shingles Prevention Study
STPS	Short-Term Persistence Substudy
UI	Uncertainty Intervals
VE	Vaccine Efficacy
VRR	Vaccine Response Rate
VZV	Varicella Zoster Virus

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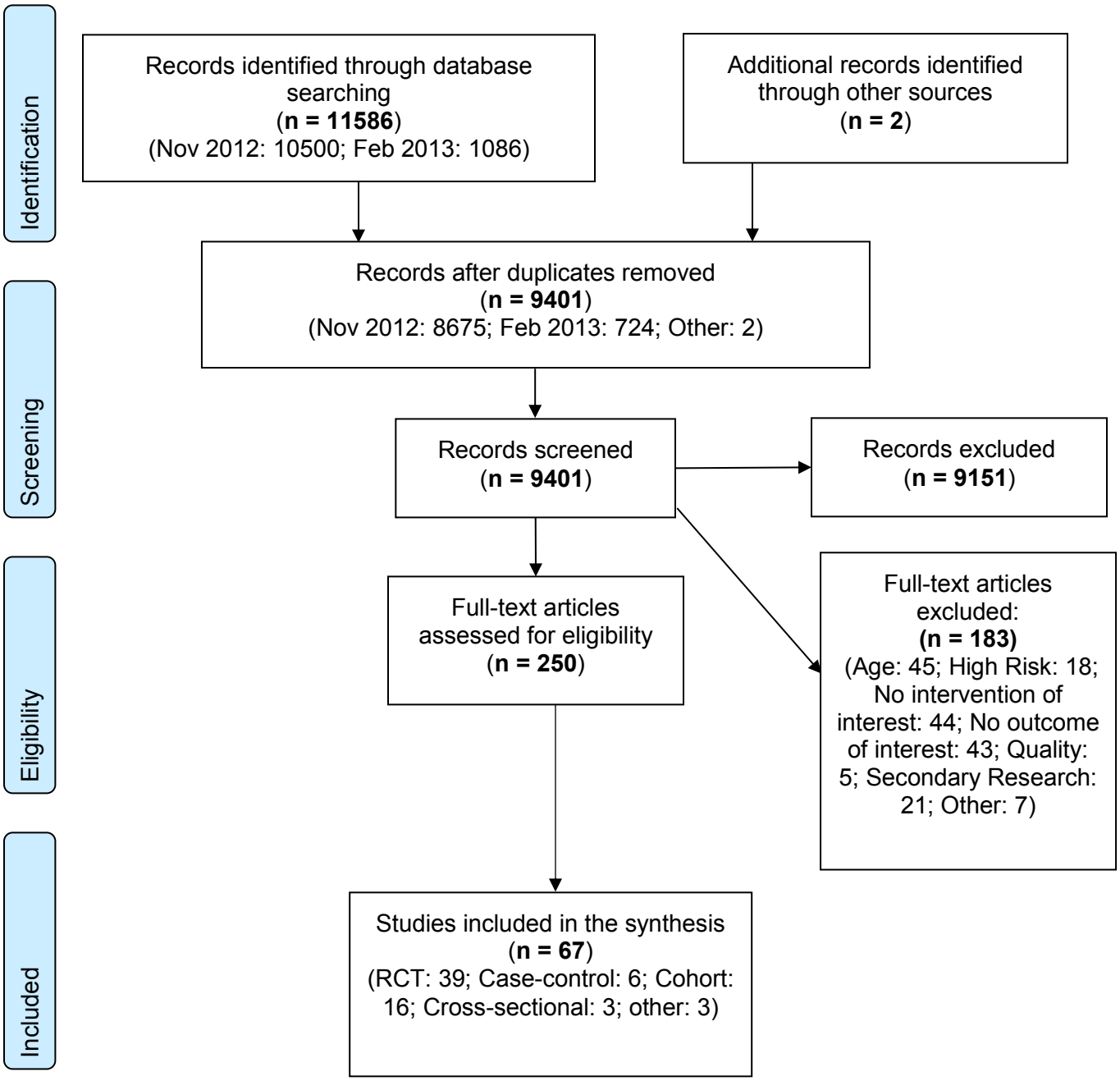
Appendix A: Search strategy and results

Database		Web of Science	Medline	EMBASE
KEYWORDS AND LIMITS	**Disease**	influenza OR flu OR h1n1	influenza.mp. or exp Influenza, Human/	influenza.mp. or exp influenza/
		AND	AND	AND
	Interven-tions	vaccin* OR immuni* OR innocul*	influenza vaccine.mp. or exp Influenza Vaccines/	vaccine.mp. or exp vaccine/
		AND	AND	AND
	Out-comes	effective* OR efficacy OR outcome OR response OR hemagglutinin OR antibod* OR safety OR adverse event OR side effect OR precaution OR tolerability OR tolerance OR toxicity OR Guillain Barre OR neurologic OR Bell's palsy OR contraindication OR signal OR complication OR undesirable effect OR failure OR mortality OR death OR hospital* OR concomitant OR parallel OR concurrent OR collateral OR joint	[(vaccin* or immuni* or innocul*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]] OR [(effective* or efficac* or outcome or response or hemagglutinin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] OR (safety or adverse or side effect or precaution or tolera* or toxicity or guillain barre or neurologic* or signal or contraindicat* or complication or undesirable or fail* or mortality or death or hospital*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] OR (concomitant or parallel or concurrent or collateral or joint or coincident).mp. [mp=title, abstract, original title, name of	(vaccin* or immun* or inoculat*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] OR (effective* or efficac* or outcome or response or hemagglutinin or haemagglutinin or antibod*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] OR (safety or adverse or side effect or precaution or toler* or toxicity or Guillain Barre or contraindicat* or signal or neurologic* or Bells palsy or complication or undesirable effect or fail* or mortality or death or hospital*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] OR (concomitant or parallel or concurrent or collateral or joint or coincident).mp. [mp=title, abstract, subject

Database		Web of Science	Medline	EMBASE
		OR coincident	substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] OR antibod*.mp. or exp Antibodies/ or exp Antibodies, Monoclonal/	headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
		AND	AND	AND
	Popula-tion	human*	Limit to humans and "all adult (19 plus years)"	Limit to human and adult 18 to 64 years
		AND	AND	AND
	Time Period[a]	2000-01-01 to 2013-02-05	Limit to 2000-Current (February 5, 2013)	Limit to 2000-Current (February 5, 2013)

Web of Science databases searched = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH. 1) November 9, 2012 with the time period: 2000-01-01 - 2012-11-09 [Web of Science] and 2000 to current [Medline and EMBASE]. 2) February 5, 2013 with the time period: 2012-11-09 – 2013-02-05 [Web of Science] and 2012 to current [Medline and EMBASE]

Appendix B: Flow diagram



Appendix C: Level of evidence based on research design and quality (internal validity) rating of evidence

Table 1. Ranking Individual Studies: Levels of Evidence Based on Research Design

Level	Description
I	Evidence from randomized controlled trial(s).
II-1	Evidence from controlled trial(s) without randomization.
II-2	Evidence from cohort or case-control analytic studies, preferably from more than one centre or research group using clinical outcome measures of VE.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees.

Table 2. Ranking Individual Studies: Quality (Internal Validity) Rating of Evidence

Quality Rating	Description
Good	A study (including meta-analyses or systematic reviews) that meets all design- specific criteria* well.
Fair	A study (including meta-analyses or systematic reviews) that does not meet (or it is not clear that it meets) at least one design-specific criterion* but has no known "fatal flaw".
Poor	A study (including meta-analyses or systematic reviews) that has at least one design-specific* "fatal flaw", or an accumulation of lesser flaws to the extent that the results of the study are not deemed able to inform recommendations.

* General design specific criteria are outlined in Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med 2001;20:21-35.

Appendix D: Summary of evidence related to immunogenicity of herpes zoster vaccines

Live vaccine studies in the general population (n=22)

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Gilbert et al, 2014[6]	Zostavax among 50-59 year olds	Randomized controlled trial (subset of ZEST trial) to assess correlates of protection	n=2491 n=1218 (vaccine group) n=1273 (placebo group)	Anti-VZV antibodies using gpELISA measured at baseline and 6 weeks GMT in vaccine group increased from 284 (95% CI 267,303) to 662 (95% CI 627, 698); GMFR was 2.31 (95% CI 2.20, 2.43) GMT and GMFR were unchanged in placebo group	Level I	Good
Levin et al, 2013[38]	Zostavax among 50-59 year olds	Randomized, double-blind, placebo-controlled multicentre study	n=2269 (subset of ZV efficacy trial n=22,439) n=1136 (vaccine group) n=1133 (placebo group)	Anti-VZV antibodies through gpELISA at baseline and week 6 GMT increase from 293.1 to 660.0 from baseline to week 6 in vaccine group, a GMFR of 2.31 while antibodies were unchanged in placebo group	Level I	Good
Levin et al, 2008[5]	Zostavax among 60 years and older	Randomized, double-blind, placebo-controlled trial Denver and San Diego	n=1395 (subset of SPS n=38,546) n=691 (vaccine group) n=704 (control group)	CMI: Responder cell frequency (RCF) assay and SFCs (IFN-gamma) via ELISPOT at baseline, week 6, and years 1, 2, and 3 Humoral immunity: Anti-VZV antibodies with gpELISA at baseline, week 6, and years 1, 2, and 3 CMI (both measures) and humoral immunity were higher among those who received vaccine, an effect that	Level I	Good

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
				persisted up to 3 years. RCF & SCF GMTs and Anti-VZV antibodies peaked at 6 weeks and decreased afterwards		
Vermeulen et al, 2012[35]	Zostavax among 60 years and older	Randomized, placebo-controlled, double-blind, trial	n=210 (all ≥60 years) n=104 (2 doses of Zostavax 6 weeks apart) n=105 (placebo)	CMI: IFN-gamma SFCs through ELISPOT at baseline, 2 and 6 weeks after each dose), and 6 months post-vaccination GMCs were higher among the vaccine group and peaked at 2 weeks post-vaccination 1; by 6 months post-vaccination 2, GMCs were higher than baseline but lower than peak levels Humoral immunity: Anti-VZV antibodies through gpELISA at baseline and 2 and 6 weeks after immunization Anti-VZV antibodies were higher among the vaccine group and peaked at 2 weeks post-vaccination 1 In general, a second dose of Zostavax did not boost VZV-specific immunity	Level I	Good
Weinberg et al, 2009[7]	Zostavax	Randomized, double-blind, placebo-controlled, trial	n=2343 (from SPS trial) n=981 (developed zoster) n=1362 (no zoster)	CMI (IFN-gamma through ELISPOT) corresponded with zoster morbidity whereas humoral immunity (Anti-VZV antibodies through gpELISA) did not correspond as strongly with morbidity	Level I	Good

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Beals et al, 2016[33]	Zostavax (in various doses intradermally and subcutaneously)	Randomised, partially-blinded parallel group study (there were concomitant placebo given) 3 clinics in Colorado and Florida	n=223 6 groups (full dose & 1/3 dose subcutaneous; full dose, 1/3 dose, 1/10 dose, and 1/27 dose intradermal) ≥ 50 with a history of varicella or residing in a varicella endemic country for 30 years or more	Anti-VZV antibodies (GMT through gpELISA, GMC through ELISPOT) pre-vaccination and at 6 weeks and 18 months Full dose subcutaneous resulted in GMFR of 1.74 (90% CI 1.48, 2.04) post 6-weeks compared to 3.25 (90% CI 2.68, 3.94) for intradermal. GMFR persisted for intradermal but not subcutaneous administration at 18 months.	Level I	Fair (no control group that did not receive vaccine, imbalance in gender distribution for some of the groups)
Diez-Domingo et al, 2015[39]	Zostavax (administered subcutaneously and intramuscular)	Open-label non-inferiority trial Germany, Spain	n=354 n=177 (IM group) n=177 (SC group)	CMI: ELISPOT assay measured for a subset of participants using at baseline and 4 weeks post-vaccination CMI was comparable between IM and SC groups Humoral immunity: VZV antibody titres measured for all participants at baseline and 4 weeks post-vaccination Humoral immunity was comparable between IM and SC groups	Level I	Fair (No control group did not receive vaccine, CMI was measured only for a subset of study population)
Gilderman et al, 2008[40]	Zostavax (refrigerator-stable versus frozen formulation)	Double-blind, randomized controlled trial	n=368 initial enrollment n=182 (refrigerated vaccine)	Anti-VZV antibodies using gpELISA measured at baseline and 28 days GMT and GMFR for refrigerator and frozen formulations were similar	Level I	Fair (on control group without vaccine)

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
			n=185 (frozen vaccine)			
Sutradhar et al, 2009[8]	Zostavax	Randomized, double-blind, clinical trial	n=1122 (from two separate multicentre trials) n=389 (50-59y years) n=733 (≥60 years)	Anti-VZV antibodies through gpELISA at baseline and 4 weeks GMTs and GMFRs were higher among both groups following vaccination, but slightly higher among 50-59 age group – adjusting for pre-vaccination titers, GMFR ratio for 50-59 versus ≥60 was 1.13 (95% CI 1.02, 1.25)	Level I	Fair (no control group that did not receive vaccine)
Vesikari et al, 2013 [36]	Zostavax (1 dose and 2 doses at 0 and 1 months or 0 and 3 months)	Phase 3, open-label, randomized trial	n=759 (all ≥70 years) n=243 (1 dose) n=203 (2 doses 1 month apart) n=198 (2 doses 3 months apart)	Anti-VZV antibodies through gpELISA at baseline and 4-weeks post-dose 1 and 2 and 12 months post last dose GMCs were similar between the 1 and 2-dose schedules at all time points	Level I	Fair (no control group that did not receive vaccine)
Levin et al, 2016[10]	Zostavax (second dose administered 10 years after first dose)	Non-randomized controlled study	n=600 n=201 (prior Zostavax, ≥70 years) n=199 (no prior Zostavax, ≥70 years) n=100 (no prior	CMI: SFCs (IFN-gamma & IL-2) via ELISPOT at baseline and weeks 1, 6, and 52 SFCs were significantly higher at baseline and up to 52 weeks after re-vaccination for those previously vaccinated compared to other groups, suggesting a residual effect of CMI that is enhanced by booster	Level II-1	Fair (no randomization, not all outcome measures were compared)

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
			Zostavax, 60-70 years) n=100 (no prior Zostavax, 50-60 years)	Humoral immunity: Anti-VZV antibodies with gpELISA at baseline and weeks 1, 6, and 52 All groups developed an increase in GMT at week 1 which peaked at week 6 while by week 52 GMTs were not significantly higher than baseline In general, baseline levels of CMI and humoral immunity were higher among younger people		
Arnou et al, 2011[41]	Zostavax (one dose)	Phase IV Open-label non-randomized study of Zostavax within 6 months of expiration 6 centres in France	n=96 n=50 between 50-59 years; n=46 ≥ 60 years	Anti-VZV antibodies through gpELISA pre-vaccination and 28-35 days after vaccination GMFR for the 50-59 age group was 3.9 (95% CI 3.0, 5.1) compared to 2.6 (95% CI 2.0, 3.4).	Level II-2	Poor (no control group, patient characteristics not reported, no description of withdrawals)
Choi et al, 2016 [42]	Zostavax (one dose) in Korean Adults	Open-label, single-arm Phase 4 study	n=180	VZV antibody GMT and GMFR at baseline and 4 weeks GMT increased from baseline of 66.9 (95% CI 59.2, 75.5) to 185.4 (95% CI 167.0, 205.9), representing GMFR of 2.8 (95% CI 2.3-3.1) GMFR for ≥60 was 2.6 while for 50-59 was 2.9	Level II-2	Poor (no control group, protocol deviation in 14 or 7.8% of subjects)
Laing et al, 2015[44]	Zostavax	Cohort	n=12	Magnitude and breadth of CD4+ T-cell response at baseline and 2, 4, and 26 weeks post-vaccination Essentially, vaccination increased the magnitude (2.3 times) and breadth (4.2 times) of CD4+ cells at one-	Level II-2	Poor (non-randomized, small sample size)

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
				month, although levels declined by 6 months		
Macaladad et al, 2007[49]	Zostavax among seronegative and low-seropositive adults	Cohort study (initially conceived of as RCT, but enrollment too low)	n=21 (adults ≥ 30 years) n=18 (vaccine group) n=3 (placebo group)	Anti-VZV antibodies through gpELISA at baseline and week 6 Antibody response was higher in vaccine group compared to placebo, but higher among low-seropositive (GMT=25.7 units/mL) than among seronegative (GMT=12.0 units/mL)	Level II-2	Poor (small sample size, very small control group)
Patterson-Bartlett et al, 2007[45]	Zostavax	Cohort study for phenotypic and functional characterization of T-cells	n=25 (20 of whom are ≥ 60 years) n=10 (vaccine group) n=10 (placebo group) n=5 (young adult controls)	Vaccine significantly increased VZV-specific Th1, memory, early effector, and cutaneous homing receptor-bearing T-cells	Level II-2	Poor
Qi et al, 2016[46]	Zostavax	Cohort study to assess defective T-memory cell differentiation	n=39	IFN-gamma ELISPOT at baseline, and day 8, 14, and 28 post-vaccination and Anti-VZV antibodies through ELISA at baseline and 28-days post-vaccination IFN-gamma T-cells increased peaked at 10 times baseline between 8 and 14 days and declined to 3 times baseline by day 28; correlation between increases in Anti-VZV antibodies and T-cell frequencies did not reach significance, suggesting these responses are independent	Level II-2	Poor

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Sei et al, 2015[47]	Zostavax	Cohort study to assess breadth, magnitude, and quality of ex vivo CD4+ & CD8+ response	n=21	The response of multiple antigens to multiple types of T-cells were assessed. Authors postulate that an increase in poly-functional CD4+ and ORF9-specific CD8+ cells contribute to efficacy	Level II-2	Poor
Weinberg et al, 2017[9]	Zostavax	Cohort study to assess differences in immune response between younger and older adults	n=58 n=25 (25-40 years old) n=33 (60-80 years old)	Older adults appear to have higher proportion of senescent and exhausted VZV-specific T-cells, leading to overall poor effector response to a VZV challenge.	Level II-2	Poor
Yao et al, 2015[43]	Zostavax among Taiwanese adults	Cohort study	n=150	Anti-VZV antibodies through gpELISA were higher 4 weeks post-vaccination, with a GMFR of 3.05 (95% CI 2.6, 3.6)	Level II-2	Poor
Sullivan et al, 2013[48]	Zostavax	Cohort study comparing B and T-cell proliferation among young and old	n=39 n=16 (25-40 years old) n=23 (60-79 years old)	There was a transient increase in B-cell proliferation in both groups, but a significant reduction in the elderly group. There were no differences in proliferation of CD4+ or CD8+ T-cells between young and old	Level II-2	N/A pending full methods
Weinberg et al, 2015 [abstract][37]	Zostavax	Cohort study	n=400 (all ≥70 years) n=201 (Zostavax ≥10 years prior) n=199 (no prior Zostavax)	Anti-VZV antibodies increased following vaccination and GMCs were similar across both groups IFN-gamma cell counts were higher in previously vaccinated group at week 6 (peak response) and year 1	Level II-2	N/A pending full methods

Live vaccine studies in immunocompromised populations (n=12)

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Mullane et al, 2013[13]	ZV_{HT} administered four times 30 days apart in populations with solid tumor malignancy, hematologic malignancy, HIV with CD4<200, autologous HSCT, and allogenic HSCT	Randomized, double-blind, placebo-controlled multicentre study	n=262 (vaccine group) n=79 (placebo group)	Anti-VZV antibodies through gpELISA and IFN-gamma ELISPOT counts pre-vaccination and 28 days after 4 doses GMFR for anti-VZV antibodies ranged from 0.9 to 2.4 depending on type of immunosuppression; For allogenic and autologous HSCT patients there were no changes in GMFR for anti-VZV antibodies. GMFR for IFN-gamma ELISPOT ranged from 0.2 to 9.0 depending on type of immunosuppression; For allogenic HSCT patients there was a significant decline in GMFR for IFN-gamma ELISPOT.	Level I	Good
Russell et al, 2015[11]	Zostavax in patients on chronic / maintenance corticosteroids	Randomized, double-blind, placebo-controlled, multicentre study	n=314 (initial enrollment, (adults ≥60 years) n=206 (VZV group) n=101 (placebo group)	Anti-VZV antibodies through gpELISA at baseline and 6 weeks GMFR among vaccine group was 2.3 (95% CI 2.0, 2.7), higher than that of placebo group with a GMFR of 1.1 (95% CI 1.0, 1.2)	Level I	Good
Winthrop et al, 2017[16]	Zostavax among rheumatoid arthritis patients on methotrexate with and without Tofacitinb	Randomized controlled trial	n=112 n=55 (Tofacitinib group started 2-weeks post-vaccination) n=57 (no	Both CMI and humoral immunity were similar among those receiving Tofacitinb and placebo at 6 weeks post vaccination: The GMFR for Anti-VZV antibodies was 2.11 in the Tofacitinib group versus 1.74 in the placebo group while the GMFR for IFN-gamma SFCs was 1.50 in the	Level I	Fair (no control group that did not receive vaccine, small sample size)

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
			Tofactinib group)	Tofacitinib group versus 1.29 in the placebo group . The magnitude of the humoral response was comparable to those seen in patients without rheumatoid arthritis while the CMI response was slightly less than in patient without rheumatoid arthritis.		
Camacho et al, 2010 [Abstract][14]	ZV_{HT} administered four times 30 days apart in adults with hematologic malignancy	Phase I randomized, double-blind, placebo-controlled study	n=80 n=61 received ZV_{HT} n=19 received placebo	Anti-VZV antibodies through gpELISA and IFN-gamma ELISPOT counts pre-vaccination and 28 days after 4 doses GMFR for anti-VZV antibodies was 1.3 (90% CI 1.1, 1.5) and 2.2 (90% CI 1.4, 3.5) for IFN-gamma ELISPOT.	Level I	N/A pending full methods
McAdam et al, 2013 [abstract][12]	Inactivated Varicella Zoster Virus vaccine - ZV_{in} (4 doses, 30 days apart) among patients with autoimmune disease on and not on biologics	Randomized, double-blind, placebo-controlled trial	n~340 n~180 (ZVin at lower Ag level) n~100 (ZV_{in} at higher Ag level) n~60 (placebo)	Anti-VZV antibodies through gpELISA and IFN-gamma through ELISPOT at baseline, postdose 2 (half of patients), postdose 3 (other half of patients), and 4 weeks after last dose At 28 days, there were statistically significant increases for both gpELISA (GMFR 1.57) and ELISPOT (GMFR 2.01) assays	Level I	N/A pending full methods
Winston et al, 2011 [abstract][50]	Heat-treated zoster vaccine (ZV_{HT}) among patients with	Randomized, double-blind, placebo-controlled trial	n=100 n=40 (vaccine group allogenic	Humoral immunity as measured through VZV-specific antibodies declined among patients with allogenic and autologous HSCT.	Level I	N/A pending full methods

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
	allogenic or autologous HSCT		HSCT) n=10 (no vaccine allogenic HSCT) n=40 (vaccine group autologous HSCT) n=10 (no vaccine autologus HSCT)	CMI as measured through IFN-gamma response were elicited among autologous HSCT patients (GMFR 7.6 at post-dose 4) but not among allogenic HSCT patients (GMFR 0.2 at post-dose 4)		
Wasan et al, 2016[17]	Zostavax among IBD patients on low-dose immunomodulators or 5-ASA or no therapy	Cohort study of patients immunosuppressed and not	n=39 n=14 (immunosuppressed – i.e. low-dose immunomodulators) n=25 (not immunosuppressed – i.e. 5-ASA or no therapy)	Immunosuppressed patients had a weaker immune response (both CMI & humoral) compared those not immunosuppressed, but their response was still significant at 2 and 6 weeks post-vaccination.	Level II-2	Fair (control group present, but small sample size and no randomization)
Hata et al, 2013[51]	Zostavax among diabetes mellitus patients	Cohort study	n=20 n=10 (healthy volunteers) n=10 (diabetic patients)	CMI: IFN-gamma through ELISPOT at baseline and months 3 and 6. SFC ratios at 6 months versus baseline were 2.3 for diabetic patients and 3.3 for healthy volunteers (not significantly different) Humoral immunity: Antibodies through immunoadherence hemagglutination (IAHA) test at baseline and months 3 and 6 No significant difference in antibody	Level II-2	Poor (non-randomized trial, small sample size)

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
				titres at 6 months between the two groups		
Irwin et al, 2013[53]	Zostavax among patients with major depressive disorder	Cohort study	n=92 (subset of the SPS study population) n=40 (MDD stratified by those on and not on antidepressant medications) n=52 (never mentally ill)	CMI: VZV-RCF and IFN-gamma ELISPOT at baseline and 6, 52, and 104 weeks Among those with MDD who were treated, VZV-RCF levels at 6 weeks were similar to non-depressed controls; Among those with MDD who were not treated, VZV-RCF at 6 weeks was unchanged from baseline; no significant differences in IFN-gamma levels across time and age groups Humoral immunity: Anti-VZV antibodies using gpELISA at baseline and 6, 52, and 104 weeks No significant differences in VZV-antibody levels across time and age groups	Level II-2	Poor (non-randomized, outcome reporting unclear, 12 of 52 initially selected in MDD group refused to participate)
Parrino et al, 2017[15]	Inactivated zoster vaccine (ZV_{in} 4 dose regimen) among patients with hematologic malignancies with anti-CD20 monoclonal antibody treatment	Open-label, single-arm Phase 1 study	n=80 (adults ≥ 18 years)	VZV IFN-gamma ELISPOT assay at baseline and 28-35 days postdose 4 GMFR 28-35 days postdose 4 was 4.34 (90% CI 3.0, 6.2)	Level II-2	Poor (no control group)
Kho et al, 2016 [abstract][52]	Zostavax among patients with end-stage renal	Cohort study	n=53 n=26 (ESRD	VZV-specific IgG titres measured at baseline and 1, 3, and 12 months post-vaccination	Level II-2	N/A pending full methods

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
	disease awaiting transplant		patients) n=27 (gender and age-matched kidney donors)	IgG titers among ESRD patients and controls were comparable and higher at all time points after baseline		
Wasan et al, 2012[18]	Zostavax among IBD patients on methrotrexate or thiopurines	Cohort study of patients ≥50 years	n=17 n=8 (low dose immunpressive therapy) n=9 (no immunosuppresive therapy)	Immunocompetent patients with IBD were able to mount a significant humoral and CMI response while immunosuppressed patients did not mount a significant humoral response but did mount a significant but reduced CMI response.	Level II-2	N/A pending full methods

Subunit (RZV) vaccine studies in the general population (n=9)

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Chlibek et al, 2013[54]	RZV (Two 50 µg doses 2 months apart with different amounts and types of adjuvant)	Phase 2 randomized controlled trial Czech Republic, Spain, United States	n=410 initial enrollment n=150 (RZV + AS01B) n=149 (RZV + ASO1E) n=73 (RZV + saline) n=38 (saline alone)	CMI: CD4+ T-cells with at least two activation markers at baseline, 1, and 3 months Response highest in those with AS01B, then AS01E, then saline Humoral immunity: Serum anti-gE and Anti-VZV antibodies at baseline, 1, and 3 months Response highest in those with AS01B, then AS01E, then saline Similar immunogenicity was noted across 50-59, 60-69, and ≥70 age groups for those given AS01B	Level I	Good
Leroux-Roels et al, 2012[24]	RZV (two doses 2 months apart), Varilrix (two doses 2 months apart), or both	Phase 1/2 open-label, randomized, parallel-group study Belgium	n=155 n=135 (age 50-70) – 45 each in the RZV, Varilrix, and RZV + Varilrix groups n=20 (age 18-30) – 10 each in RZV and RZV + Varilrix groups	CMI: CD4+ T-cells with at least 2 immune markers at baseline and months 1, 2, 3, and 12 for all patients; older adults who received RZV alone and met certain criteria were also sampled at months 30 and 42 Up to 12 months, CD4+ T-cells were higher with RZV than with Varilrix and not different between RZV and RZV + Varilrix groups By 42 months, CD4+ T-cells were lower than at 12 months but higher than baseline Humoral immunity: Anti-VZV and	Level I	Fair (no control group that did not receive vaccine)

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
				anti-gE titres at baseline and months 1, 2, 3, and 12 for all patients; older adults who received RZV alone and met certain criteria were also sampled at months 30 and 42 Up to 12 months, anti-VZV GMCs were higher with RZV than with Varilrix and not different between RZV and RZV + Varilrix groups; the anti-gE humoral response rate was higher than for anti-VZV By 42 months, antibody levels were lower than at 12 months but higher than baseline		
Vink et al, 2017 (55)	RZV (2 doses two months apart IM and SC administration) among Japanese adults	Phase3, open-label, randomized trial	n=60 n=30 (subcutaneous) n=30 (intramuscaular)	Anti-gE antibodies through ELISA at baseline and 1 and 12 months post-dose 2 There was a decline in anti-gE antibodies between 1 and 12 months post-dose 2, but an increase in levels above baseline; there was no difference between SC versus IM injection	Level I	Fair (small sample size)
Diez-Domingo et al, 2016 [abstract](34)	RZV (two doses 2 months apart) among European adults	Randomized clinical trial	n=23,289, ≥50 years (from ZOE-50 and ZOE-70 studies)	Humoral response: anti-gE GMC at baseline and 1-month post-second dose 38.0 times increase in anti-gE above baseline CMI: CD4+ T-cell frequencies with two activation markers at baseline and 1-month post-second dose	Level I	N/A pending full methods

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
				21.2 times increase in CD42+ frequency above baseline		
Grupping et al, 2017 (ID week poster)[25]	RZV in patients previously vaccinated (5 years ago or more) with live vaccine	Phase 3, matched, open-label, prospective trial	n=430 n=215 (previously vaccinated) n=215 (not previously vaccinated)	CMI: CD4+ T-cells with at least two activation markers at baseline, 1 month post-dose 1, and 1 month post-dose 2 Humoral immunity: anti-gE antibody concentrations baseline, 1 month post-dose 1, and 1 month post-dose 2 Measure of CMI and humoral immunity were similar at baseline for the two groups; by 1 month post-dose 2 they had increase significantly	Level I	N/A pending full methods
Chlibek et al, 2016[22]	RZV (Two 50 µg doses 2 months apart)	Phase 2 open-label, single-group trial Czech Republic, Germany, Sweden, Netherlands	n=166 initial enrollment n=129 at month 48 n=119 at month 72	CMI: CD4+ T-cells with at least two activation markers) at 48, 60, 72 months CD4 counts peaked at month 3 and then declined, but higher than pre-vaccination levels – Pre-vaccination:119.4 (Q1-3, 67.8,286.9); at 36 months 640.0 (Q1-3 403.0-1405.4); at 72 months 477.3 (Q1-3 231.4, 1037.0) Humoral immunity: Anti-gE antibody concentrations at 48, 60, 72 months Anti-gE antibodies peaked at month 3 and then declined, but higher than pre-vaccination levels – Pre-vaccination: 1121.3 mIU/mL (Q1-3 624.2, 2309.0); at 72 months 8159.0 (Q1-3 5451.2, 12212.4)	Level II-2	Poor (no control group – at least for the 72 month arm – initial study at control groups but only measured to 36 months)

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Godeaux et al, 2017[23]	RZV (two doses 2 months apart) among adults with a prior history of herpes zoster	Phase III, non-randomized trial	n=96 initial enrollment divided equally across 50-59, 60-69, and ≥70	Anti-gE GMCs and mean geometric increase at baseline and 28 days post-second dose GMC across all participants increased from 2398 (95% CI 1779 3233) to 47,759 (95% CI 42,259, 53, 794); mean geometric increase was 19.9	Level II-2	Poor (no control group, limited methods section)
Lal et al, 2013[56]	RZV (two doses 2 months apart)	Phase 1, open-label study Conducted in Australia but all patients were ethnically Japanese	n=39 n=20 (age 18-30) n=19 (age 50-69)	Anti-gE antibodies and Anti-VZV antibodies at baseline and months 1 and 3 Among the older patients, anti-gE GMC increased from 2,123 to 65,589 (31-fold increase) while anti-VZV GMC increased from 1284 to 12883 (11-fold increase); response was higher among those aged 18 to 30	Level II-2	Poor (no control group, small sample size)
Pauksens et al, 2017 (ID week poster)[21]	RZV	Phase 3b, open-label, long-term extension cohort study with 9 years follow-up	n=70	CMI (CD4+ cells with at least two activation markers) and humoral immunity (anti-gE antibody levels) peaked at month 3 but at 9 years was still higher than baseline (3.4 times for CMI and 7.4 times for humoral). Levels plateaued between years 4 and 9	Level II-2	N/A pending full methods

Subunit vaccine studies in immunocompromised populations (n=5)

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Berkowitz et al, 2015[26]	RZV (three doses at 0, 2, 6 months) in HIV+ patients	Phase ½, randomized, placebo controlled study	3 cohorts of HIV positive patients n=123 n=94 on ART, CD4≥200 n=14 on ART, CD4 50-199 n=15 ART-naïve, CD4≥500 n=112 completed 18 month follow-up (67 in RZV group, 45 in control group) Mean age 46, range 23-74	CMI: CD4+ T-cells expressing at least 2 activation markers at baseline and months 1, 2, 3, 6, 7, and 18 Among the ART, high CD4 and ART-naive high CD4 patients, Geometric mean ratio was higher for RZV than placebo: 21.95 (70%CI 12.97, 38.02); increases persisted to month 18 Humoral immunity: Anti-gE antibody concentrations pre-vaccination and at months 1, 2, 3, 6, 7, and 18 Among the ART, high CD4 and ART-naive high CD4 patients, Geometric mean ratio at 7 months was higher for RZV than placebo: 46.22 (70%CI 33.63, 63.53); increases persisted to month 18 No benefit to third dose	Level I	Good
Stadtmauer et al, 2014[27]	RZV (2 and 3-dose regimes) in autologous HSCT transplant patients	Phase 1/2a randomized, observer-blind placebo-controlled trial	n=121 (initial enrollment) – n=99 remained by month 15 n=30 (3 doses AS01B) n= 29 (3 doses AS01E) n=31 (2 doses AS01B)	CMI: CD4+ & CD8+ cells with at least 2 activation markers at baseline, month 4, and month 15 CMI was higher among all vaccine groups compared to saline, a response that persisted to the end of the study Humoral immunity: anti-gE antibody concentrations at baseline, month 4, and month 15 GMCs were higher among all vaccine	Level I	Fair (fairly high dropout rate by end of study, not all outcome comparison done)

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
			n=30 (3 doses saline)	groups compared to saline, a response that persisted for at least one year after last vaccination; GMCs decreased between 29-46% from month 4 to 15 Combined CMI & humoral response was superior in 3-dose AS01B compared to AS01E ($p<0.25$) and compared to 2-dose AS01B ($p<0.15$)		
Oostvogels,. 2017 (ID Week poster)[28]	RZV in patients with hematologic malignancy	Phase 3 observer-blind, placebo-controlled trial	n=562 n=415 in humoral immunogenicity group (vaccine =217, placebo=198) n=132 in cell-mediated immunogenicity group (vaccine =69, placebo=16)	CMI: CD4+ T-cells expressing at least two activation markers at baseline, 1-2 months post-dose 1, and 1 month post-dose 2 (n=132) CMI VRR was ~80% compared to <10% in vaccine vs. placebo 1 month post-dose 2 Humoral immunity: anti-GE antibody levels at baseline, 1-2 months post-dose 1, and 1 month post-dose 2 (n=415) Humoral VRR was 80% compared to around 0% in vaccine vs. placebo 1 month post-dose 2	Level I	N/A pending full methods – study is ongoing
Vink 2017 (ID Week Poster)[30]	RZV in patients with solid tumors before & after immunosuppressive therapy	Phase 2/3 observer-blind, placebo-controlled trial	n=232 n=117 (vaccine group, 90 pre-chemo, 27 on chemo) n=115 (placebo group, 91 pre-chemo, 24 on	CMI: CD4+ T-cells expressing at least two activation markers at baseline and months 1, 2, 6, and 12 post-vaccination in patients yet to start chemotherapy Adjusted GM frequency ratio was 9.9 (95% CI 3.6-27.2) at month 2 between vaccine & placebo group; 17.6% (month 12) and 50.0% (month	Level I	N/A pending full methods

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
			chem)	2) of the pre-chemo group met criteria for CMI vaccine response Humoral immunity: Anti-GE antibody levels at baseline and months 1, 2, 6, and 12 post-vaccination in all patients Adjusted GMC ratio was 23.2 (95% CI 17.9-30.0) at month 2 between vaccine & placebo group; While GMC declined with time in vaccine group, it was higher for vaccine group than placebo group at all points of follow-up		
Vink (2), 2017 (ID Week Poster)[29]	RZV in renal transplant patients on chronic immunosuppression	Phase 2/3 observer-blind, placebo-controlled trial	n=264 n=132 (vaccine group) n=132 (placebo group)	CMI was assessed in 72 patients (36 in each group): CD4+ T-cells expressing at least two activation markers at baseline, 1-2 months post-dose 1, and 1 month post-dose 2 Adjusted GM frequency ratio was 17 (95% CI 5.9, 20.4) at 1 month post-dose 2 Humoral immunity was assessed in 240 patients (121 vaccine, 119 placebo): anti-GE antibody levels at baseline, 1-2 months post-dose 1, and 1 month post-dose 2 Adjusted GMC ratio was 14.0 (95% CI 10.9, 18.0) at 1 month post-dose 2	Level I	N/A pending full methods

Head-to-head comparisons of live and subunit vaccines (n=1)

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Weinberg et al, 2017 (abstract)[32]	Zostavax RZV	Unclear	Unknown – patients were either 50-70 with no vaccine or 70+ who had received Zostavax at least 5 years ago; at entry they received Zostavax or RZV	CMI & humoral immunity measured at days 0, 30, 90, and 365. Higher memory CD4+ & CD8+ response detected in RZV group	Unknown	N/A

Concomitant administration with other vaccines (n=3)

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
MacIntyre et al, 2010[19]	Zostavax with concomitant administration of Pneumovax 23 vaccine	Randomized, double-blind, placebo-controlled trial	n=473 (initial enrollment) n=237 (concomitant vaccination) n=236 (Pneumovax Day 0, Zostavax Day 28)	Anti-VZV antibodies through gpELISA at baseline and week 8 GMT ratio (concomitant to non-concomitant) was 0.70 (95% CI 0.61, 0.80), suggesting lower response for concomitant administration; however, the estimated GMFR for concomitant administration did meet acceptable antibody response in absolute terms	Level I	Good
Levin et al, 2018[20]	Zostavax with concomitant administration of influenza vaccine	Randomized, double-blinded, placebo-controlled trial	n=882 (all ≥50 years) n=441 received Zostavax and influenza vaccine concurrently n=441 received	Anti-VZV antibodies through gpELISA, measured at baseline and 4 weeks post-vaccination Post-vaccination, GMT were non-inferior according to authors in concomitant administration group versus non-concomitant group: GMT ratio 0.87 (95% CI 0.80, 0.95); GMFR	Level I	Good

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
			Zostavax 4 weeks after influenza	in concomitant group was 1.9 (95% CI 1.76, 2.05)		
Schwarz et al, 2017[31]	RZV with concomitant administration of influenza accine	Phase 3, randomized, open-label, multicentre clinical trial	n=828 (all ≥50 years) n=413 (Coadministration – received RZV at day 0 and month 2; flu vaccine at day 0) n=415 (Control – received RZV su at month 2 & 4; flu vaccine at day 0)	Anti-gE antibodies measured at baseline, day 21, and months 2, 3, and 5 The GMC ratio of control to concomitant administration groups was 1.08 (95% CI 0.97, 1.20) demonstrating non-inferiority of RZV. Non-inferiority was also demonstrated for all four influenza vaccine strains.	Level I	Fair (non-blinded)