An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI)‡

Update on the Use of Herpes Zoster Vaccine

PROTECTING CANADIANS FROM ILLNESS

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

Canada

TO PROMOTE AND PROTECT THE HEALTH OF CANADIANS THROUGH LEADERSHIP, PARTNERSHIP, INNOVATION AND ACTION IN PUBLIC HEALTH.

—Public Health Agency of Canada

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PREAMBLE

The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada (hereafter referred to as the Agency) with ongoing and timely medical, scientific, and public health advice relating to immunization. The Agency 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 the Agency's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

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SUMMARY TABLE OF INFORMATION CONTAINED IN THE NACI STATEMENT

The following table highlights key information for immunization providers. Please refer to the remainder of the statement for details.

1. What	**What is Herpes Zoster (HZ, shingles)?** HZ is a manifestation of reactivation of the *varicella zoster virus* (VZV). Herpes zoster infection is characterized by pain and a unilateral vesicular eruption, usually in a single dermatome. It arises from the reactivation of latent VZV from sensory ganglia present from previous chickenpox infection. Immunosuppressed persons are at increased risk for herpes zoster. **What is Herpes Zoster Vaccine (HZV)?** HZV is a live, attenuated virus vaccine containing a lyophilized preparation of the Oka/Merck strain of varicella-zoster virus. Additional information can be found in the Canadian Immunization Guide (http://www.phac-aspc.gc.ca/publicat/cig-gci/p04-herp-zona-eng.php)
2. Who	**Who should be immunized?** HZV is recommended for the prevention of HZ and its complications in the following groups: 1. Persons 60 years and older without contraindications; 2. Individuals ≥50 years can be considered for immunization; 3. Individuals on low dose immunosuppressive therapy and may be administered to individuals on anti-TNF biologics on a case by case basis after review with an expert in immunodeficiency; 4. There is insufficient evidence to recommend for or against the administration of HZV in individuals with a history of HZ Ophthalmicus; 5. There is insufficient evidence to recommend the use HZV in individuals with HIV, post-organ or hematopoietic stem cell transplant or in those receiving high dose corticosteroids, chemotherapy or immune suppressing medications listed in Table 1 of the Statement Update on the Use of Herpes Zoster Vaccine.
3. How	**Dose and Schedule** A single dose of vaccine (entire contents of the reconstituted vial, 0.65 mL) should be administered subcutaneously. 1. The vaccine can be given to those with or without a prior history of HZ. 2. It is recommended that the vaccine be given at least one year following the last episode of HZ 3. The need for revaccination has not yet been defined and duration of protection from HZ vaccination is unknown beyond 5 years. **Coadministration** HZ vaccine can be co-administered (using a different site) with pneumococcal vaccine.

4. Why	Evidence supports the use of HZ vaccine in immunocompetent individuals over age 50. There are also data to support the safety of vaccine in some immunocompromised groups. Complications of acute HZ are potentially severe and may include sight-threatening eye infections, central nervous system infection, nerve palsies including the Ramsay-Hunt Syndrome, neuromuscular disease including Guillain-Barré Syndrome, and secondary bacterial infections. The most frequent complication of acute HZ is post-herpetic neuralgia (PHN) which often has a major adverse impact on quality of life, especially in elderly persons. Treatment options for HZ and PHN are of limited effectiveness. HZ vaccine reduces the incidence of HZ and post-herpetic neuralgia

I. INTRODUCTION

In January 2010 the National Advisory Committee on Immunization (NACI) published a statement of recommendations regarding the administration of the live, injectable, attenuated herpes zoster vaccine (Zostavax™, Merck Canada, Inc.). In the prior statement, NACI recommended the use of herpes zoster vaccine for the prevention of herpes zoster (HZ) and its complications in persons 60 years and older without contraindications. Since the development of the 2010 statement new data has been published with regards to the administration and safety of herpes zoster vaccine. The new data has provided further clarity on the issues that include but are not limited to, age indications for administration of herpes zoster vaccine, immunization in immunocompromised hosts, concomitant administration of herpes zoster vaccine with Pneumovax™23, vaccination following a prior episode of HZ, and reports of the recurrence or exacerbation of herpes zoster ophthalmicus (HZO) following administration of herpes zoster vaccine. This update will attempt to address these issues to further guide the administration of herpes zoster vaccine to Canadian adults. Questions regarding cost-effectiveness, acceptability of vaccine programs and feasibility will be addressed by other provincial or federal groups.

In order to inform the recommendations of the National Advisory Committee on Immunization (NACI) made in this update, a systematic review of the literature was undertaken. This review focused on emerging literature since the previous statement as well as specific areas highlighted for review. Articles were obtained using a PubMed search from August 31, 2008 to September 30, 2012, using the search terms “zoster” and “Canada,” “zoster” and “vaccine,” “Zostavax™” and “immunocompromised,” “Zostavax™” and “Pneumovax™23,” “Zostavax™” and “Herpes Zoster Ophthalmicus,” or “Zostavax™” and “timing.” Relevant articles were chosen by two members performing simultaneous reviews of the literature. Recommendations and levels of evidence evaluations were agreed to by consensus of NACI members and were based on previously published NACI guidelines.

II. METHODS

In brief, the broad stages in the preparation of a NACI statement are:

1. knowledge synthesis (retrieve and summarize individual studies, rank the level and quality of the evidence);
2. synthesis of the body of evidence of benefits and harms, considering the quality of the evidence and magnitude of effects observed;
3. translation of evidence into a recommendation.

Further details regarding this process are outlined in: *Evidence-Based Recommendations for Immunization: Methods of the NACI, January 2009, CCDR.* (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/09vol35/acs-1/index-eng.php)

NACI reviewed the key questions for the proposed literature review including age indications for herpes zoster vaccine administration, immunization of immunocompromised hosts, coadministration of herpes zoster vaccine and Pneumovax™23, and benefit of vaccination in persons who have had prior episode of shingles. The knowledge syntheses were performed by Dr. Allison Mah, Internal Medicine Resident, Dr. Oliver Baclic, Medical Specialist with the Agency, and Dr. Deepali Kumar, Infectious Diseases Specialist, and supervised by the Working

Group. Following critical appraisal of individual studies, summary tables with ratings of the quality of the evidence using NACI's methodological hierarchy (Table 3) were prepared, and proposed recommendations for vaccine use were developed. The Working Group Chairperson and an Agency Medical Specialist presented the evidence and proposed recommendations to NACI on February 8, 2013. Following thorough review of the evidence and consultation at the NACI meetings of February 8, 2013 and June 6, 2013, the committee voted on specific recommendations. The description of relevant considerations, rationale for specific decisions, and knowledge gaps are described in the text.

III. AGE INDICATIONS FOR HERPES ZOSTER VACCINE

III.1 Efficacy and Effectiveness in Persons ≥ 60 years

The efficacy of the live attenuated injectable Oka/Merck herpes zoster vaccine in healthy ≥60 year olds was shown in the Shingles Prevention Study (SPS) and discussed previously in the first NACI statement on herpes zoster immunization. The SPS showed a 61% reduction in the burden of illness caused by HZ in persons aged greater than or equal to 60 years who were vaccinated with the herpes zoster vaccine.[1] It also showed a reduction in the incidence of HZ by 51% and a reduction in the incidence of post-herpetic neuralgia by 66%.

Following the SPS, study participants were re-enrolled in the Short Term Persistence Substudy (STPS.) The individuals enrolled in the STPS included 7320 vaccine recipients and 6950 placebo recipients. The groups were followed for a further 1.36 +/- 0.29 years or 0.98 +/- 0.3 years respectively. Total follow-up time from vaccination included time while enrolled in the SPS, time between completion of the SPS and enrollment in the STPS, and time in the STPS. The incidence of herpes zoster in the herpes zoster vaccine group was 8.4 cases/1000 person years. The incidence of herpes zoster in the placebo group was 14 cases/1000 person years. Vaccine efficacy was 50.1% (95% CI, 14.1-71.0) for herpes zoster burden of illness, 60.1% (95% CI, -9.8 - 86.7) for incidence of postherpetic neuralgia and 39.6% (95% CI, 18.2 - 55.5) for incidence of herpes zoster. These values are related to cases occurring between 3.3 and 7.8 years after vaccination. This study showed persistent but declining benefit of herpes zoster vaccine over time. The data from this study showed statistically significant benefit of herpes zoster vaccine up to 5 years after vaccination. There was some evidence of efficacy at 7 years but this was not statistically significant. Beyond 7 years the efficacy of herpes zoster vaccine is unknown.[2] Once published, data from the Long Term Persistence Substudy (LTPS) is anticipated to provide further clarity to herpes zoster vaccine efficacy over time.

Tseng et al. performed two retrospective studies to look at herpes zoster vaccine effectiveness and safety postmarketing in immunocompetent adults 60 years of age or older. In one study, they examined cohorts from the Kaiser Permanente Southern California health plan over a three year time period and compared the number of HZ cases in vaccine recipients compared to matched unvaccinated controls. The vaccinated group had a rate of 6.4 cases of herpes zoster per 1000 person years (95% CI, 5.9-6.8). This is in contrast to the control group which had a rate of herpes zoster occurrence of 13 cases per 1000 person years (95% CI, 12.613.3). This comparison yielded a hazard ratio of 0.45 (95% CI, 0.42-0.48) for vaccine associated risk reduction of HZ.[3]

III.2 Efficacy and Effectiveness in Persons 50-59 years

Following the findings of the SPS, Schmader et al. examined the efficacy of Zostavax™ in the 50-59 year old age group. The Zostavax™ efficacy and safety trial (ZEST) included 22,439 healthy subjects aged 50-59 with a history of varicella or who resided in a VZV-endemic area for greater than thirty years. These individuals were randomized to receive either herpes zoster vaccine or placebo. The primary endpoint was the incidence of confirmed HZ cases. In the herpes zoster vaccine group, 30 cases of HZ were reported out of 11,211 persons randomized to receive vaccine. In the placebo arm, 99 cases of HZ occurred in the 11,228 individuals randomized to placebo. This gave a vaccine efficacy for prevention of herpes zoster of 69.8% (95% CI, 54.1% - 80.6%.)[4] There was no difference in systemic adverse events between the vaccine and placebo recipients with a statistically significant increased rate of injection site reactions in the herpes zoster vaccine group.

Sutradhar et al. performed an analysis of immunogenicity of Zostavax™ in persons 50-59 years old compared to persons 60 years and older by extracting data from two previous randomized controlled trials that included a relatively large number of individuals in this age group. They analyzed the geometric mean titer (GMT) of VZV Ab at 4 weeks postvaccination and the geometric mean fold rise (GMFR) of VZV Ab from prevaccination to 4 weeks postvaccination. The analysis compared the GMT and GMFR in persons in the 50-59 year old age group to that seen in persons in the greater than 60 year old age group. The GMT and GMFR were found to be similar between the two age groups. Statistical analysis found the VZV Ab response induced by herpes zoster vaccine in the 50-59 year old age group to be noninferior to that induced in individuals 60 years and older. More frequent adverse events were reported in the younger age group with 5.8% reporting a vaccine-related systemic adverse event in the 50-59 year old age group compared to 2.9% reported by those 60 years and older.[5]

In another study, Tseng et al. performed a large observational study of 193,083 individuals ≥50 years of age from the Vaccine Safety Datalink database who received vaccination with herpes zoster vaccine over a two year period. The only significantly increased risk identified in this large group of vaccine recipients was allergic reactions within 7 days of vaccination with a relative risk of 2.13 (95% CI 1.87-2.4) in vaccine recipients. The majority of the cases reported as allergic reactions were, in fact, vaccine site related reactions. No other safety concerns were identified in this analysis.[6]

IV. HERPES ZOSTER VACCINE IN PERSONS WITH A PRIOR HISTORY OF HERPES ZOSTER

The actual risk of HZ recurrence in immunocompetent adults with a prior history of HZ, has not been firmly established and previously reported incidence has varied based on the methods used and duration of follow-up. Recently, Yawn et al. examined medical records of 1669 Olmsted County (Minnesota) residents >22 years old and found a 5.7% (95% CI 4.4-6.9%) recurrence rate over eight years in persons who were immunocompetent at the time of their first HZ episode.[7] This is a number comparable to some estimates of incidence rates for first episodes of HZ. The authors reported a recurrence rate of 1.7% (95% CI 1.0 - 2.3%) at 2 years after the initial HZ episode. Cumulative recurrence rates at 4, 6, and 8 years after the initial episode were 3.2% (95% CI 2.3-4.2%), 4.4% (95% CI 3.3-5.4%) and 5.7% (95% CI 4.4-6.9%) respectively. Since recurrence rates in the first two years were similar to rates in the

subsequent years, this suggests that having a recent episode of herpes zoster may not be protective for subsequent episodes.

Vermeulen et al. measured immunogenicity of sequential herpes zoster vaccinations administered 6 weeks apart in persons without a prior history of HZ and compared these to a placebo group. The ELISPOT geometric mean count (GMC) of VZV Ab after the first vaccination with herpes zoster vaccine increased from 16.9 SFCs(spot forming cells)/10^6prevaccination to 32.8 (95% CI, 23.5-45.8) at 6 weeks postvaccination. Subsequent vaccination resulted in a GMC of 42.9 (95% CI, 28.6-64.5) at 6 weeks postvaccination. There was no additional immunogenicity provided by administration of a second dose of herpes zoster vaccine within a short time interval of 6 weeks. In this study, no vaccine attributable severe adverse events were reported. Rates of vaccine-related adverse events were 52.9% and 63.3% following the first and second administrations of herpes zoster vaccine respectively, compared to rates of 11.4% and 11.9% in the placebo recipients respectively. Rates of adverse events after the second dose of herpes zoster vaccine were related to increased injection site reactions in this group (61.2%) versus after the first dose (49.0%). However, rates after both the first and second administration of herpes zoster vaccine are similar to rates of injection site reactions seen in prior studies of herpes zoster vaccine safety.[8]

Administration of herpes zoster vaccine in individuals with a prior history of herpes zoster has been shown to be safe in the literature. Mills et al. found no increase in systemic adverse events in persons with a known history of herpes zoster vaccinated with Zostavax™ compared to those individuals receiving placebo.[9] There were a significantly greater number of injection site related adverse events in the herpes zoster vaccine group compared to placebo (45.9% vs. 4.2%). The 101 individuals in this study had a herpes zoster history that was greater than 5 years prior to the proposed vaccination, did not have recurrent herpes zoster, and had not received prior vaccination with Varivax™ or Zostavax™.

In the study by Mills et al., Zostavax™ induced a significantly higher GMT of VZV Ab and GMFR compared to placebo.[9] The geometric mean fold-rise (GMFR) from before vaccination to 4 weeks post-vaccination was 2.1 (95% CI 1.8-2.4) in vaccine recipients compared to 1.0 (95% CI 0.9-1.1) in placebo recipients. This study was performed with individuals with a prior history of herpes zoster, with most recent HZ episodes occurring greater than 5 years prior to study enrollment, suggesting that herpes zoster vaccination is immunogenic with a detectable increase in antibody response even in persons with a prior history of herpes zoster. However, as previously discussed in the original NACI statement on herpes zoster vaccination, VZV Ab titers do not necessarily correlate with vaccine efficacy. Caution should be exercised when extrapolating immunogenicity to suggest vaccine efficacy. This study by Mills et al. did not examine the impact of vaccination on the incidence of future HZ episodes in individuals with a prior history of HZ.

Tseng et al. examined medical records and performed a matched cohort study comparing 1,036 individuals who had received herpes zoster vaccine 180-730 days after an episode of herpes zoster to 5,180 individuals who had a history of herpes zoster but had never received the vaccine. The study was performed using data from immunocompetent individuals ≥60 years old who were part of the Kaiser Permanente Southern California health records. In the vaccinated cohort, 4 cases of clinically confirmed herpes zoster recurrence occurred compared to 25 cases in the unvaccinated cohort. This gave an overall incidence of recurrent HZ of 1.9% (95% CI 0.52-4.87) in the vaccinated cohort compared to 2.41% (95% CI 1.56-3.56) in the unvaccinated cohort. While these numbers showed a trend towards lower recurrence rates in the vaccinated group this was not statistically significant due to the low number of total events.[10]

V. HERPES ZOSTER VACCINE IN PERSONS WITH A HISTORY OF HERPES ZOSTER OPHTHALMICUS (HZO)

In a large cohort study, Tseng et al. showed that HZO naïve HZ vaccine recipients had a reduced risk of HZO (HR 0.37; 95% CI, 0.23-61) compared to unvaccinated persons. [6] There are now published reports of exacerbations of HZO in persons immunized with herpes zoster vaccine, in individuals with a prior history of herpes zoster ophthalmicus. NACI is aware of 7 cases of exacerbation of herpes zoster ophthalmicus which were temporally associated with the administration of herpes zoster vaccine. Three of these cases are available for review in the literature and four additional cases are reviewed in abstract form.[11-13]

Sham and Levinson reported a case of a patient who received herpes zoster vaccine three and a half years after his first presentation with herpes zoster ophthalmicus, off topical steroids, who developed a severe worsening of his anterior uveitis three weeks following vaccination.[11] Khalifa et al. described a case of a patient with a history of recurrent interstitial keratitis using topical steroids who presented with a more severe flare of her interstitial keratitis 35 days after herpes zoster vaccine administration.[12] More recently, Hwang et al. described a case of a 63-year-old man with a history of stable HZO off topical steroids for 3.5 years who presented with acute recurrence of his keratouveitis. The patient presented 2 weeks after vaccine receipt but reported symptoms that had started within days of vaccination.[13] Four additional cases of recurrent HZO temporally associated with Herpes Zoster vaccine administration have been presented in abstract form after a review of the Canada Vigilance Database and World Health Organization.[14] Upon review of these observations, however, it is difficult to establish a causal link between herpes zoster vaccine and recurrence of HZO and further evaluation is required.

VI. HERPES ZOSTER VACCINE IN IMMUNOCOMPROMISED INDIVIDUALS

In general, individuals can be immunocompromised as a result of their underlying illness or medications that suppress immune function. For the purposes of live vaccine administration, underlying conditions causing immunocompromise include transplant, hematologic malignancy, and infection with human immunodeficiency virus. Autoimmune, inflammatory or chronic diseases (e.g. diabetes), or solid tumors by themselves do not impair immunity enough to contraindicate live vaccines.

Medications causing immunosuppression include significant doses of glucocorticoids (defined as prednisone ≥20mg daily or equivalent for at least 2 weeks), chemotherapy agents, biologics (e.g.: anti-TNF agents), and other classes of drugs. Refer to *Tables 1 and 2* for a list of immunosuppressive medications. Many of these therapies have their greatest impact on cell-mediated immunity and antibody production can also be adversely affected. Some chronic cancer therapies are hormonal (tamoxifen, hydroxyurea, gonadotropin release inhibitors) and have no significant immunologic effects. Some therapies for inflammatory conditions (such as hydroxychloroquine, sulfasalazine, or auranofin) are also not considered immunosuppressive.

In general, live vaccines are contraindicated in immunosuppressed individuals; however, given the disproportionate burden of disease and risk of complications from herpes zoster and the increasing use of biologics for a variety of diseases, immunocompromised individuals are an

important group to consider when discussing vaccination with a live attenuated viral vaccine such as herpes zoster vaccine.

Table 1: Immunosuppressive medications (excluding biologics)

Immunosuppressive medication	Example brand name (company)
6-mercaptopurine*	PURINETHOL® (Novopharm Ltd.)
Alemtuzumab	MabCampath® (Genzyme Canada, Div. Of Sanofi-Aventis Canada Inc.)
Anti-thymocyte globulin	Thymoglobulin® (Genzyme Canada, Div. Of Sanofi-Aventis Canada Inc.)
Azathioprine*	IMURAN (Triton Pharma Inc.)
Basiliximab	SIMULECT™ (Novartis Pharmaceuticals Canada Inc.)
Cyclophosphamide	PROCYTOX (Baxter Corp.) CYTOXAN
Cyclosporine	NEORAL™ (Novartis Pharmaceuticals Canada Inc.)
High-dose systemic corticosteroids (2 mg/kg per day for a child or 20 mg/day or more of prednisone or its equivalent for an adult) for 14 days or more*	
Leflunomide	ARAVA® (Sanofi-Aventis Canada Inc.)
Methotrexate*	
Mitoxantrone	
Most cancer chemotherapies (except tamoxifen,hydroxyurea, and gonadotropin release inhibitors which are not considered immunocompromising) - If 3 months post-chemotherapy and the cancer is in remission, the person is not considered immunocompromised	
Mycophenolate mofetil	CellCept® (Hoffman-LaRoche Ltd.)
Sirolimus	Rapamune® (Pfizer Canada Inc.)
Tacrolimus	Prograf® (Astellas Pharma Canada Inc.)

*For lower doses of these medications (such as used for rheumatologic conditions), see text and recommendations.

Table 2: Biologic Immunosuppressive Medications**

Anti-TNF antibodies***	Example brand name (company)
Infliximab	REMICADE® (Janssen Inc.)
Adalimumab	Humira® (Abbott Laboratories Ltd.)
TNF receptor blockers	
Etanercept	Enbrel® (Immunex Corp.)

Other Non-TNF Biologics	
Abatacept	Orencia™ (Bristol-Myers Squibb Canada)
Rituximab	RITUXAN® (Hoffman-LaRoche Ltd.)

Tables 1 and 2 adapted from: *Guidelines to Determining Immunosuppressing Conditions or Medications for which MMR is contraindicated.* Nova Scotia Department of Health and Wellness. Product monographs for drugs authorized by Health Canada can be found at Health Canada's *Drug Product Database.*

**Although infliximab, adalimumab, etanercept and other drugs with a similar mechanism of action are considered immunosuppressive, recent data suggest that HZ vaccine may be administered safely to those receiving these medications for autoimmune conditions because HZ vaccine is meant to boost responses in those who already have primary immunity to varicella zoster virus, see text and recommendations. Little data on herpes zoster vaccine responses are available for people on non-TNF biologics.

***These are the commonly studied anti-TNF antibodies in the context of herpes zoster vaccination although other products with a similar mechanism of action may be licensed in Canada.

The prior NACI statement on zoster vaccine recommended against administration of herpes zoster vaccine to individuals with congenital or acquired immune deficiency or those who had recently used or were using immune suppressive medications. Several studies have been conducted examining databases and medical records from individuals with underlying rheumatologic or autoimmune diseases, including patients with immunocompromise due to anti-TNF agents. These studies have shown increased incidence rates of HZ and hospitalization due to HZ in this population compared to the general population.[15-17]

VI.1 Rates of Herpes Zoster while Immunocompromised or on Immunosuppressive Drugs

Wolfe and Chakravarty examined rates of herpes zoster in a population of patients with rheumatoid arthritis or non-inflammatory musculoskeletal (MSK) disorders. Mean age of the two cohorts was 60.1 and 67.0 years respectively. They found rates of herpes zoster of 13.2 per 1,000 patient years (py) (95% CI, 11.9-14.5) in patients with rheumatoid arthritis and 14.6 per 1,000 patient years (95% CI, 11.2-18.1) in patients with non-inflammatory MSK disorders.[15] McDonald et al. conducted a retrospective cohort study of more than 20,000 patients who were treated for rheumatoid arthritis. They reported an incidence of herpes zoster in RA patients of 9.96 per 1,000 patient years.[17] In this study, risk factors for HZ were older age, prednisone use, and chronic lung, renal, and liver diseases. However, those that received anti-TNF biologics (also called biologics or TNF-receptor blockers) had a reportedly lower risk of HZ. Specifically, etanercept (HR 0.62) and adalimumab (HR 0.53) were associated with lower risk of HZ. A more recent study by Winthrop et al. compared the rates of HZ in persons who had recently initiated anti-TNF agents (n=33,324) versus those that had recently initiated nonbiologic therapies (n=25,472).[18] In the anti-TNF users, 310 cases of HZ were identified giving a crude incidence rate of 12.1 per 1,000 py (95% CI 10.7-13.6) for rheumatoid arthritis, 11.3 per 1,000 py (95% CI 7.7-16.7) for inflammatory bowel disease, and 4.4 per 1000 py (95% CI 2.8-7.0) for psoriasis, psoriatic arthritis, or ankylosing spondylitis. Concomitant corticosteroid use of >10mg per day significantly increased the risk of HZ (HR 2.13, 95%CI 1.64-2.75). These rates were similar to those on nonbiologic therapies. Therefore, the study suggested that the risk of HZ was not elevated in persons using anti-TNF medications. Also, risks were similar when various

biologics were compared (infliximab, etanercept, adalimumab). In contrast, Strangfeld et al. reported on over 5000 patients prospectively enrolled in a German biologics registry when they initiated biologic therapy. In this study, crude incidence rates were overall lower than those reported in the above studies and ranged from 11.1 per 1,000 py in those receiving monoclonal antibodies, 8.9 per 1,000 py specifically for those on etanercept, and 5.6 for those on non-biologic disease modifying agents.[19] This study suggested that risk is increased while receiving anti-TNF treatments but was overall lower than described in other studies. This may be due to the limited number of herpes zoster episodes in the Strangfeld study. In both the Winthrop and Strangfeld study, patients could be on concomitant corticosteroids. One reason the Strangfeld and Winthrop study may differ in their results is due to the possibility that the German patients were on higher doses of concomitant corticosteroids, thereby increasing their risk of herpes zoster. As well, Garcia-Doval et al. found that the incidence of HZ was 6.5/1000 person-years in persons using anti-TNF therapy. They reported an increased rate of hospitalization (32 per 100,000 patient-years) due to herpes zoster in patients with rheumatologic diseases being treated with anti-TNF agents compared to the expected rate in the general population.[16]

Blank et al. examined rates of herpes zoster in an urban HIV clinic population and found an incidence rate of 9.3/1,000 person years in the current HAART era.[20] Factors found to be associated with herpes zoster outbreak included recent initiation of antiretroviral therapy, detectable viral load and a CD4 count less than 500. Pergam et al. looked at solid organ transplant recipients from a US Veterans Affairs healthcare system and found an incidence rate of herpes zoster of 22.2/1,000 person years in this population.[21] Manuel et al. reported on the occurrence of zoster in lung transplant recipients at a Canadian center.[22] They found that in the cohort of 239 patients, 55.1 cases per 1000 person-years of follow-up occurred for a cumulative incidence of 5.8% at 1 year, 18.1% at 3 years and 20.2% at 5 years post-transplant. Although there was no immunocompetent comparison group in this study, these rates are significantly greater than those previously reported in the general population.

Recurrence of herpes zoster in immunocompromised persons is also significant. Yawn et al. determined the incidence of HZ recurrence in immunocompromised persons 8 years after the initial episode, which was 12% (95% CI, 5.8-17.7) compared to 5.7% (95% CI, 4.4-6.9) in immunocompetent persons (p=0.006).[7]

VI.2 Herpes Zoster Vaccine Efficacy and Safety in Immunocompromised or those on Immunosuppressive Drugs

Although herpes zoster vaccine is not approved for use in immunocompromised patients, off label administration of the vaccine occurs. Several studies have looked retrospectively at the safety of herpes zoster vaccine in groups of patients with underlying autoimmune diseases or receiving immunosuppressant medication. Zhang et al. examined a claims database from Aetna (a nationwide health plan in the United States) of 44,115 individuals ≥50 years of age with rheumatoid arthritis, ankylosing spondylitis, psoriasis, psoriatic arthritis or inflammatory bowel disease. Of this large population, only 514 patients received herpes zoster vaccine and had also had complete claims history up to 30 days after vaccination. Of these subjects a total of 47 subjects used anti-TNF agents at some time in the 30 days before and 30 days after vaccination. None of these patients developed HZ in the thirty days following vaccination.[23] In this study, the authors also reviewed low dose immunosuppression (ie immunosuppressive agents such as methotrexate ≤0.4 mg/kg/week, azathioprine ≤ 3.0 mg/kg/day and 6-mercaptopurine ≤1.5 mg/kg/day, administered at the doses used for rheumatologic conditions) with HZ vaccine. Of the 514 persons who received HZ vaccine and had complete claims

history, 34 (6.6%) were using methotrexate, 1 was receiving azathioprine, 5 were receiving 6-mercaptopurine, and 48 (9.3%) used oral glucocorticoids. None of these patients developed HZ within one month of vaccination.

Similarly, Naidus et al. administered Zostavax™ to 62 patients with hematologic conditions. Of these 31 had a history of hematologic malignancy (16 of whom were in complete remission and 15 who had disease but no recent chemotherapy). In this group, no vaccine-related zoster was reported. In addition, 31 patients who had previously undergone hematopoietic stem cell transplant (HSCT) received herpes zoster vaccine. Of these, 5 had received an allogeneic hematopoietic stem cell transplant and 26 had received an autologous HSCT. These patients received herpes zoster vaccine between 173 and 4,334 days after transplant.[24] At the time of vaccination, three patients were receiving steroids, one patient was on bortezomib and five were on maintenance lenalidomide. During the study period, one patient developed herpes zoster three weeks after vaccination with herpes zoster vaccine. However, it was unknown whether this was due to wild-type virus or vaccine virus. Of note, 25% were receiving acyclovir at the time of vaccination and 37% had discontinued acyclovir within 24 hours of receipt of vaccine. This may have significantly reduced any detectable adverse events and also potentially the immunogenicity of the vaccine.

In another study by Zhang et al. a retrospective cohort study was performed examining those ≥60 years of age with immune-mediated disease. A total of 463,541 Medicare patients with underlying autoimmune disorders including ankylosing spondylitis, inflammatory bowel disease, psoriatic arthritis, psoriasis and rheumatoid arthritis were analyzed. Of these patients, 18,683 were vaccinated with herpes zoster vaccine but the actual date of vaccination was known for 7,780 patients. Analysis of baseline risk of HZ in unvaccinated patients in this study population found a 1.2-2 fold greater risk of HZ in patients exposed to glucocorticoids. The authors first analyzed incidence rates of HZ within 42 days of vaccination. In 7,780 individuals, less than 11 HZ cases were seen within 42 days after vaccination resulting in an incidence rate of 7.8 cases per 1,000 person-years (95%CI 3.7-16.5). This rate is within the range shown in other studies of those with immune-mediated disease. Of the vaccine recipients, 633 were on biologic agents at the time of vaccination. No cases of HZ occurred in the 42 days following vaccination in the group on biologics and no safety concerns were identified. The HZ incidence rate after 42 days from vaccination was determined to be 6.7 cases per 1,000 patient years (95% CI 5.7-7.9) in those who received herpes zoster vaccine compared to 11.6 cases per 1,000 patient years (95% CI, 11.4-11.9) in unvaccinated patients followed during the same time period. These values were significantly different and the adjusted hazard ratio for herpes zoster associated with vaccination was 0.61 (95% CI, 0.52-0.71).[25] This study suggests that herpes zoster vaccine significantly reduced the incidence of HZ in persons with immune-mediated disease, and there were no safety concerns identified in individuals who were on biologic agents at the time of vaccination.

Herpes zoster vaccine has also been studied in individuals on low doses of corticosteroids equivalent to between 5-20 mg/day of prednisone for at least 2 weeks prior to vaccine administration and 6 weeks following vaccination. In these individuals, herpes zoster vaccine was found to be immunogenic as compared to placebo with a GMFR of 2.3 (95% CI 2.0-2.7) vs. 1.1 (95% CI 1.0-1.2).[26]

Benson et al. performed a randomized double-blind placebo controlled trial examining safety and immunogenicity of 2 doses of herpes zoster vaccine in 395 patients with HIV infection with CD4 counts greater than 200 and undetectable viral loads, who were stable on antiretrovirals for greater than 6 months. In the vaccine recipients, 5.1% (95% CI 2.9-8.2%) experienced pre-

specified primary safety endpoints or serious adverse events, none of which were deemed vaccine related, compared to 2.1% (95% CI 0.3-7.3%) in the placebo group with a p-value of 0.26. Although there was no increase in vaccine attributable severe adverse events, there were significantly more injection site reactions in the herpes zoster vaccine group.[27]

It is important to consider that most individuals receiving herpes zoster vaccine have been previously exposed to the Varicella Zoster Virus. Therefore, this decreases the risk usually associated with live vaccine administration, even if immunocompromised, as individuals receiving the HZ vaccine should already have some immunologic memory to the virus. This memory may protect immunosuppressed individuals from developing active disease from vaccine administration. This risk will need to be re-evaluated in the future as cohorts that were immunized with varicella vaccine in childhood enter the age group where they become eligible for herpes zoster vaccine.

Given the high burden of illness in patients with immune compromise, the safety and efficacy of herpes zoster vaccine is an important area of ongoing research. Another important question for future research is whether herpes zoster vaccine administration prior to solid organ transplant results in decreased rates of herpes zoster following solid organ transplant when these patients become immunosuppressed.

VII. COADMINISTRATION OF HERPES ZOSTER VACCINE WITH PNEUMOVAX™23

In the previous statement, NACI recommended separating herpes zoster vaccine and Pneumovax™23 administration by a minimum of 4 weeks. These recommendations were based on the paper from MacIntyre et al. that found lower VZV GMT at four weeks following simultaneous administration of Zostavax™ and Pneumovax™ 23.[28]

The ability to concomitantly administer vaccines is beneficial in a primary care setting to decrease the required number of patient visits and increase compliance with recommended vaccines. Tseng et al. performed a retrospective cohort study in the Kaiser Permanente Southern California healthcare database of 14,366 persons >60 years old, comparing individuals who received Zostavax™ and Pneumovax™23 simultaneously, and individuals who received Zostavax™ between 30 to 365 days after receiving a dose of Pneumovax™23. In the group with concomitant administration of vaccine, the herpes zoster incidence rate was 4.54 (95% CI, 3.43 -- 5.89) per 1,000 person-years calculated after 1.72 years of follow-up. In the non-concomitant group the herpes zoster incidence rate was 4.51 (95% CI, 3.42 -- 5.83) per 1,000 person-years when followed for 1.79 years. The adjusted hazard ratio comparing the rates of herpes zoster in the two cohorts was 1.19 (95% CI, 0.81-1.74.) This suggests an undetectable difference or a small effect size in risk of herpes zoster in the cohort who received concomitant administration of herpes zoster vaccine and Pneumovax™23 as compared to the cohort that did not receive concomitant vaccine administration.[29]

VIII. AREAS OF FUTURE RESEARCH

1. Persistence of vaccine efficacy in persons≥ 50 years of age.
2. The need for booster doses of herpes zoster vaccine in the long-term.
3. Efficacy of immunization in persons with prior history of herpes zoster.

4. Assessing safety of herpes zoster vaccine in individuals with a prior history of HZO and the association of herpes zoster vaccine with the recurrence of HZO.
5. Further information on the vaccination of immunocompromised populations especially those receiving low dose immunosuppression and biologics.
6. Vaccination of transplant populations, prior to or after transplantation.
7. Further study on coadministration of herpes zoster vaccine and Pneumovax^{TM}23.

IX. HERPES ZOSTER VACCINE RECOMMENDED USAGE

Since the release of the original NACI statement on the administration of herpes zoster vaccine, several issues have arisen. New research regarding herpes zoster and vaccination are presented in this update. Specific updated recommendations for the use of herpes zoster vaccine are presented below.

- **Herpes zoster vaccine is recommended for the prevention of herpes zoster and its complications in persons 60 years and older without contraindications (NACI recommendation A, good).** This recommendation is unchanged from the prior statement and further supported by ongoing evidence for the safety and efficacy of herpes zoster vaccine.

- **Herpes zoster vaccine may be used in patients aged 50 to 59 years (NACI recommendation B, good).** This recommendation is unchanged from the prior statement but the level of evidence has been upgraded. The herpes zoster vaccine has been shown to be both safe and efficacious in this age group. While all patients aged ≥50 years may be expected to derive some benefit from HZ vaccination, the greatest benefit will be seen in those 60 years and older. As the duration of protection from herpes zoster vaccination is unknown beyond 5 years, it is uncertain whether vaccination at younger ages will provide ongoing protection at older ages when the incidence of herpes zoster is highest. Due to the potential for waning efficacy of the vaccine, booster administration may be required in these patients and this should be an area of ongoing research.

- **Herpes zoster vaccine may be administered to individuals ≥50 years old with a prior history of herpes zoster (NACI recommendation B, good). Based on expert opinion, it is recommended that the vaccine be given at least one year following the last episode of herpes zoster.** No increase in adverse events has been observed in vaccine recipients with a prior history of herpes zoster. As well, the incidence of recurrent herpes zoster may be higher than originally thought and therefore this population may benefit from the protection afforded by vaccination. No studies to date have shown a reduction in herpes zoster recurrence in individuals with a history of herpes zoster who have been vaccinated although trends towards benefit have been reported. Expert opinion suggests waiting at least one year post HZ episode prior to the administration of herpes zoster vaccine. NACI believes that determining the efficacy of herpes zoster vaccination in persons with a history of herpes zoster is a future research priority.

- **NACI believes that there is insufficient evidence at this time to recommend booster doses of herpes zoster vaccine (NACI recommendation I, insufficient).** The duration of protection provided by herpes zoster vaccine remains unknown beyond 5 years and it is not known whether booster doses of vaccine are beneficial. This remains an area of ongoing

research.

- **NACI concludes that there is insufficient evidence to recommend for or against the administration of herpes zoster vaccine in individuals with a history of herpes zoster ophthalmicus (NACI recommendation I, insufficient).** Cases of recurrent HZO have been reported after administration of herpes zoster vaccine, although causality has been difficult to determine. Herpes zoster ophthalmicus has the potential to recur at any time and HZ vaccine should not be given to persons with active HZ. If considering immunization of individuals with a history of HZO, it is important to discuss these cases with an ophthalmologist and ensure that patients with a history of HZO no longer have active disease. Patients with a history of HZO should be informed by their healthcare provider that cases of recurrent HZO following vaccine have occurred, although causality has not been established, and the risk of recurrent HZO relative to the potential benefit of preventing future recurrences is unknown.

- **NACI concludes that there is insufficient evidence to recommend the use of herpes zoster vaccine in individuals with HIV, post-organ or hematopoietic stem cell transplant or in those receiving high dose corticosteroids, chemotherapy or immune suppressing medications as outlined in Table 1 (recommendation I, insufficient).** These groups are at increased risk of herpes zoster, however safety and efficacy of herpes zoster vaccine in these individuals is not clearly determined in the literature. If patients are going to be initiated on immunosuppressive medications, administration of herpes zoster vaccine prior to immunosuppression should be considered. A period of 4 weeks should be allowed to elapse between vaccine administration and initiation of immune suppressing medications or treatments as 4 weeks is the duration of viremia that may be expected to occur following vaccination. If the immune suppressing medication is discontinued, a period from 3 days to greater than 1 year, depending on the specific medication, should elapse before vaccination with live attenuated vaccine such as herpes zoster vaccine can be considered. For duration of action of specific immune suppressing medications, consultation with an expert in immunodeficiency should be undertaken prior to vaccination.

- **Herpes zoster vaccine can be administered to individuals on low dose immunosuppressive therapy (NACI recommendation B, fair).** While herpes zoster vaccine is generally contraindicated in those who are immunocompromised, several retrospective studies have not shown any safety concerns when herpes zoster vaccine was administered to individuals with inflammatory disorders receiving low dose prednisone (<20 mg/day), methotrexate ≤0.4 mg/kg/week, azathioprine ≤ 3.0 mg/kg/day and 6-mercaptopurine ≤1.5 mg/kg/day. It is important to consider that unlike other live vaccines, herpes zoster vaccine is not used for eliciting a primary immune response and persons receiving this vaccine should already have immunity to varicella. Therefore, it is reasonable to consider herpes zoster vaccine in patients on lower doses of immunosuppressive agents.

- **Herpes zoster vaccine may be administered to individuals on anti-TNF biologics on a case by case basis after review with an expert in immunodeficiency (NACI recommendation B, fair).** This includes monoclonal antibodies that are TNF-alpha antagonists and also TNF-receptor blockers (see Table 2). Not enough data are available for non-TNF biologics such as abatacept and rituximab. For anti-TNF biologics, some data show that the risk of HZ disease in persons treated with biologics remains similar to those that receive non-biologic therapies although studies consistently show that the addition of corticosteroids increases the incidence of HZ. Immunosuppression may be greater in those who are on additional treatments such as prednisone, azathioprine or methotrexate for the inflammatory disease. Retrospective data demonstrate safety of herpes zoster vaccine in

patients receiving biologics for inflammatory conditions and show that HZ does not develop in the 30-42 days post-vaccination. It is important to consider that unlike other live vaccines, herpes zoster vaccine is not used for eliciting a primary immune response and persons receiving this vaccine should already have immunity to varicella. Therefore, it is reasonable to consider herpes zoster vaccine in patients on biologics on a case by case basis after review with an expert in immunodeficiency.

- **Pneumovax^{TM}23 may be administered concomitantly with herpes zoster vaccine at a different body injection site (NACI recommendation A, good).** This is a change from the previous NACI recommendation. The previous recommendation was based on a study that showed antibody titers for herpes zoster vaccine were lower with concomitant administration. There is since a study that showed no increase in cases of herpes zoster in those who received concomitant vs. sequential administration of vaccines.

TABLES

Table 3. Summary of Vaccine Studies

Evidence for age indications for vaccination						
STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
Schmader K et al., 2012 (2)	ZOSTAVAX™	Randomized, double blind, placebo controlled	7,320 vaccine and 6,950 placebo recipients from the SPS population of 38,546	Compared to SPS, vaccine efficacy for HZ burden of illness decreased from 61.1% to 50.1%, for incidence of PHN from 66.5% to 60.1%, and for the incidence of HZ from 51.3% to 39.6% (although not statistically significant). Analysis of vaccine efficacy in each year after vaccination for all 3 outcomes showed a decrease in vaccine efficacy after year 1, with a further decline thereafter. Vaccine efficacy after year 5 was estimated to be uncertain.	Level I	Good

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
Schmader K et al., 2012 (4)	ZOSTAVAX™	Randomized, double blind, placebo controlled	11,184 vaccine and 11,212 placebo recipients aged 50-59 years	Zostavax™ had a vaccine efficacy for preventing HZ of 69.8%. There were 30 cases of HZ in the vaccine recipients (1.99/1,000 person years) compared to 99 cases in the placebo recipients (6.57/1,000 person years)	Level I	Good
Sutradhar C et al., 2009 (5)	ZOSTAVAX™	Randomized, double blind, controlled trial	389 vaccine recipients aged 50-59 and 733 vaccine recipients aged >/= 60	Geometric mean several fold rise (GMFR) from baseline to 4 weeks post vaccination was non-inferior in vaccinees aged 50-59 (GMFR 2.6 [95% CI 2.4-2.9]) compared to those aged greater than 60 (GMFR 2.3 [95% CI 2.1-2.4])	Level I	Fair (No validated correlates of VZV immunity)

Evidence for the timing of Zostavax™ vaccination following a zoster episode						
STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
R. Mills et al, 2010 (9)	ZOSTAVAX™ (~89,000 PFU/0.65mL)	Randomized, double blind, placebo controlled, crossover, 9 center study	101 subjects, ≥50 years of age with a history of HZ ≥5 years prior to screening	No serious AEs within the 28-day safety follow-up. The estimated geometric mean titer (GMT) ratio (vaccine/placebo) was 2.07 (95% CI: 1.48, 2.88). The geometric mean fold-rise (GMFR) from pre vaccination to week 4 post-vaccination was 2.1 (95% CI: 1.8, 2.4).	Level I	Fair (No validated correlates of VZV immunity)
Tseng HF et al., 2012 (10)	ZOSTAVAX™	Matched cohort study	1,036 vaccinated individuals (5,180 non-vaccinated controls), ≥60 with a recent (180-730 days prior to vaccination) episode of herpes zoster	The short term (average 3.3 years) incidence of recurrent herpes zoster was 0.99 (95% CI, 0.02–5.54) and 2.20 (95% CI, 1.10–3.93) cases per 1000 person-years among those <70 years (vaccinated and unvaccinated cohorts, respectively). Such a low risk suggests that one should evaluate the necessity of immediately vaccinating	Level II-2	Good

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
				immunocompetent patients who had a recent HZ episode.		
Vermeulen JN et al., 2012 (8)	ZOSTAVAX™ (~23,000 PFU/0.5mL)	Randomized, double blind, placebo controlled, 5 center study	210 subjects, ≥60 years of age with no history of HZ or VZV-containing vaccine	Vaccine was generally well-tolerated and immunogenic in adults ≥60 years old. A second dose of ZV was generally safe, but did not boost VZV-specific immunity beyond levels achieved post dose 1.	Level I	Fair (No validated correlates of VZV immunity)

Evidence for the safety of Zostavax™ in immunocompromised individuals						
STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Number of Participants***	***Summary of Key Findings Using Text or Data***	***Level of Evidence***	***Quality***
Zhang J et al., 2012 (21)	ZOSTAVAX™	Retrospective cohort study	463,541 Medicare beneficiaries ≥60 with rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, or inflammatory bowel disease	Median duration of follow-up was 2.0 years; 4.0% of patients received HZ vaccine. HZ vaccination was associated with a hazard ratio of 0.61 (95% CI, 0.52-0.71) for HZ risk after 42 days. Among 633 patients exposed to biologics at the time of vaccination or within the subsequent 42 days, no case of HZ or varicella occurred.	Level II-2	Good
Zhang J et al., 2011 (23)	ZOSTAVAX™	Retrospective cohort study	44,115 Aetna beneficiaries ≥50 with rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, or inflammatory bowel disease	1.2% of patients received HZ vaccine. 27 (4.9%) of vaccinated patients were exposed to biologics at the time of vaccination with no case of HZ occuring 30 days after vaccination. The incidence rates of HZ were similar in vaccinated and unvaccinated patients (standardized incidence	Level II-2	Good

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Number of Participants***	***Summary of Key Findings Using Text or Data***	***Level of Evidence***	***Quality***
				ratio, 0.99; 95% confidence interval, 0.29 to 3.43)		
Naidus E et al., 2012 (24)	ZOSTAVAX™	Retrospective analysis	Data from 62 patients with hematologic malignancy who received vaccination was assessed for any adverse events	No adverse reactions to vaccination were documented. One patient developed HZ during the study period	Level II-2	Good
Benson C et al., 2012 (27)	ZOSTAVAX™	Randomized, double blind, placebo controlled trial	395 patients with HIV infection with CD4 counts above 200 and undetectable viral load exposed to 2 doses of vaccine or placebo	No serious vaccine attributable events occurred in the vaccine or placebo recipients. 5.1% (95% CI 2.9 - 8.2%) of vaccine recipients experienced adverse events compared to 2.1% (95% CI 0.3 - 7.3%) in placebo recipients. This difference was largely due to injection site reactions.	Level I	Good

Evidence for concomitant Zostavax™ and Pneumovax™23 immunization						
STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Number of Participants***	***Summary of Key Findings Using Text or Data***	***Level of Evidence***	***Quality***
Macintyre CR et al., 2010 (28)	ZOSTAVAX™, Pneumovax 23™	Randomized, blinded, placebo controlled 18 center study	473 persons ≥60	VZV geometric mean titers Ab response induced by ZV administered concomitantly with PP V23 was inferior to that induced non-concomitantly indicating a potential risk of decrease in ZV immunogenicity	Level I	Fair (no validated correlates of VZV immunity
Tseng HF et al., 2011 (29)	ZOSTAVAX™, Pneumovax 23™	Retrospective cohort study	14,366 persons ≥60 (7,187 concomitantly and 7179 non-concomitantly immunized)	HR comparing the incidence rate of HZ in the two cohorts was 1.19 (95% CI, 0.81--1.74) suggesting no evidence of an increased risk of HZ in concomitant administration of zoster and pneumococcal vaccine	Level II-2	Good

Table 4. Levels of Evidence Based on Research Design

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 vaccine efficacy.
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 5. Quality (internal validity) Rating of Evidence

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.

Table 6. NACI Recommendation for Immunization -- Grades

A	NACI concludes that there is **good** evidence to recommend immunization.
B	NACI concludes that there is **fair** evidence to recommend immunization.
C	NACI concludes that the existing evidence is **conflicting** and does not allow making a recommendation for or against immunization; however other factors may influence decision-making.
D	NACI concludes that there is **fair** evidence to recommend against immunization.
E	NACI concludes that there is **good** evidence to recommend against immunization.
F	NACI concludes that there is **insufficient** evidence (in either quantity and/or quality) to make a recommendation, however other factors may influence decision-making.

LIST OF ABBREVIATIONS

Abbreviation	***Term***
Ab	antibodies
AE	Adverse Events
CD4	cluster difference 4
GMC	geometric mean count
GMFR	geometric mean fold rise
GMT	geometric mean titer
HAART	highly active antiretroviral therapy
HIV	Human immunodeficiency virus
HSCT	hematopoietic stem cells transplant
HZ	herpes zoster
HZO	herpes zoster Ophthalmicus
MSK	musculoskeletal
PFU	Plaque forming units
py	patient year
SFS	spot forming cells
SPS	Shingles Prevention Study
STPS	Short Term Persistence Substudy
TNF	Tumor necrosis factor
US	United States
VZV	Varicella Zoster Virus
ZEST	Zostavax™ efficacy and safety trial

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