2012 Antigen Review for the New Zealand National Immunisation Schedule: Varicella-zoster virus

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Te Whare Wānanga o Tāmaki Makaurau

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Executive summary

This review summarises selected literature on the use of vaccines against varicella zoster virus (VZV) and herpes zoster (HZ) virus published between 2009 and 2012. During an edit of this review in 2014, reference updates were inserted where the data referenced had been published since 2013. A full review of data and vaccination schedules was not conducted.

VZV infection is highly infectious with a basic reproduction number estimate of around 8-10. Primary VZV infection is the cause of VZV disease (commonly known as chickenpox). Following primary infection, the VZV exhibits latency where the virus remains dormant in the trigeminal and dorsal root ganglia. In about 10–30% of cases, VZV reactivates later in life producing a disease referred to as herpes zoster (HZ), commonly known as shingles. In the majority of children, VZV infection is a mild and self-limiting disease but complications requiring hospitalisation and mortalities do occur. Secondary bacterial infections and VZV encephalitis are the most common morbidities.

In a typical year, New Zealand (NZ) is estimated to experience approximately 50,000 chicken pox infections (almost equal to the birth cohort), of which 150 to 200 result in hospitalisation, one to two cases result in residual long term disability or death and 0.5 to 1.0 cases result in congenital VZV syndrome. About two-thirds of the burden is borne by otherwise healthy children and less than one-tenth by children associated with immune suppression. From 1994 to 2002 there were also nine deaths associated with VZV, two were children aged five to nine years, four were adults aged 30 to 64 years and three were adults over the age of 65 years.

The first VZV vaccine was licenced in Japan in 1986 and the United States (US) licenced VZV vaccines for routine used in 1995. Since this time, VZV vaccines have been demonstrated to have excellent safety profiles and are very effective at controlling disease. A vaccine containing 14 times the amount of virus as the VZV vaccines has been licenced for use in older adults to protect against HZ and associated complications.

Safety of VZV vaccines

VZV vaccines have been available since 1995 and in general are well tolerated. Breakthrough VZV disease is seen post-vaccination in rare cases. VZ post vaccination is also reported rarely. VZV vaccine substantially decreases the risk of HZ among vaccinated children by around four- 12 times. Secondary transmission can rarely occur. Accidental vaccination in pregnancy has not shown any safety concerns to date.

In children aged 12 - 23 months of age, there is a recognised increased risk of febrile seizures seven - 10 days following a first dose vaccination with measles, mumps, rubella, VZV combination vaccines (MMRV) compared with measles, mumps, rubella, + VZV (MMR+V) vaccines separately. Neither vaccine has been found to be associated with increased risk of febrile seizures among children four years and older.

Effectiveness, immunogenicity and efficacy of VZV vaccine

Single dose vaccine programs are about 70-80% effective but outbreaks of VZV do occur. Most studies suggest that a two dose vaccine program increases the effectiveness significantly. Attaining high vaccine coverage is an important factor in disease control. In contrast to VZV primary infection, VZV vaccination does not seem to provide lifelong immunity against VZV. The need for a booster dose at some point after childhood vaccination has yet to be determined. Concomitant administration with diphtheria, tetanus toxoids, acellular pertussis and inactivated polio vaccine (DTaP-IPV), 7-valent pneumococcal conjugate vaccine (PCV-7), hepatitis A vaccine (HAV) or quadrivalent meningococcal conjugate vaccine (MenACWY) does not affect immunogenicity.

Immigrants from countries with a low prevalence of VZV, particularly from tropical countries are at greater risk for infection during adulthood. VZV vaccination is immunogenic for paediatric transplant patients, patients undergoing alloHCT and kidney and liver transplant patients. However serology should be monitored periodically to ensure protection is maintained in these groups. VZV vaccine is poorly immunogenic in people with HIV.

Vaccine options and schedules for VZV

Two single valent vaccines, Varilrix® (GSK) and Carivax® (Merck) and two quadrivalent MMRV vaccines, Priorix-tetra® (GSK) and Pro-Quad® (Merck) are licensed and available for paediatric VZV vaccination in NZ. Most countries using VZV vaccine routinely recommend two doses and/or have a catch-up programme for early adolescents. A one-dose schedule is likely to still result in VZV outbreaks and breakthrough cases. A two-dose schedule is more effective and significantly less likely to result in outbreaks provided coverage is maintained at around 90% for the first dose.

There is evidence to support the administration of VZV vaccine to healthy susceptible family contacts of children with malignancy.

In countries where VZV vaccine is on the childhood immunisation schedule, the first dose is generally given between 11 and 18 months. For countries that have moved to a two-dose schedule, the second dose is administered between 15 and 23 months or between four and six years usually in combination with the MMR vaccine. MMR + V is likely to be the preferred vaccine if used in children under 48 months of age. MMRV is appropriate at any age for the second dose.

If NZ were to follow international practice, the options for including a VZV vaccine on the current immunisation schedule with the least disruption could be two doses administered at 15 months and four years of age as MMR + V followed by MMRV.

Implications for skin infections

This literature search has been unable to identify any recently published papers specifically addressing the effect of VZV vaccine on secondary skin infections. However, VZV is a significantly modifiable risk factor for superficial and invasive bacterial infections.

Implications for older cohorts

Mathematical models generally predict an increase in HZ over the next few decades following the institution of a childhood programme due to the reduction in natural boosting form circulating wild type VZV, followed by a rapid decline to below pre-vaccine levels as the birth cohorts become vaccinated. However, as of early 2013, it is not known whether the introduction of childhood mass VZV vaccination does significantly alter the epidemiology of HZ. Studies that have investigated this issue have been unable to attribute any increase in incidence of HZ to the childhood VZV vaccine programme. It is important to continue to monitor the international epidemiological data on this issue.

HZ virus infection and vaccine

HZ occurs most commonly with increasing age (>50 years), impaired immunity, and a history of VZV in the first year of life. The lifetime risk of reactivation of VZV causing HZ is estimated to be approximately 20 to 30% and it affects 50% of those who live to at least 85 years.

Zostavax® is the first and only vaccine available for the prevention of HZ, and is licensed in NZ for use in people aged 50 years and older. This vaccine has an adverse event profile similar to that of placebo. HZ vaccine has been found to significantly reduce the incidence of HZ in people aged 50 to 59 years. The effectiveness of HZ vaccine in preventing HZ does not appear to be compromised when co-administered with 23-valent pneumococcal vaccine (PPV23). There is evidence of the persistence of HZ vaccine efficacy for up to five years after vaccination, although vaccine efficacy is uncertain beyond that point.

Although Zostavax® is approved by the US Food and Drug Administration (FDA) for use in adults aged 50 years or older; this vaccine is routinely administered only to patients aged 60 years or older, largely due to vaccine supply issues. HZ vaccine is being considered for the 70 - 79 year age group in Germany and has been recommended for use in adults aged 60 - 79 years on the National Immunisation Programme of Australia but a government decision is pending. In the UK a recommendation has been made that a universal HZ vaccination programme for adults aged 70 up to and including 79 years should be introduced depending on cost.

Scheduling of HZ vaccine

As of early 2013, a single dose of HZ vaccine is recommended to the elderly. As yet, the requirement for a booster dose has not been confirmed. The introduction of a childhood VZV immunisation programme brings forward the ethical question of whether to introduce HZ vaccination for older adults.

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Prepared as part of a Ministry of Health contract

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This review is one of a series of 18 antigen reviews presented in 15 individual reports.

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Abbreviations

ACIP	Advisory Committee on Immunisation Practices
AE	Adverse Events
AEFI	Adverse Event Following Immunisation
CDC	Centers for Disease Control and Prevention
DTaP-IPV	Diphtheria, Tetanus Toxoids, acellular Pertussis and Inactivated Polio Vaccine
EPI	Expanded Program on Immunization (WHO)
HAV	Hepatitis A vaccine
HIV	Human Immunodeficiency Virus
HSV	Herpes Simplex Virus
HZ	Herpes zoster
ICD-9	International Classification of Diseases, Ninth Revision
IMPACT	Immunization Monitoring Program, Active
LAV	Live Attenuated Vaccine
MenACWY	Quadrivalent Meningococcal Conjugate Vaccine
MMR	Measles, Mumps and Rubella Vaccine
MMRV	Measles, Mumps, Rubella and Varicella Vaccine
NCIRS	National Centre for Immunisation Research and Surveillance (Australia)
NZ	New Zealand
PCR	Polymerase Chain Reaction
PHN	Post herpetic neuralgia
PCV-7	7-valent pneumococcal conjugate vaccine
PPV-23	23-valent pneumococcal vaccine
SAE	Serious Adverse Events
SCCS	a self-controlled case series
SNP	Single Nucleotide Polymorphism
US	United States
V	Varicella
VAERS	Vaccine Adverse Events Reporting System
vOka	Vaccine Oka virus
vVZV	Vaccine varicella zoster virus
VZV	Varicella zoster virus
VZVIP	Varicella zoster vaccine identification program (Europe)
WHO	World Health Organization
wtVZV	Wild type varicella zoster virus

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1. Background Varicella-zoster virus infections

VZV is a human alphaherpesvirus most closely related to herpes simplex virus-1 (HSV1) and HSV2. VZV causes varicella zoster disease (chicken pox) as the primary infection and establishes long-life persistence in sensory ganglia: reactivation from latency produces the clinical syndrome referred to as herpes zoster (HZ, shingles) (1). VZV is a highly contagious pathogen, exclusive to humans, and is typically acquired through inhalation of aerolised virus.

In the majority of children, VZV infection is a mild and self-limiting disease but complications requiring hospitalisation and fatalities do occur. Secondary bacterial infections and VZV encephalitis are the most common morbidities. Serious complications include central nervous system involvement, pneumonia, secondary invasive bacterial infections and even death. Primary infection in adults is rare but has a higher rate of complications, with pneumonia being the most common. VZV pneumonia often requires mechanical ventilation and carries an overall mortality rate of 10%–30% despite appropriate antiviral therapy. Adults with VZV are 25 times more likely to develop severe disease than children.

Herpes zoster (HZ, shingles) is the most common manifestation of VZV reactivation. About one third of a population experience HZ with the incidence increasing after the age of 60 years as cell-mediated immunity to VZV declines (2). Recurrence is greater in females than males (about 7% after eight years compared with 4% of males). Post herpetic neuralgia (PHN) can be a significant healthcare challenge – PHN is defined as dermatomal distribution of pain that persists for more than three months after HZ.

Pregnant women and their unborn babies are particularly vulnerable to VZV. Maternal VZV occurring in the first half of pregnancy can cause the rare but devastating congenital VZV syndrome, whereas infection very late in pregnancy may cause neonatal VZV infection. Women who contract VZV while pregnant have an estimated 10- 20% risk of developing VZV pneumonia, which is a higher rate than observed in non-pregnant women.

Immunocompromised people are also vulnerable to both VZV and HZ; these individuals include those taking immunosuppressive medications, such as cancer treatment and certain anti-inflammatory drugs, or organ transplant patients, and those with human immunodeficiency virus (HIV) infection.

VZV infection is followed by the production of VZV-specific antibody and VZV-specific T-cell mediated immunity. T-cell immunity to VZV is more important than the antibody response, since VZV-specific T cell-mediated immunity maintains the latency of VZV in ganglia. The immune response is also boosted by subclinical reactivation of latent virus or environmental exposure to virus. Importantly, the incidence of zoster increases with age as VZV-specific T cell-mediated immunity declines. The frequency of VZV-specific memory CD4+ T cells is significantly influenced by age (3).

2. Methodology for review

2.1 Objectives

The objectives for this review have been informed by the general specifications for the 2012 New Zealand (NZ) antigen review and the specific specifications for VZV vaccines. These are listed below. The dates for publication are between 2009 and 2012 as per the brief. This is not a systematic review or a critique of the literature. The choice of articles reviewed is based on the purposeful selection of recent reviews and studies that may best inform policy discussions around the use of VZV and zoster vaccines for NZ.

- General specifications
  - Safety
  - Effectiveness
  - Implementation issues (practicality and possible impact on uptake)
  - The differences that need to be considered for each age group such as the variable severity of diseases and issues for vaccination
  - Different options of placement on the schedule, based on international findings and best practice
  - Different vaccine options and comparisons between the options
- Specific service specifications for VZV vaccines
  - Different schedule options as described in the literature.
  - Implications of the large burden of disease from skin infections in NZ (and the specific type of skin infections), and international data relating to reductions in skin infections that have resulted from offering the vaccine (and the specific type of skin infections).
  - Investigation of whether there should be a one or two-dose schedule.
  - Evidence for providing the vaccine to household contacts of high risk.
  - International evidence regarding how the VZV vaccine should be administered, including whether it should be combined with the MMRV vaccine or be administered separately.
  - Contraindications for adding the MMRV vaccine to the Schedule.
  - Considerations of international best practise concerning eligibility.
  - Implications for older children and older people as natural immunity boosting in the community wanes.
  - Implications for children who have already had the vaccine.
  - Considerations of the HZ vaccine for adults.
  - Duration of protection provided by vaccines.

2.2 New Zealand epidemiology

VZV is not a notifiable disease in NZ. Limited information is available from reports from Auckland Healthcare, Healthcare Waikato, Canterbury Health, Capital Coast Health, Middlemore Hospital and ESR.

2.3 Literature search

2.3.1 Medline search terms and strategy

MeSH term: Varicella Vaccines

959

Limit to Humans, English, 2009 – current

213

NOT Costs

199 Remove duplicates

184 (keep and view)

2.3.2 Cochrane Library search terms and strategy

Search term Varicella Vaccin*

Limit to Cochrane Reviews, Other Reviews, Trials 2009-present

5 results (keep and view)

2.3.3 Scopus search terms and strategy

Scopus search terms and strategy

Varicella Vaccin* Published 2011 – present

643

Limit to: Medicine, humans, English

453

Exclude Letter, Short survey, editorial and erratum

405 (keep and view)

Reject social science articles. Delete duplicates

Final Endnote Library 482 Articles

2.3.4 Grey literature

Conference abstracts were sought to include data that has not yet been published, particularly from the key infectious diseases conferences for 2011 and 2012 – there were no abstracts or posters accessed.

2.3.4 Additional searches

Where questions arose additional searches were undertaken to ensure there was no further available data. Where articles were missing they were accessed and added to the library. A further 11 articles were accessed and 158 were removed from the final library.

2.3.5 Final library

The final library includes 324 references. Where systematic reviews and/or meta-analysis were available the preceding literature was excluded from the review.

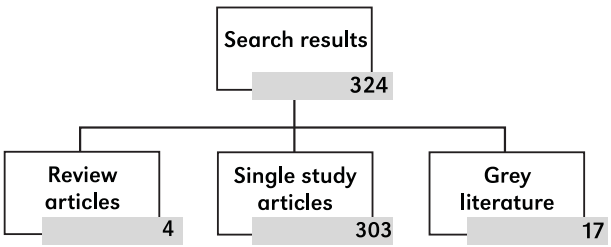

Figure 1. Flow of selection of articles for review

2.4 Participants/populations

The population for a universal programme are infants and targeted vaccination all ages and older adults.

2.5 Interventions

2.5.1 Varivax®

Varivax® in a live attenuated virus vaccine against VZV produced by Merck Sharp and Dohme Ltd. Each 0.5 mL dose of Varivax® contains a minimum of 1350 PFU (plaque forming units) of Oka/Merck varicella virus. Each dose also contains approximately 18 mg of sucrose, 8.9 mg of hydrolysed gelatin, 3.6 mg of urea, 2.3 mg of sodium chloride, 0.36 mg of monosodium L-glutamate, 0.33 mg of sodium phosphate dibasic, 57 µg of potassium phosphate monobasic, 57 µg of potassium chloride. The product also contains residual components of MRC-5 cells and trace quantities of neomycin and bovine calf serum from MRC-5 culture media.

2.5.2 Varilrix®

Varilrix® is a live attenuated virus vaccine against VZV produced by GlaxoSmithKline Ltd (GSK). Each dose contains not less than $10^{3.3}$ plaque-forming units (PFU) of the VZV. It also includes the excipients amino acids, human albumin, lactose, neomycin sulphate, polyalcohols.

2.5.3 Priorix-Tetra®

Priorix-Tetra® is a live attenuated vaccine against measles, mumps, rubella and VZV manufactured by GlaxoSmithKline Ltd. It contains attenuated Schwarz measles, RIT 4385 mumps (derived from Jeryl Lynn strain), Wistar RA 27/3 rubella and Oka VZV strains of viruses, separately produced in chick embryo cells (mumps and measles) or human diploid MRC5 cells (rubella and VZV). Each 0.5 mL dose of reconstituted vaccine contains not less than $10^{3.0}$ $CCID_{50}$ of the Schwarz measles, not less than $10^{4.4}$ $CCID_{50}$ of the RIT 4385 mumps, not less than $10^{3.0}$ $CCID_{50}$ of the Wistar RA 27/3 rubella and not less than $10^{3.3}$ PFU of the varicella virus strains.

2.5.4 ProQuad®

ProQuad® is a live attenuated virus vaccine against measles, mumps, rubella and VZV manufactured by Merck Sharp and Dohme Ltd. ProQuad® contains M-M-R® II (Measles, Mumps and Rubella Virus Vaccine Live): Measles Virus Vaccine Live is a more attenuated line of measles virus, derived from Enders' attenuated Edmonston strain and propagated in chick embryo cell culture; Mumps Virus Vaccine Live, the Jeryl Lynn™ (B level) strain of mumps virus propagated in chick embryo cell culture; Rubella Virus Vaccine Live, the Wistar RA 27/3 strain of live attenuated rubella virus propagated in WI-38 human diploid lung fibroblasts; and (2) Varicella Virus Vaccine Live (Oka/Merck), the Oka/Merck strain of VZV propagated in MRC-5 cells (Varivax®).

2.5.5 Zostavax®

Zostavax® is a live attenuated virus vaccine manufactured by Merck Sharp and Dohme Ltd. Each dose contains a minimum of 19,400 PFU of the Oka/Merck strain of VZV and 41.05 mg of sucrose, 20.53 mg of hydrolysed porcine gelatin, 8.55 mg of urea, 5.25 mg of sodium chloride, 0.82 mg of monosodium L-glutamate, 0.75 mg of sodium phosphate dibasic, 0.13 mg of potassium phosphate monobasic, 0.13 mg of potassium chloride; residual components of MRC-5 cells including DNA and protein; and trace quantities of neomycin and bovine calf serum.

2.6 Study designs

The studies included in this update are meta-analysis, systematic reviews, reviews, randomised controlled trials, and observational studies using database matching.

3. Epidemiology of VZV

VZV circulates as five distinct clades that exhibit predominance in different geographical areas. Clade 1 is most common in Europe and North America, clade 2 is predominant in Asia and clade 5 is most predominant in Africa. As expected, immigration has redistributed European, African and Asian clades. The Oka virus used to derive VZV vaccines is a clade 2 strain (1).

In temperate climates, VZV is acquired almost universally during childhood; attack rates are substantially lower in tropical areas (1). In temperate climates, the rates of hospitalisation with VZV are highest in children zero - four years, which is more than 20 times that for those >15 years of age, although the risk of severe disease, usually with VZV pneumonitis, increases with age (4).

Whereas the prevalence of other human herpes viruses has declined in developing countries, VZV epidemics continue to produce high infection rates. Episodes of HZ in older individuals provide a constant mechanism for reintroducing the virus, causing VZV infection in naïve individuals who are in close contact and who then spread the virus to other susceptible individuals. Approximately 50% of individuals will develop HZ by 80 years of age. The annual risk for adults over 60 years of age is 1.1/100 (5).

3.1 New Zealand epidemiology – VZV

In NZ, it is expected that 90% of children will have had VZV infection before adolescence, and a peak in incidence is seen in the five - nine year age group. With higher participation rates in early childhood services, a greater proportion of infections may now be occurring in pre-school aged children.

VZV is not a notifiable disease in NZ, so accurate data collection is limited for uncomplicated VZV infection and hospital discharge data relies on accurate coding. This may result in under reporting of complications secondary to VZV.

In the absence of a vaccine programme, VZV annual incidence is likely to approximate to the birth cohort; this means that in a typical year, NZ was estimated to experience approximately 50,000 chicken pox infections. NZ hospital admission numbers have increased from approximately 50 per annum in 1970 to approximately 300 in 2002. Most of these hospitalisations occur in people without underlying medical conditions, with only 4% of hospitalisations involving people with an underlying immune deficiency (4). The rate of hospital discharges for the zero to four and five - nine years age groups was higher compared with older age groups, because the disease is most common in childhood. However, adults, adolescents and infants are more likely to suffer severe illness or the complications of VZV.

Based on overseas rates, it is estimated that up to one case of congenital VZV syndrome may be expected in NZ each year, although few have been reported. Mortality data are available for the period 1980 - 2002. Nine deaths were attributed to VZV over the 14-year period 1980 - 1993, of which, four occurred in children, two in infants and three in adolescents or adults. None of the cases who died had a contributory cause of death recorded. From 1994 – 2002, there were also nine deaths associated with VZV, two were children aged five to nine years, four were adults aged 30 - 64 years and three were adults over the age of 65 years (6). Larger series, from other developed temperate climate countries, suggest that up to 10% of VZV deaths may involve individuals with immunosuppression (6).

In 2011, there were a total of 792 notifications of VZV infections based on the weekly data collated from the virology laboratories of Auckland Healthcare, Healthcare Waikato, Canterbury Health, Capital Coast Health, Middlemore Hospital and ESR.

There is no current NZ data available on the burden of disease from HZ.

3.2 Summary of epidemiology VZV

In developed countries with temperate climates, like NZ, approximately 90% of children will have had VZV infection prior to adolescence. The annual risk for developing HZ after the age of 60 years is 1.1/100. In NZ, it is estimated that nearly the entire birth cohort will experience VZV primary infection as a child, and approximately one third of the adult population will experience HZ infection. There is approximately one death associated with VZV in NZ every 1 – 2 years, with most deaths occurring in adults.

4. Safety

4.1 Objective

The objective of this section is to review the most recent safety data for licenced VZV vaccines and HZ vaccines.

4.2 Outcomes

Outcomes are vaccine safety, including adverse events following immunisation (AEFI) and serious adverse events (SAE). Some of the information in this section is a summary taken directly from the abstracts or as exerts from the full paper, with the authors conclusion taken as a direct quotation.

4.3 Overview

Reports of Adverse Events (AE) following VZV vaccine in the US Vaccine Adverse Event Reporting System (VAERS) indicate a rate of 2.6 per 100,000 doses during the first 10 years of licensure. VZV vaccine can cause mild self-limiting rash in healthy recipients within the first six weeks. Some children with severe undiagnosed immune deficiencies have developed progressive infection by Oka vaccine virus but treatment with acyclovir has been effective in most cases.

4.4 Safety of VZV vaccination

4.4.1 Adverse Events Following Immunisation with VZV vaccines

Varivax® was licensed in Europe in 2003, and from October 2003 to September 2008, 3.3 million doses were distributed. The recent safety profile of the Oka/Merck VZV vaccine in Europe has been presented based on spontaneous reporting of specific adverse events possibly related to VZV, together with results from the European Union Varicella Zoster Virus Identification Program (VZVIP) during the first five years of experience after its introduction in Europe.

During this period, 1006 spontaneous AE reports were analysed from the post-marketing AE database and 88% were considered non-serious. The rate of AE after the distribution of 3.3 million doses was three reports per 10,000 doses (7). This is a similar rate to the three - four reports per 10,000 doses recorded after global distribution of 55.7 million doses over the first 10 years (Merck data). The AEs of interest selected for the five year review were: breakthrough cases of VZV in a vaccine recipient within 42 days after vaccination; incidence of HZ; neurologic adverse events; pneumonia or pneumonitis; and suspected secondary transmission. A summary of the findings of a review of five years safety data is presented below. The paper focussed on these selected AEs and the other serious AEs were not defined (7).

4.4.1.1 Breakthrough VZV following vaccination with VZV vaccine

In addition to routine safety surveillance, the VZVIP in Europe analyses clinical samples to establish whether AEs are associated with wild-type (wtVZV) or VZV vaccine-type (vVZV) strains. Over five years, samples from 76/585 cases with selected AEs were collected. Of 55 VZV-positive/typeable samples, wtVZV was detected in 40 and vVZV in 15 samples. Most rashes (32/44) within 42 days after vaccination were associated with wtVZV. There were 261 spontaneous reports of breakthrough VZV. Four of the reported cases (1.5%) were considered to be serious. For breakthrough VZV, 6/9 cases were wtVZV-positive; none were vVZV-positive. One case of mild encephalitis was associated with vVZV. One of three cases of suspected secondary vVZV transmission was confirmed. Most wtVZV was clade 3 and clade 1. The findings confirm that Oka/Merck vaccine is generally well tolerated (7).

4.4.1.2Herpes zoster following vaccination with VZV vaccine

In the five year European surveillance 2003-2008, there were 44 spontaneous reports of HZ. Samples for PCR were available for 17 of the cases and of these nine were VZV-positive (eight vVZV, one wtVZV). These occurred between seven days and 1280 days (median, 154 days) after vaccination in individuals aged 10 months to 57 years (median age at time of vaccination, 20 months). Ninety-three percent of vaccinated individuals were children with 77% being younger than five years of age at the time of the vaccination and 36% being aged two years or under. The age at time of event ranged from 15 months to 57 years (median, 29.5 months). Three of the samples were eventually found to contain herpes simplex virus (HSV) by PCR (7).

An investigation of the Kaiser Permanente Northwest paediatric population was undertaken to determine

the proportion of suspected HZ cases that could be confirmed by VZV PCR, the proportion of confirmed cases associated with the vaccine-type virus; and to describe the VZ-specific acute IgM and IgG responses associated with suspected HZ episodes. There were 14 vaccinated children with suspected HZ and six cases were confirmed VZV by PCR, two cases were due to vaccine-type virus. Serum VZV IgM and IgG were not useful for diagnosis of HZ among vaccinated children (8).

No cases of HZ in vaccinated adults caused by the Oka strain have been recorded (5).

A large population based surveillance, among under 20 year olds in California from 2000 - 2006, revealed the incidence of HZ among children <10 years of age declined by 55%, from 42 cases reported in 2000 (74.8/100,000 persons; 95% CI: 55.3-101.2) to 18 reported in 2006 (33.3/100,000; 95% CI: 20.9-52.8; p<0.001). During the same period, the incidence of HZ among 10 – 19 year olds increased by 63%, from 35 cases reported in 2000 (59.5/100,000 persons; 95% CI: 42.7-82.9) to 64 reported in 2006 (96.7/100,000; 95% CI: 75.7-123.6; p<0.02). Among children aged <10 years, those with a history of VZV vaccination had a four - 12 times lower risk for developing HZ compared with children with history of VZV disease. The authors concluded that VZV vaccine substantially decreased the risk of HZ among vaccinated children and that its widespread use will likely reduce overall HZ burden in the US. However, they were unable to account for the increase in HZ incidence among 10 to 19-year-olds which needs to be confirmed from study (9).

4.4.1.3 Neurological adverse events

In the European safety review, there were 16 reports of selected neurologic adverse events notified after Oka/Merck VZV vaccination. These were ataxia (n = 8), encephalitis/encephalopathy (n = 5), meningitis (n = 1), inflammation within the central nervous system (n = 1), and acute disseminated encephalomyelitis (n = 1). The outcome in all cases when provided was favourable (n = 9) (7).

4.4.1.4 Pneumonia

Two cases of pneumonia were reported in the European safety review. One case was in a 14-month-old child occurring one day after vaccination and the second case occurred in a two-year-old child seven months after vaccination. Both events were serious, but the children recovered without sequelae. No samples were collected from either child for PCR analysis (7).

4.4.1.5 Stevens Johnson syndrome after VZV vaccination

A case of Stevens Johnson syndrome in a 12 year old boy has been reported. This case of Stevens Johnson syndrome was preceded by VZV vaccination performed as part of school protocol (10). [Reviewers comment: SJS after VZV infection has been reported previously]

4.4.1.6 Secondary transmission of VZV virus following VZV vaccination

Three non-serious cases of suspected secondary transmission of vVZV were reported in the European safety review. Samples of vesicles/pustules from the three cases were analysed, supporting vVZV transmission in only one case. In one case, a five month-old male infant developed a zoster-like rash on the cheek seven days after his sister received the vaccine, this was found to be negative for VZV, but HSV1 was identified. The second case was in an infant who presented with scattered vesicles 11 days post-vaccination. Then, 13 days after VZV onset in her child, the mother developed wtVZV-positive VZV. The third case was when vVZV transmission was confirmed in a 20-month old female infant who developed HZ on the left shoulder five months after vaccination. Fourteen days after the onset of this event, her 35-year-old father developed a generalised VZV-like rash, with uncountable lesions, also positive for vVZV. The father had experienced VZV at age five years. Neither the girl nor her father had a history of immune deficiency (7).

A case report from China of a 23-year-old female kindergarten teacher who presented to hospital with a mild case of VZV reported VZV vaccine strain vOka, resembling Varilrix® but not Varivax® nor Biken strains, was isolated from the skin lesion. The teacher was reported not to have received VZV vaccine. Retrospective analysis suggested the transmission came from a five year old boy in her class who had developed HZ 13 months after receiving Varilrix®. This was the first report in China in which an adult with VZV was attributable to vaccine virus and the sixth report internationally of transmission of vaccine virus to a susceptible adult (11).

A case of neonatal vaccine strain VZV infection has been reported in the US, in a 25-day-old infant developed VZV 22 days after her mother received VZV vaccine postpartum. Infection with vaccine-strain VZ virus was confirmed by genetic analysis. The mother had no post-vaccination rash nor did other contacts have rash or recent vaccination. This is the first known documented case of vOka in new-born associated with postpartum maternal vaccination in the absence of

post-vaccination rash and the first report of laboratory-confirmed vOka in the absence of contact with an individual with a post-vaccination rash. The infant had no contact with any individual with a rash and only her mother had been recently vaccinated. It was suggested that the most plausible transmission mechanism considering the absence of maternal post-vaccination rash, was direct exposure of the infant to the vaccine during vaccination of the mother. As the infant was present in the room when her mother was vaccinated, and the vaccine-filled syringe was cleared of air bubbles prior to injection, it was hypothesised that aerosolisation of the vaccine could have resulted in a direct transmission of vOka to the infant. The authors also postulated that direct inoculation of vaccine from the mother's injection site onto the infant's mucosa or conjunctiva may have occurred (12).

4.4.2 Quadrivalent measles, mumps, rubella, VZV vaccine and the risk of febrile seizures

MMRV vaccine, ProQuad® (Merck), was licensed in the US in 2005. The vaccine has been associated with an increased risk for febrile seizures in 12 - 23 month old children compared with MMR + V administered separately at the same visit. In February 2008, the Advisory Committee on Immunization Practices (ACIP) was alerted to preliminary evidence of a twofold increased risk of febrile seizures after the combination MMRV vaccine when compared with separate MMR and VZV vaccines. Using 2000-2008 Vaccine Safety Datalink data for seizures and fever visits among children aged 12 - 23 months, the seizure risk among MMRV vaccine recipients (n = 83,107) was compared with that of MMR + V recipients (n = 376,354). Seizure and fever significantly clustered seven - 10 days after vaccination with all measles-containing vaccines, but not after VZV vaccination alone. Seizure risk, during days seven to 10, was higher after MMRV than after MMR + V (relative risk: 1.98; 95% CI 1.43-2.73). The excess risk for febrile seizures seven - 10 days after MMRV compared with separate MMR + V was 4.3 per 10,000 doses (95% CI: 2.6-5.6). It is well documented that fever and seizure are elevated 7 - 10 days after vaccination among 12 – 23 month old children following their first dose of a measles-containing vaccine. The analysis concluded that one additional febrile seizure results for every 2300 doses of MMRV given instead of separate MMR + V (13).

A subsequent review concluded that there was no increased risk of febrile seizures in four – six year olds associated MMRV or MMR +V. The review was conducted among four - six year-olds identified with seizures in the emergency department and hospital from 2000 – 2008, and outpatient visits for fever from 2006 – 2008, during days 7 - 10 and 0 - 42 after MMRV and MMR + V. From 2006 - 2008, 86,750 children received MMRV; from 2000 to 2008, 67,438 received same-day MMR + V. Seizures were rare throughout days 0 to 42 with no peak seen during days 7 - 10. There was one febrile seizure 7 - 10 days after MMRV and none after MMR + V. The absolute risk for febrile seizure 7 - 10 days after MMRV was 1 per 86,750 doses or 1.2 per 100,000 doses. The risk for febrile seizures 7 - 10 days after MMR + V was no higher than 1 febrile seizure per 18,282 doses of same-day, separately administered MMR + V, or 0 per 100,000 doses. A risk greater than one febrile seizure per 15,500 MMRV doses and one per 18,000 MMR + V doses was ruled out with 95% level of confidence (14).

4.4.3 Safety of VZV vaccination in immune compromised groups

A number of recent studies conducted in the US and Europe has demonstrated the safety, immunogenicity, and effectiveness of VZV vaccine administered to various immunocompromised groups. A summary of these studies was presented in 2012. The studies examined the immune response to VZV vaccine in children suffering from haematological malignancies, inflammatory bowel disease, HIV with CD4+ counts of at least 200 cell/ml, atopic dermatitis, and juvenile rheumatic diseases. The conclusions were that the vaccine was immunogenic in most cases and that MMRV combination vaccine is associated with a small increased risk of seizure; thus, it is recommended that the age for the first dose should be at least 48 months (15).

In immunocompromised children, where HZ occurs more rapidly than in healthy children, there is a significantly lower risk for HZ in children who have been vaccinated compared with unvaccinated children (5).

4.4.4 Safety of VZV vaccination during pregnancy

Infection with VZV during pregnancy is associated with a risk of congenital VZV syndrome and maternal complications. As VZV vaccine is a live attenuated vaccine, it is contraindicated for pregnant women. A recent update on vaccination in pregnancy found no reports of congenital VZV syndrome after exposure to VZV vaccine during pregnancy. A registry was established by the manufacturer in collaboration with the CDC to monitor maternal and fetal outcomes of women who were inadvertently immunised with VZV

vaccine in the three months before conception or at any time during pregnancy. Among the 737 women with pregnancy outcomes available, there were no patterns of defects and no infants were born with features consistent with congenital VZV syndrome among any of the women enrolled or among the seronegative women. Exposure to either live or inactive vaccines during pregnancy has not been associated with an increased risk of adverse pregnancy outcomes, there have been no infants born with CRS or VZV syndrome following rubella or VZV vaccination of the mother at any time during pregnancy (9, 16).

4.5 Safety of HZ vaccine

One of the largest safety reviews for HZ vaccine is that of AE data collected from 193,083 adults aged 50 and older receiving a HZ vaccine at one of eight managed-care organisations participating in the Vaccine Safety Datalink project in the US. The vaccine was found to be safe and well tolerated with no increased risk for the adverse event groupings of cerebrovascular events, cardiovascular events, meningitis, encephalitis, encephalopathy, and Ramsay-Hunt syndrome or Bell's palsy. A small increased risk of allergic reactions one to seven days after vaccination was reported (17).
A post marketing observational study, of 29,000 people ≥ 60 years of age who received HZ vaccine in a managed care organisation in the US, did not identify any safety concerns within 42 days of receiving the vaccine (18).

4.5.1 Safety and tolerability of HZ vaccine in older adults ≥50 years

Data was reviewed from eight managed-care organisations participating in the Vaccine Safety Datalink project in the US. A total of 193,083 adults aged 50 and older receiving a HZ vaccine from 1 January 2007 to 31 December 2008 were included. Pre-specified AEs were identified by aggregated International Classification of Diseases, Ninth Revision (ICD-9) codes in automated health plan datasets. The authors used a case-centred design, whereby, the date of the adverse event was the key anchor time point to follow back to vaccination date. The length of the risk window(s) for the potential adverse event varied from 1 - 42 days after vaccination depending on the event of interest. The risk of allergic reaction was significantly increased within 1 - 7 days of vaccination as assessed by the case-centred method (RR 2.13, 95% CI: 1.87-2.40). No increased risk was found for the adverse event groupings: cerebrovascular events, cardiovascular events, meningitis, encephalitis, encephalopathy, and Ramsay-Hunt syndrome or Bell's palsy. The HZ vaccine is generally safe and well-tolerated with a small increased risk of allergic reactions 1 - 7 days after vaccination (17).

A randomised, double-blind, multicentre study with 210 subjects ≥60 years old compared immunity and safety profiles after one and two doses of HZ vaccine, separated by six weeks, compared with placebo. Participants were followed for 42 days after each vaccination and AEs were recorded on a standardised vaccination report card. No serious vaccine-related AEs occurred. A second dose of vaccine was generally safe, although VZV-specific immunity was not boosted beyond levels achieved post dose one (19).

Another recent placebo controlled study evaluated the general safety of HZ vaccine in adults ≥60 years old by assessing the rates of SAEs in 5,983 participants who received HZ vaccine compared with 5,997 participants who received placebo. The study group comprised of 96.2% Caucasians residing in the US (88.7%) and living in independent residences (96.9%). Within the primary 42-day follow-up period, 84 vaccine subjects and 67 placebo subjects reported SAEs. The estimated risk of SAEs within 42 days was 1.41% for vaccinated versus 1.12% for placebo recipients, (relative-risk = 1.26; 95% CI 0.91, 1.73); indicating no statistically significant difference between groups. During the 182-day follow-up period, 340 vaccine subjects and 300 placebo subjects reported SAEs. The estimated risk of SAEs within 182 days was 5.68% for vaccine versus 5.01% for placebo, (relative-risk = 1.13; 95% CI 0.98, 1.32), indicating no statistically significant difference between groups. There were 24 fatal SAEs in the vaccine group and 17 in the placebo group (relative risk = 1.41; CI: 0.77, 2.60); six and five, respectively, with SAE onset during the primary 42-day follow-up period. No deaths were deemed vaccine-related (20).

4.5.2 A case of bullous pemphigoid after HZ vaccine administration

The development of autoimmune disorders and an increase in autoimmune phenomena have been reported following vaccinations in a number of cases. Blistering skin disorders, such as pemphigus vulgaris and bullous pemphigoid, have also developed following various vaccinations. A case of bullous pemphigoid that developed in a 72-year-old male after receiving the HZ vaccine has been described in the USA (21).

4.6 Summary vaccine safety

In general, VZV vaccines are considered to be safe and well tolerated.

Breakthrough VZV disease is seen post-vaccination in rare cases. HZ post vaccination is also reported rarely. VZV vaccine substantially decreases the risk of HZ among vaccinated children by round four- 12 times. Rare post vaccination neurological events, pneumonia and Stevens Johnson syndrome have been reported. Secondary transmission can rarely occur.

In children aged 12 - 23 months of age, there is an increased risk of febrile seizures 7 - 10 days following vaccination with MMRV compared with MMR + V vaccines separately, for the first dose of VZV vaccine. Accidental vaccination in pregnancy has not shown any safety concerns to date.

In adults, HZ vaccine is considered safe and well tolerated with no increase in adverse events, other than a small increased risk of allergic reactions 1 - 7 days after vaccination.

5. Immunogenicity, efficacy, effectiveness and vaccine impact

5.1 Objective

The objective of this section is to review the most recent publications on the immunogenicity, efficacy and effectiveness of currently licenced VZV vaccines.

5.2 Outcomes

Outcomes are summaries of results of studies and reviews on immunogenicity, vaccine efficacy / breakthrough cases and vaccine impact against VZV infection, VZV associated morbidity and mortality including skin infections and HZ.

5.3 Review

5.3.1 Immunogenicity

5.3.1.1 Immunogenicity of a two-dose regimen of a combined measles, mumps, rubella and VZV live vaccine (ProQuad®) in infants from nine months of age

Vaccination against measles, mumps, rubella and VZV is recommended in many developed countries for infants from 12 months of age. However, measles vaccination at nine months of age is recommended by the World health Organization (WHO) in the Expanded Program on Immunization (EPI) schedule. An open-label, randomised, comparative study evaluated the immunogenicity (and safety) of a two-dose schedule of ProQuad® (MMRV vaccine) given at a three-month interval in healthy infants from the age of nine months. For measles, the non-inferiority of the response rate post-dose two was reached when dose one was administered at 11 months compared with 12 months (98% and 99% respectively), but was not reached when dose one was administered at nine months (95%). The response rate to measles post dose one increased with age, from 73% at nine months to 88% at 11 months and 90% at 12 months. For mumps, rubella and VZV, response rates were not different after dose one (>95%) or dose two (>99%) regardless of whether dose one was administered at nine, 11 or 12 months of age. This supports that the age of administration of the first of a two-dose regimen of ProQuad® may be lowered to 11 months. Dose one may be administered at nine months if early protection is required with a second dose administered promptly with a minimum of three-month interval between doses (22).

5.3.1.2 Immunogenicity of a measles-mumps-rubella-VZV vaccine given as a second dose in children up to six years of age

Two doses of MMR are widely recommended and consideration is being given to a similar schedule for VZV vaccine. A combined MMRV could be considered for this second dose in children previously vaccinated separately with MMR and VZV vaccines. In this study, 390 healthy children aged 15-75 months (median 54 months) previously immunised with MMR and VZV vaccines were randomly allocated to receive MMRV or separate injections of MMR and VZV vaccines. Baseline seropositivity rates were 96.4% for measles, 94.3% for mumps, 99.5% for rubella, and 97.9% for VZV. Post-immunisation, seropositivity rates were 99.5% for measles and mumps and 100% for rubella and VZV in the MMR+V group and 100% for all four antigens in the MMRV group; a 26.2- and 27.2-fold increase in VZV titre was observed in the MMR+V vaccine and MMRV groups, respectively. MMRV had non-inferior immunogenicity (and similar safety profiles) to a second dose of licensed MMR + V vaccine administered concomitantly (23).

5.3.1.3 IgG antibody response in children with VZV wild-type infection and vaccination

In contrast to VZV primary infection, VZV vaccination does not appear to provide lifelong immunity against VZV. Immune correlates of protection are needed in the post vaccination era and therefore a better understanding on the mechanisms of immunity to VZV is required. A novel VZV line assay has been developed based on five different recombinant VZV antigens and used to study the anti-VZV IgG composition in 125 children (72 with a history of VZV infection and 53 with VZV vaccination). The results indicated that wild-type VZV infection induces a more diverse immune response against VZV than does vaccination and it may be possible to discriminate serologically between vaccine-induced and naturally-induced immunity to VZV (24).

5.3.2 Impact and effect of vaccine programs

5.3.2.1 Impact of VZV vaccination on hospitalisation

5.3.2.1.1 Single dose schedule

The VZV vaccination program was introduced into the US in 1995. Two national databases have been used to describe the effect of the mature one-dose VZV vaccination program on VZV morbidity. Data from the National Hospital Discharge Survey and Nationwide Inpatient Sample were analysed to describe trends in VZV-related hospitalisations during the one-dose vaccination era (2000-2006) compared with those in the pre-vaccination era (1988-1995). VZV-related hospitalisations were defined by using ICD-9 codes. Results were extrapolated to represent national estimates. During the one-dose vaccination period, there were an estimated 24,488 VZV-related hospitalisations, a rate of 0.12 per 10,000 population. During the preceding period this rate was 0.42 per 10,000 ($p<0.01$). During the one-dose vaccination era, the estimated annual average number of VZV-related hospitalisations was significantly lower and decreased by ≥65% in all age groups compared with those in the pre-vaccination era ($p<0.001$ for all age groups). The hospitalisation rate during the one-dose vaccination era estimated from the Nationwide Inpatient Sample was 0.09 per 10,000 population. The data indicate that VZV vaccination in children has prevented 50,000 VZV-related hospitalisations in the US from 2000 - 2006 (25).

5.3.2.1.2 Decline in VZV-related ambulatory visits and hospitalisations in the United States since routine VZV vaccination

Estimates of VZV-related ambulatory and hospital discharges for the US population were calculated for the pre- (1993-1995) and post- (1996-2004) vaccine licensure periods using a range of national surveys. The rate of VZV-related ambulatory discharges decreased by 66% from 106.6 per 100,000 (95% CI: 80.5-132.6) in the pre-licensure period to 36.4 per 100,000 population (95% CI: 29.3-43.5) in the post-licensure period ($p < 0.001$). The decrease was significant across all age groups <45 years, with the greatest reduction (98%) occurring among patients 0 - 4 years of age. The incidence of VZV-related hospital discharges decreased by 53% from 30.9 per 100,000 (95% CI: 24.4-37.3) to 14.5 per 100,000 population (95% CI: 12.1-16.8; $p < 0.001$). This difference was significant among patients <14 years of age. The rates of VZV-related ambulatory discharges were decreased significantly for both whites and non-whites during post-licensure period. However, the ambulatory discharge rates remained higher for non-whites than for whites. Decreases in VZV-related hospital discharges were statistically significant for both whites and non-whites (26).

5.3.2.1.3 The effect of funded VZV immunisation programs on VZV-related hospitalisations in IMPACT centres, Canada, 2000-2008

Canadian data from the 12 Immunization Monitoring Program Active (IMPACT) centres, that represent 90% of paediatric tertiary care beds in Canada, was analysed to determine whether the number of VZV-related hospitalised cases had declined by 2008 following the sequential introduction of publicly funded programs. Active surveillance was conducted for VZV-related hospitalisations and complications from 1999 onward. Publicly funded routine immunisation programmes at 12 or 15 months of age were introduced by five provinces and territories in 2000 - 2002 (earlier programmes) and by eight provinces and territories in 2004 to 2007 (later programmes). VZV-related hospitalisations, from 2000 - 2008 in the province/territory with early programmes, were under surveillance by three IMPACT centres, whereas the provinces and territories with later programmes were under surveillance by the remaining nine centres. Between 2000 and 2008, the number of VZV-related hospitalisations in IMPACT centres declined relatively sooner in provinces and territories with earlier programmes (by 2002 - 2003), compared to those with later programmes (only by 2007 - 2008). In 2008, VZV-related hospitalised cases declined by 88% in the earlier programme centres and by 81% in the later programmes centres. In all IMPACT centres, the greatest decline occurred in the one - four year age group (90% decline), with smaller declines in both the under one year and five - nine year age groups (78% and 76% decline, respectively). Breakthrough disease accounted for 39 (2%) cases, with the proportion due to breakthrough increasing from 0.9% in 2000 - 2001, to 2% in 2003 - 2004 and 9.5% in 2007 - 2008. The majority (72%) of breakthrough cases were in immunocompromised children. The publicly funded VZV vaccination programs have led to a significant decline in VZV-related hospitalisations in Canadian children both as the results of direct effects of vaccination as well as probable indirect effects on those outside the vaccinated cohort (27).

5.3.2.2 Impact of VZV vaccination on epidemiology (and hospitalisation)

5.3.2.2.1 Impact of universal vaccination on the epidemiology of VZV in Veneto, Italy

In 2005, universal VZV vaccination was introduced in the Veneto region, Italy. Trends in VZV incidence and hospitalisation rates, before and after vaccine introduction, were examined and vaccine effectiveness was assessed. VZV incidence rates for 2000 - 2008 were calculated from the mandatory regional surveillance data and from a special surveillance system based on reports from a sample of paediatricians that followed more than 40,000 children during the study period. To evaluate hospital admission rates, the regional hospital discharge registry was analysed. The vaccine coverage rate was 6.8% in the 2004 birth-cohort and 78.6% in the 2008 cohort. VZV incidence in zero - 14 year-olds was 6137 per 100,000 person-years in 2000 and 4005 per 100,000 person-years in 2008; hospitalisation rates were 18.7 and 8.4 respectively. Incidence rates significantly decreased 2.5 years after beginning the universal vaccination, while hospitalisation rates showed a significant decrease one year earlier. There was a significant decline of both VZV incidence and hospitalisations especially in one - four year-old children. Two years after the implementation of the programme VZV cases steadily declined in all age groups (28).

5.3.2.2.2 Impact of universal VZV vaccination in Navarre, Spain 2006-2010

Universal VZV vaccination was introduced to the childhood immunisation schedule of Navarre, Spain in 2007. The impact of this programme on the incidence of VZV in both vaccinated cohorts and in the unvaccinated was evaluated (VZV is a notifiable disease in Spain). The annual incidence by age groups between 2006 and 2010 were analysed. Hospital admissions with VZV or complicated VZV as the principal diagnosis were obtained from the minimum basic data set on hospital discharges for the years 2006 - 2009. The incidence of VZV decreased by 93.0%, from 8.04 cases per 1,000 inhabitants in 2006 to 0.56 per 1,000 inhabitants in 2010 (p=<0.0001). In children from one to six years (vaccinated cohorts), the incidence of VZV fell by 96.3%. In the cohorts vaccinated at 10 and 14 years, a decrease of 93.6% was also observed and 85.0% in those at 15 - 19 years. In the unvaccinated age groups falls of 88.2% in children under one year, 73.3% in those of 7 - 9 years, and 84.6% in people over 20 years were observed. In 2006, there were 25 hospital admissions due to VZV in Navarre and in 2009 this figure decreased to seven. The introduction of universal VZV vaccination in Navarre resulted in a rapid reduction of the incidence of VZV in both vaccinated and unvaccinated people (29).

5.3.2.2.3 Impact of vaccination against VZV on the reduction of disease incidence in children and adolescents from Florianopolis, Brazil

Official epidemiologic surveillance data from Brazil for the 1997-2007 period were used to evaluate the impact of VZV vaccination which targeted all children under two years of age in Florianopolis (the capital city of the state of Santa Catarina), since 2002, comprising five years before and six years post introduction of the vaccine. VZV incidence in Florianopolis was compared with the incidence in the rest of the state for four age groups (< one year, one - four, five - nine, and 10-14 years). Among the 135,311 cases of VZV in the state of Santa Catarina during the 1997-2007 period, 70% were children under 10 years of age. The effectiveness of VZV vaccine ranged from 27 - 38% among the age groups, but reached statistical significance only for children one - four years old. The findings supported effectiveness in reducing VZV incidence in Florianopolis in this age group (30). [Note, only abstract available, full text in Portuguese]

5.3.2.2.4 Epidemiological characteristics of VZV from 2000 to 2008 and the impact of nationwide immunisation in Taiwan

Starting in 2004 in Taiwan, VZV vaccine was offered to children aged one year. The epidemiological characteristics of VZV from 2000 - 2008, and the change of VZV epidemiology after the mass VZV immunization were assessed. ICD-9-CM codes related to VZV or chickenpox (052, 052.1, 052.2, 052.7, 052.8, and 052.9) were analysed for all young people less than 20 years of age through the National Health Insurance database of Taiwan from 2000 - 2008. Case numbers of VZV or chickenpox declined significantly after implementation of the vaccination programme in 2004. Winter, particularly January, was the epidemic season of VZV. A significant post-vaccination decrease in incidence among preschool children was found, especially three - six year old children. The peak incidence was 66 per 1000 for four and five year-old children before vaccination (2000 - 2003), and the peak incidence was 23 per 1000 for six year-old children in 2008 ($p < 0.001$). VZV-related hospitalisation also significantly decreased in children younger than six years following implementation of the vaccine (31).

5.3.2.2.5 Impact of the routine VZV vaccination programme on VZV epidemiology in Germany

Routine VZV vaccination with a single dose for children 11 to 14 months was recommended in Germany in 2004. A country-wide VZV sentinel surveillance system was initiated in 2005, to detect trends of disease frequency and vaccine uptake, and to evaluate the vaccination programme. A convenient sample of approximately 1,000 paediatricians and general practitioners was recruited to report on a monthly basis on VZV cases seen in their practice, and on VZV vaccine doses administered. Sentinel data from April 2005 to March 2009 show a reduction of 55% in VZV cases in all ages; 63% in the age group zero - four years and 38% in five – nine year olds. The number of vaccine doses in all regions and physician groups increased during the same period. The number of reported cases as well as administered vaccines differed between physician groups and regions with different reimbursement policies. Earlier reimbursement and vaccine doses were associated with an earlier decrease in VZV cases. Besides reimbursement policies the availability of vaccination schedules influenced vaccine uptake. Sentinel surveillance provided valid data on trends for VZV associated morbidity, vaccine uptake and the age distribution of cases (32).

5.3.2.3 Impact of the national VZV vaccination programme in Australia on congenital and neonatal VZV:

Routine VZV vaccination for children aged 18 months commenced in Australia from November 2005. Active national prospective surveillance was carried out for congenital and neonatal VZV using the Australian Paediatric Surveillance Unit for 3.5 years from June 2006. Around 1300 clinicians reported monthly according to predefined case criteria. During the study period, the mean monthly return rate of Australian Paediatric Surveillance Unit report cards was 93.7%. Two cases of congenital VZV (0.19 per 100,000 live births per annum) and 16 cases of neonatal VZV (2.0 per 100,000 live births per annum) were identified. During 2008 and 2009, no cases of congenital VZV were reported; neonatal VZV rates declined to 0.7 per 100,000 live births per annum, a significant trend ($p = 0.005$) and a reduction of over 85% compared with rates during 1995-1997 (the pre-vaccination era). Eleven of 16 neonatal cases followed prenatal maternal infection; seven of the 11 infections were acquired from children, four of whom were living in the same household. Ten (62.5%) infants with neonatal VZV were admitted to hospital, one of whom developed VZV pneumonitis requiring ventilator support. Only one infecting contact had been vaccinated. This supports a reduction of congenital VZV and a significant reduction of neonatal VZV in Australia following the introduction of universal VZV vaccination (33).

5.3.3 Outbreaks of VZV in vaccinated populations – single dose vaccine

53.3.1 Report of VZV outbreak in a low vaccination coverage group of otherwise healthy children in Italy

An outbreak occurred in a preschool in Southern Italy during January-May 2009, among children with vaccination coverage of 53.9% for one dose. This was a small community in Puglia with 41 children enrolled. The attack rates for unvaccinated and vaccinated children were 72.3% and 12.7%, respectively. The vaccine effectiveness against disease was 82.4%. These findings support the routine use of a second dose of vaccine for all children without a history of disease (34).

5.3.3.2 VZV outbreak in a village in Uruguay

A VZV outbreak occurred in a Uruguayan village that introduced a single dose of VZV vaccine in 1999 and had achieved high vaccination rates. Cases that occurred in the kindergarten and schools in the village were investigated. Vaccination cards were examined, history of VZV and clinical characteristics of the episode were obtained. An estimate was made of the vaccine's effectiveness. There were 37 cases of VZV reported, 14 occurring in previously vaccinated children, in a total population of 313 children. The global effectiveness of the vaccine was 80%, and 100% for severe cases. A shift of cases towards older ages was demonstrated; vaccinated children had a trend towards less fever and lower number of lesions. Immunisation of healthy unvaccinated children, mainly adolescents, interrupted the outbreak. The authors recommended that during an outbreak situation strategies should consider 'catch-up' vaccination in non-immunised adolescents without a previous history of VZV (35).

5.3.3.3 A VZV outbreak in a school with high one-dose vaccination coverage, Beijing, China

VZV vaccine is available in the private sector in China, with a single dose recommended for children aged ≥12 months. A VZV outbreak in a school in Beijing with high VZV vaccination coverage was investigated. VZV among vaccinated students was defined as VZV occurring >42 days after vaccination. Students' vaccination status was verified with immunisation records and clinical presentations were collected from healthcare practitioners. Of the 951 students, 934 (98%) had no prior history of VZV infection. Among these students, 916 had received one dose of VZV vaccine and two had received two doses, representing 98% vaccination coverage, before the outbreak. A total of 87 cases occurred during the outbreak; most were breakthrough VZV (86/87, 99%) and mild disease (83/87, 95%) in vaccinated persons. Age at vaccination (<15 months vs. ≥15 months) and time since vaccination before outbreak (<five years vs. ≥five years) were not associated with development of breakthrough VZV. Single-dose VZV vaccination was 89% effective in preventing any VZV and 99% in preventing moderate/severe VZV. This supports that a single dose of VZV vaccine is effective in reducing VZV incidence and mitigating disease severity. However, a second dose is more likely to prevent outbreaks (36). (Full article in Chinese)

5.3.3.4 An outbreak of VZV among schoolchildren in Taipei

An outbreak occurred in an elementary school in southern Taipei from April through May 2007. A retrospect cohort study was performed by using a self-administered questionnaire to parents. Ten out of sixteen VZV cases were vaccinated. Overall vaccine coverage was 71.2%. The sensitivity and specificity of self-reported vaccination status was 0.900 (95% CI: 0.864, 0.935) and 0.611 (95% CI: 0.514, 0.701). Vaccine effectiveness was estimated to be 69.3% -100.0% against any disease severity of VZV. Overall vaccine effectiveness against moderate or severe VZV was 85.5%. Attending 'cram school' was associated with the risk of developing the VZV illness (RR = 13.39; 95% CI: 5.38, 33.31). Unvaccinated students tended to show moderate to severe (>50 lesions) disease (RR = 4.17; 95% CI: 1.15, 15.14). The low vaccination coverage results in continuing VZV outbreaks in Taipei (37).

5.3.3.5 VZV breakthrough infection and vaccine effectiveness in Taiwan

In order to evaluate the breakthrough VZV infection rate, factors associated with breakthrough infection and the vaccine effectiveness, recipients of VZV vaccinations were identified through Taiwan's National Immunization Information System and data on breakthrough infections among these recipients were collected by using Taiwan's National Health Insurance Claims Database for analysis. From 2000 – 2007, 1,057,345 persons received a VZV vaccination. VZV breakthrough infection occurred in 22,640 (2.1%) vaccinees and 170 (0.016%) required hospitalisation for VZV disease. Annual breakthrough infection rates ranged from 0.12% to 2.04%. The mean age of vaccination was 1.6 years (median 1.3 years) and the mean age at breakthrough infection was 3.9 years. The mean interval between vaccination and the breakthrough infection was 2.3 years. The rate was significantly lower in regions where free VZV vaccinations were available than in regions where they were not ($p<0.001$). VZV breakthrough infection was significantly more likely to occur at five and six years of age among the vaccinees, who received vaccination between 12 months and 23 months of age ($p<0.001$). The overall vaccine effectiveness against VZV was 82.6% and against VZV-related hospitalisation it was 85.4% for the 2000 – 2005 period (38).

5.3.3.6 The effectiveness of VZV vaccine in China

Although the vaccines contain the same strain of virus, the vaccines licensed in China are from different manufacturers than the one licensed in the US. A matched case-control study was conducted to assess the effectiveness of the three VZV vaccines in use in China. In 2005, 1000 VZV cases were enrolled from Guangzhou, China, and compared with 1000 controls matched by age and place of residence. The three VZV vaccines used in China (Varilrix® from GlaxoSmithKline, Changchun and Shanghai from Changchun and Shanghai Institutes of Biologic Products, respectively) had similar effectiveness: Varilrix® 86.4% (95% CI: 72.6, 93.2), Changchun 79.5% (95% CI: 58.1, 90.0), and Shanghai 92.6% (95% CI: 68.9, 98.2). Vaccine effectiveness was higher during the first year after vaccination than during the subsequent five years, but the differences did not reach statistical significance. The VZV vaccines used in China are highly effective in preventing clinical VZV (39).

5.3.4 Two dose VZV vaccination programs – impact on epidemiology and outbreaks

In June 2006 ACIP expanded its June 2005 recommendation for a second dose of VZV vaccine during outbreaks to a recommendation for routine school entry second dose VZV vaccination.

5.3.4.1 Effectiveness of two doses of VZV vaccine in children

The effectiveness of two doses of VZV vaccine in the US was assessed in a case-control study by identifying children ≥four years of age with PCR-confirmed VZV and up to two controls matched by age and paediatric practice. Children from 28 practices in southern Connecticut were enrolled. Effectiveness was calculated using exact conditional logistic regression. From July 2006 - January 2010, of the 71 case subjects and 140 matched controls enrolled, no cases (0%) vs. 22 controls (15.7%) had received two doses of VZV vaccine, 66 cases (93.0%) vs. 117 controls (83.6%) had received one dose, and five cases (7.0%) vs. one control (0.7%) had not received any VZV vaccine (P<.001). The effectiveness of two doses of the vaccine was 98.3% (95% CI: 83.5%-100%; p<0.001). The matched odds ratio for two doses vs. one dose of the vaccine was 0.053 (95% CI: 0.002-0.320; p< 0.001). Odds of developing VZV were 95% lower for children who received two doses compared with one dose of VZV vaccine (40).

5.3.4.2 Impact of two-dose vaccination on VZV epidemiology in Connecticut

Following the 2006 ACIP recommendation that children receive two doses of VZV vaccines, the reported incidence and case-specific data in Connecticut were compared for 2005 - 2008. The number and size of school outbreaks of VZV decreased dramatically during the study period, with 42 outbreaks during the 2005 – 2006 school year (mean size, 14; range, 5–62) and only two outbreaks during the 2008 –2009 school year (mean size, 5; range, 3–6). VZV incidence decreased from 48.7 cases per 100,000 persons in 2005 to 24.5 in 2008. Age-specific incidence decreased significantly ($p < 0.05$) among children aged one to 14 years. The implementation of routine two-dose VZV vaccination for children was associated with a significant reduction in VZV incidence and school outbreaks with the impact being observed soon after implementation. The authors noted that the full potential of the two-dose strategy has probably not yet been reached (41).

5.3.4.3 Incremental effectiveness of second dose VZV vaccination for outbreak control

To evaluate the effectiveness of a second dose of VZV vaccine for outbreak control, a US study conducted in Philadelphia used a self-administered questionnaire to collect VZV disease and vaccination information. Students eligible for second-dose vaccination were one-dose vaccine recipients without prior VZV disease. A breakthrough VZV case was defined as a maculopapulovesicular rash in a student with onset >42 days after one-dose vaccination without other apparent cause. Vaccine effectiveness was evaluated using survival analysis techniques and analysed by vaccine status (first dose versus second dose). Multivariable Cox proportional hazard models were used to identify statistical interactions and adjust for confounders. The questionnaire response rate was 92% (342/370). Of the 286 eligible students, 187 (65%) received a second-dose of vaccine. The crude attack rate was 9/187 (5%) among second-dose recipients; 43/99 (43%) among one-dose recipients, and 5/6 (83%) among unvaccinated students. Second-dose recipients had milder rashes, compared with one-dose or unvaccinated students. The adjusted incremental second-dose vaccine effectiveness was 76% (95% CI: 44%-90%) for students with classroom exposure. Incremental effectiveness was similar (79%) when immune response time was extended from four days to seven days after receipt of the second-dose. The second-dose of vaccine during outbreak control resulted in a substantial reduction in VZV incidence for students with classroom exposure. The second-dose of VZV vaccine was an effective intervention to reduce disease transmission in this institution-based outbreak (42).

5.3.4.4 Immunogenicity of measles-mumps-rubella-VZV (MMRV) vaccine followed by one dose of VZV vaccine in children

In a randomised, comparative study in France, 458 children aged 15 months - two years and two - six years who had previously received MMR, were given either one dose of a combined MMRV vaccine (Priorix-tetra® , MMRV group) or concomitant MMR and VZV vaccines (Priorix and Varilrix®, MMR+V group). Both groups then received another dose of VZV vaccine (Varilrix®) 42-56 days later. In the two age groups, VZV seroconversion rates were ≥ 97.6% (MMRV), ≥ 96.6% (MMR+V) post-dose one, and 100% in both groups post-dose two. Post dose two, anti-VZV antibody geometric mean titres (GMT) increased

14.1 and 12.6-fold (MMRV), and 9.8 and 13.1-fold (MMR+V), respectively for each age group. The MMRV vaccine was demonstrated to be an immunogenic (and safe) substitute for a second dose of MMR vaccine in young children. The increase in anti-VZV antibodies observed after a second dose of VZV vaccine was supported a two-dose schedule for VZV vaccine (43).

5.3.4.5 An outbreak of VZV in two-dose VZV vaccine recipients

In October 2006, the Arkansas Department of Health was notified of a VZV outbreak among students where some had received a second dose during an outbreak-related vaccination campaign in February 2006. The outbreak was investigated using a school-wide parental survey with a follow-up survey of identified cases. Vaccination status was verified using state and local immunisation records. Limited laboratory testing confirmed circulation of wtVZV, including VZV in two-dose vaccine recipients. Vaccination information was available for 871 (99%) of the 880 children. VZV vaccination coverage was 97% (39% - two doses; 58% - one dose). VZV was confirmed by PCR in five (42%) of 12 lesion specimens and by IgM in one (6%) of 16 serum specimens. VZV was reported in 84 children, including 25 (30%) two-dose and 53 (63%) one-dose recipients. Attack rates among two dose recipients (10.4%) and one-dose recipients (14.6%) were not significantly different (RR = 0.72, 95% CI: 0.44-1.15). All two-dose recipients and 80% of one-dose recipients reported having 50 or fewer skin lesions. This was noted to be the first outbreak to document VZV in both one- and two-dose vaccine recipients with similar effectiveness shown for both groups (44).

5.4 VZV vaccination for people at high risk of complications

5.4.1 Pregnant women

5.4.1.1 Susceptibility to VZV among pregnant women

A cross-sectional study investigating the susceptibility to VZV among pregnant women was carried out at the Departments of Gynaecology and Obstetrics in the province of Lecce, Italy, where 539 pregnant women were recruited and face-to-face interviews were conducted. VZV IgG tests were performed. The prevalence of VZV susceptibility among pregnant mothers was found to be 10.6%. The prevalence of IgG antibodies increased significantly with increasing age, from 62.5% in the age group 15 - 19 years to 94.4% in the age group 40 - 49 years. The susceptibly of this proportion of child-bearing women prompted the recommendation for routine counselling, VZV IgG antibody screening and VZV vaccination in the absence of a history of VZV infection in order to reduce the risk of fetal complications and the associated health care costs (45).

5.4.1.2 Seroprevalence of VZV among pregnant women in Hong Kong

The seroprevalence (serum IgG titre) was compared with self-reported history of VZV infection among pregnant women in Hong Kong. Pregnant women undergoing first trimester screening for Down syndrome over a three-month period were recruited for the study. Positive immunity was found in 477 (95.4%) of the 500 recruited women, and those with positive, negative, or uncertain history of infection had similarly high seroprevalence (96.4, 90.5, and 95.9% respectively). The mean age of infection from self-recalled history was 8.61 (SD ±4.69) years, and only 3% recalled infection after age 18. Insufficient knowledge on the disease and vaccination was demonstrated. VZV immunity was high among pregnant women, the majority were infected during childhood and infection over the age of 18 was very rare. In contrast to the Italian study above, it was concluded in this study that universal antenatal screening or vaccination for all women in the reproductive age would not be cost-effective in Hong Kong (46).

5.4.2 Immigrants

5.4.2.1 Seroprevalence of VZV and predictors for seronegativity in the Amsterdam adult population

In Amsterdam, first-generation immigrants especially those that migrated after the age of 11 years, were more likely to be anti-VZV seronegative compared to those arriving at an earlier age or those born in the Netherlands. Seroprevelance was detected in 90% of Moroccan immigrants, 91% of Surinamese or Antillean immigrants and 91% Turkish compared with 97-98% Netherlands-born. This study suggested that about 4 – 8% of the general adult Amsterdam population was susceptible to infection with VZV, and that susceptibility was higher in some immigrant groups. Awareness is needed for vulnerable persons such as pregnant women, patients with haematological malignancies or organ transplants in particular among first-generation immigrants (47).

5.4.2.2 Comparison of two strategies to prevent VZV outbreaks in housing facilities for asylum seekers

The proportion of adults with positive VZV serology is lower in populations from tropical countries. Therefore immigrants from tropical countries to countries with a temperate climate are at risk of acquiring VZV infection during adulthood. In Switzerland, two different strategies to prevent VZV outbreaks in housing facilities for asylum seekers arriving in the Canton of Vaud were assessed. The first strategy consisted of a rapid response with isolation of the affected individuals and vaccination of the susceptible contacts. The second strategy consisted of a general vaccination upon arrival of all asylum seekers aged 15 - 39 years with no history of chickenpox. The rapid response strategy was applied from May 2008 to January 2009. Eight hundred and fifty-eight asylum seekers arrived in the Canton and an attack rate of 2.8% (seven cases among 248 exposed asylum seekers) was observed. From February 2009 to May 2010, the general vaccination strategy was applied, a period during which 966 asylum seekers were registered. This second strategy prevented any outbreak, thus supporting the recommendation that the general vaccination strategy was more effective. It was also more sustainable and ethically preferable, although associated with higher cost (48).

5.4.3 Children and adults with HIV

5.4.3.1 Effectiveness of VZV vaccine in children infected with HIV

Although, VZV vaccine is given to clinically stable HIV-infected children, its effectiveness is unknown. In a hospital in New York, US, medical records of closely monitored HIV-infected children were reviewed, including those receiving HAART, between 1989 and 2007. VZV immunisation and development of VZV or HZ were noted. Effectiveness was calculated by subtracting from one the rate ratios for the incidence rates of VZV or HZ in vaccinated versus unvaccinated children. The effectiveness of the vaccine was 82% (95% CI, 24%-99%; $p = 0.01$) against VZV and 100% (95% CI, 67%-100%; $p < 0.001$) against HZ. When the analysis was controlled for receipt of HAART, vaccination remained highly protective against HZ (49).

5.4.3.2 Immunogenicity of a live attenuated VZV vaccine in VZV-seropositive HIV-infected adults

HZ is common in HIV infected patients in spite of antiretroviral therapy. A randomised controlled trial, assessed the immunogenicity (and safety) of a VZV as a candidate for protecting HIV-infected adults against HZ. Sixty-seven HIV-infected and 15 uninfected subjects, 18 - 65 years old, were enrolled.

The cell-mediated responses to two doses of the VZV vaccine in HIV-infected subjects were lower and less consistent than that of HIV-uninfected age-matched controls. Age and ethnicity did not affect the responses of HIV-infected subjects to the vaccine, neither did the nadir (lowest level) CD4+ count. Compared with placebo recipients, the two doses of VZV vaccine significantly increased VZV-specific values and tended to increase the ELISPOT values of HIV-infected vaccinees. Overall, the immunogenicity of the VZV used in this study was low in HIV-infected subjects. The higher dose formulation HZ vaccine has been demonstrated to be safe and effective in elderly individuals that had a significant age-related, rather than HIV-related, decline in VZV-specific cell mediated immunity and the authors note a study assessing the safety and immunogenicity of this vaccine in HIV-infected adults is in progress (50).

5.4.4 Organ transplant patients

5.4.4.1 Sustainability of humoral responses to VZV vaccine in paediatric transplant recipients

In a multi-centre study in Canada, 21 children aged one–18 years who were awaiting solid organ transplantation, and had no past history of receiving VZV vaccine or any previous clinical history of VZV infection, were given two doses of VZV vaccine pre-transplantation. After the first dose of vaccine, 19 of the 21 patients who had analysable samples, had seroprotective levels of antibody. Protective antibody levels were maintained at 12 and 24 months and there were no cases of breakthrough VZV. The seroprotection acquired following completion of the two-dose regimen was sustained after the immunosuppressive therapy for the two year post-transplant follow-up (51).

5.4.4.2 Safety and immunogenicity of the live attenuated VZV vaccine following T replete or T cell-depleted related and unrelated allogeneic hematopoietic cell transplantation (alloHCT)

A single-centre study in the US reviewed the medical records of allogeneic hematopoietic cell transplantation (alloHCT) patients aged <20 years old who were disease free for the following 10 months. The patients had received VZV vaccine if they were >24 months post transplantation and were off all immunosuppressive therapy. Before vaccination, all 44 patients were seronegative to VZV. Overall, 64% (28 of 44) patients seroconverted following one dose of the vaccine. Fourteen patients who did not respond to the first dose, received a second dose, 11 patients seroconverted following the second dose demonstrating that the VZV vaccine is immunogenic when given according to pre-set clinical and immunological milestones (52).

5.4.4.3 VZV immunisation in paediatric liver transplant recipients

A single centre study from Switzerland studied 79 paediatric liver transplant recipient patients (median age 7.8 years) who were at least one year post transplantation and at least two months free of an episode of acute rejection. Patients received two standard intramuscular doses of VZV vaccine (Varilrix®, GlaxoSmithKline Biologicals SA, Rixensart, Belgium) given two months apart. For 7/32 (21.9%) of the children an additional third dose was required to generate sufficient anti-VZV titres. No breakthrough cases of VZV disease were reported during follow-up (median 4.1 years) (53).

5.4.4.4 VZV vaccination in paediatric kidney and liver transplantation

A recent literature review of the efficacy and safety of live-virus attenuated vaccines in patients before and after transplantation found that in all paediatric transplant candidates, humoral and cellular immunity against VZV should be consistently monitored to assess waning immunity under immunosuppressive treatment in order to estimate the risk of severe VZV disease after exposure in these patients (54).

5.4.5 VZV vaccination of susceptible contacts of children with malignancy

A recent review of VZV in children with cancer has summarised that there is already good evidence to support the administration of VZV vaccine to healthy susceptible family contacts of children with malignancy (55).

5.5 VZV vaccination reducing the complication of secondary skin infections

The literature search did not find any studies specifically addressing the impact of VZV vaccines on skin infections for the past four years. However, the role of VZV vaccine in preventing serious skin infections is implied as VZV-associated skin infection are well established to be a major cause of VZV-associated hospitalisations, with bacterial infection being most common VZV related complication.

5.6 VZV vaccination for post exposure prophylaxis

5.6.1 Effectiveness of VZV vaccines as post-exposure prophylaxis

A prospective cohort study was conducted in 67 patients susceptible to VZV infection consulting at the Preventive Medicine Department of the Val d'Hebron Hospital, Spain, after household exposure to VZV. Post-exposure prophylaxis with VZV vaccine was administered within the first five days after contact. Subjects were interviewed by telephone between four and eight weeks after vaccination to ascertain whether VZV disease had occurred and, if so, its severity. Effectiveness of the VZV vaccine in preventing any type of disease was estimated to be 62.3% (CI 95%: 47.8-74.9) and 79.4% (CI 95%: 66.4-88.9) in preventing moderate and severe disease. No statistically significant differences were found when effectiveness was analysed by gender, age, or days elapsed since exposure. The administration of VZV vaccines within five days of exposure was moderately effective in preventing chickenpox and effective in attenuating the illness (56).

5.6.2 Effectiveness on post-exposure vaccination of VZV and its influencing factors in elementary schools in Beijing

From May to July 2007, VZV cases from 49 elementary schools in four districts in Beijing were observed prospectively. A study included 7882 children who were from the same classrooms, same floor or same bungalow areas as the VZV cases. Vaccination status, history of VZV and onset of rashes were collected to calculate the secondary attack rate among those children under observation. Vaccine effectiveness was also calculated. The protective rate for post-exposure vaccination among children under observation was 85%. The protective rates were higher when the first case had received VZV vaccine before the onset, the vaccine was administered soon after the exposure or when there were fewer VZV cases in the schools. For children in the same class, same floor or bungalow as VZV cases before post-exposure vaccination, the average rates of protection by vaccination were 84% and 87%, respectively. When the first case had received VZV vaccine prior to the onset, the post-exposure protection rates reached 92% and 93%, respectively, higher than that when the first case had received no vaccination. When the administration of vaccine occurred directly after the occurrence of first VZV case, the rates of the effectiveness of vaccine were 83% and 93%, both of which were higher than that of vaccine administered after the occurrence of two or three cases. However, in those schools where bungalows were used as classrooms, but without bus from school, canteen or student lodgings, it seemed that post exposure vaccination was more effective in preventing VZV from occurring. VZV vaccination after exposure in elementary schools in Beijing was effective in prevention and control of the disease. The immediate administration of vaccine coupled with the isolation of cases appeared to maximize the effectiveness the vaccine strategy (57).

5.7 Impact of HZ vaccination

The declining cell-mediated immunity to VZV in the elderly can result in virus reactivation manifesting as HZ (shingles) and post herpetic neuralgia (PHN). To prevent virus reactivation, a VZV vaccine (Zostavax®; Merck) to boost cell-mediated immunity to VZV has been developed.

5.7.1 Efficacy of live HZ vaccine in preventing HZ and post-herpetic neuralgia

A review of the efficacy of HZ vaccine in preventing HZ and PHN concluded that Zostavax® significantly reduced burden of disease due to HZ (>50%) and PHN (>66%). It concluded that HZ vaccine is safe, effective and highly recommended for the immunisation of immunocompetent individuals over the age of 60 years who have not history of recent HZ (58).

5.8 Modelling predictions of impact of VZV vaccines

It has been suggested that the incidence of HZ may increase due to lack of natural boosting under large-scale vaccination with the VZV vaccine. Several countries have published mathematical models.

5.8.1 Modelling the impact of VZV vaccination on VZV and HZ, Finland

A model in Finland was based on serological data on VZV infection, case-notification data on HZ, and new knowledge about close contacts relevant to transmission of infection. According to the analysis, a childhood programme against VZV would increase the incidence of HZ by up to more than two thirds in the next 50 years. This will be due to an increase in case numbers in the 35 years age group. As of early 2013, the middle-aged group are over-represented in the population of Finland, causing an increase in the burden of HZ irrespective of vaccination against VZV. Under two different model scenarios, the incidence of HZ first increases after onset of vaccinations. Under both scenarios, it takes at least 75 years, until the incidence of HZ would be smaller than without mass vaccination. The authors commented that the model predicts that VZV vaccinations will lead to a substantial increase in the incidence of HZ. However, the magnitude and time scale of this effect depend on the age structure of the population and the way reactivation of VZV is modelled (59).

5.8.2 Modelling the impact of a combined VZV and HZ vaccination programme on the epidemiology of VZV, England

This study looked at two-dose VZV childhood programmes, and assessed the combined impact of VZV vaccination in childhood and HZ vaccination of the elderly. Results suggested that a two-dose schedule is likely to reduce the incidence of VZV to very low levels, provided first dose coverage is around 90% and second dose coverage is in excess of 70%. Childhood vaccination is expected to increase the incidence of HZ for more than 40 years after introduction of the programme, the magnitude of this increase being influenced primarily by the duration of boosting following exposure to the VZV. Though this increase in HZ incidence can be partly offset by vaccination of the elderly, the effectiveness of this combined strategy is limited, as much of the increase occurs in those adults too young to be vaccinated. Childhood vaccination at intermediate levels of coverage (70% and 60% for first and second dose coverage respectively) is expected to lead to an increase in adult VZV. At high coverage (90% and 80% coverage) this is unlikely to be the case. Therefore, a single-dose policy may result in significant numbers of breakthrough cases of VZV whereas a two-dose schedule is likely to lead to a low incidence of VZV, provided coverage is maintained at around 90% for the first dose. An increase in HZ incidence is still expected following VZV vaccination in childhood which will only be partly ameliorated by introduction of HZ vaccination in the elderly (60).

5.8.3 Modelling the impact of one- and two-dose VZV vaccination on the epidemiology of VZV and HZ, Canada

To examine the potential impact of one-dose versus two-dose VZV vaccination programmes on VZV and HZ incidence, using Canada as an example, the impact of adding a second dose of VZV vaccine in 2010 (four years after the introduction of one-dose VZV vaccination) using three scenarios was modelled. Assuming 90% coverage, the base case model (range: min; max) predicts that one-dose vaccination will reduce VZV and HZ cases by 64% (14%; 96%) and 5% (-2%; 22%), respectively, over 80 years.

1. Infant program (two doses given at one year of age, 90% coverage)
2. Pre-school (vaccination at one and five years of age, 86% coverage)
3. Grade four (vaccination at one and nine years of age, 90% coverage)

Adding a second dose was predicted to reduce VZV and HZ by an additional 22% (0%; 82%) and 6% (0%; 14%), respectively. Most VZV cases prevented by the second dose are single dose breakthrough infections. Adding a two-dose programme was considered likely to achieve high population-level effectiveness against VZV. However, the incremental benefit of a second dose is highly dependent on the effectiveness of the first dose and its impact on HZ (61).

5.8.4 Modelling the impact of one-dose vs. two-dose vaccination regimens on the epidemiology of VZV, Australia

Models in Australia suggest that compared to a one-dose vaccination strategy (Australia's current vaccination schedule), a two-dose strategy is expected to not only produce fewer natural VZV cases (5% versus 13% of pre-vaccination state, respectively) but also considerably fewer breakthrough VZV cases with a greater than eightfold reduction in breakthrough infections with the two-dose strategy, compared to the one dose strategy. With either a one-dose strategy or two-dose strategy vaccination programmes, the authors predicted that HZ incidence would increase for the first 30 years following vaccination. In the long term, once individuals from every cohort in the population have been vaccinated, HZ incidence is expected to decrease. A two-dose strategy would be expected to produce a greater number of HZ cases than a one-dose strategy between 30 and 60 years after vaccination which would then decline sharply. A two-dose infant vaccination programme would be a better long-term strategy for Australia (62).

5.8.5 Impact of childhood vaccination program on HZ in adults

The baseline incidence of HZ prior to introduction of HZ vaccine is not well described, and it is still unclear whether introduction of VZV vaccination programmes have altered the epidemiology of HZ. The predictions of an increase in HZ cases following implementation of VZV vaccines have not been consistently observed. Increases in HZ have been detected both prior to vaccine use and in countries who do not use VZV vaccine.

Long term follow-up of vaccinated children found HZ in 7/7000 vaccinated children aged one - 17 years representing 0.14 cases per 1000 person years compared with 0.3/1000 person years in the pre-vaccine period. The pre vaccine estimate is considered to be an underestimate as not all children would have experienced VZV (5).

5.8.5.1 Childhood vaccination programme and incidence in HZ

A decline in VZV but an uncertain impact on HZ following VZV vaccination has been reported in Victoria, Australia. VZV vaccine was licensed in Australia in 1999 and publicly funded in 2005. VZV hospitalisation rates have declined 7% per year (95% CI 5-9%) from 2000 - 2007, predominately, in children under five (12% per year, 95% CI 9-16%). A similar decline was seen in community data. The HZ hospitalisation rate had increased from 1998 to 2007 (5% per year, 95% CI 3-6%), starting before introduction of VZV vaccine. Among those aged 80 and over, the hospitalisation rate increased 5% per year (95% CI 3-7%) from 1998 to 2007. Based on community data HZ increased from 2001. This indicates that the initial rise in HZ was due to other factors, which may have continued irrespective of VZV vaccine introduction (63).

5.8.5.2 HZ incidence among insured persons in the United States and impact of VZV vaccination

In the US, a retrospective cohort study was performed to assess the HZ incidence among insured persons for 1993 - 2006. HZ incidence was reported to have increased for the entire study period and for all age groups, with greater rates of increase observed between 1993 - 1996 ($p<0.001$). HZ rates were higher for females than males throughout the study period ($p<0.001$) and for all age groups ($p<0.001$). HZ incidence did not vary by state VZV vaccination coverage. There was no evidence to attribute the increase to the VZV vaccine programme (64).

5.9 Concomitant administration of VZV vaccines with other vaccines

VZV vaccines for children and HZ vaccines for adults may have the potential to be given with other childhood vaccines on the national immunisation schedule.

This review reports on data on concomitant administration of VZV containing vaccines with other vaccines.

5.9.1 MMRV administered with other vaccines given in childhood

5.9.1.1 The immunogenicity of DTaP-IPV (Kinrix™) co-administered with MMR vaccine with or without VZV vaccine in healthy pre-school age children

In a open-label phase IIIb non-inferiority study, 478 healthy four to six year olds from 11 centres in the US, were randomised to receive Kinrix™+MMR+V on day 0 (group one), or Kinrix™+MMR on day 0, followed by VZV vaccine at month one (group two). DTaP-IPV immunogenicity was measured before and one month post-vaccination (prior to VZV vaccination in group two). One month post-vaccination more than 95% of subjects in both groups had booster responses to diphtheria, tetanus and pertussis antigens and all subjects had seroprotective anti-poliovirus antibody titres. Immune responses in group one were non-inferior to group two for responses to DTaP-IPV antigens according to pre-specified criteria. The concomitant administration of VZV vaccine with Kinrix™ and MMR did not impact the immunogenicity of diphtheria, tetanus, pertussis or poliovirus antigens. (65).

5.9.1.2 Immunogenicity of MMRV and PCV-7 administered concomitantly in healthy children

A US study evaluated 1027 healthy 12 – 15 month old children, who lacked vaccination and clinical histories for measles, mumps, rubella, VZV, and HZ, but had written documentation of receipt of a three-dose primary series of PCV-7. The children were randomly assigned to receive either MMRV plus PCV-7 (group one), PCV-7 followed six weeks later by MMRV (group two), or MMRV followed six weeks later by PCV-7 (group three). Immunogenicity was evaluated six

weeks after each vaccination. For all three groups, the antibody response rate was at least 97% for measles, mumps, and rubella, 88% for VZV, and 98% for all seven of the *Streptococcus pneumoniae* serotypes. The immune responses to all antigens present in MMRV and PCV-7 were similar whether administered concomitantly or sequentially (66).

5.9.1.3 Immunogenicity of two tetravalent (measles, mumps, rubella, VZV) vaccines co-administered with hepatitis A and pneumococcal conjugate vaccines to children 12-14 months of age

Single-dose tetravalent measles, mumps, rubella, VZV vaccine, Priorix-Tetra®, stored refrigerated (GSK+4C) or frozen (GSK-20C) were compared with ProQuad® (Merck-20C), when co-administered with hepatitis A vaccine and PCV-7. A total of 1783 healthy 12-14 month olds were randomised to GSK+4C (n = 705), GSK-20C (n = 689) or Merck-20C (n = 389), administered concomitantly with HAV (Havrix®) and PCV-7 (Prevnar®). Seroresponse rates (day 42) were >97% for measles and rubella viruses and >92% for mumps virus, in all groups. Non-inferiority of GSK+4C and GSK-20C vaccines versus Merck-20C was demonstrated for seroresponse rates to measles, mumps and rubella viruses (lower 97.5% confidence interval above -5%, -10% and -5%, respectively). For VZV, seroresponse rates were 57.1%, 69.8% and 86.7% in the GSK+4C, GSK-20C and Merck-20C groups, respectively. For either GSK vaccine, non-inferiority was not shown (lower 97.5% confidence intervals <-15%). Geometric mean concentration (GMC) ratios for anti-VZV demonstrated non-inferiority (lower 97.5% confidence interval 0.5) versus Merck-20C for GSK-20C only. GMC ratios for antibodies to HAV and to PCV-7 pneumococcal serotypes also met non-inferiority criteria for both GSK groups compared with Merck-20C. Non-inferiority of GSK measles, mumps, rubella, VZV vaccines versus Merck-20C was demonstrated for responses to measles, mumps and rubella viruses, but non-inferiority was not fully demonstrated for VZV (67).

5.9.1.4 Immunogenicity of a quadrivalent meningococcal conjugate vaccine administered concomitantly with MMRV in healthy toddlers

An open-labelled, randomised phase III study in the US assessed the immune response to MenACWY-CRM at alternative visits in older infants and concomitant use with MMRV at 12 months of age. Two age groups were concurrently enrolled: seven – nine month old infants, who received two doses of MenACWY-CRM at seven - nine and 12 months, were randomised 1:1 to receive MenACWY-CRM with or without MMRV at 12 months, and 12-month-old infants who received MMRV only at 12 months. Concomitant administration of MMRV with MenACWY-CRM did not affect the immune response to either vaccine. The two-dose series of MenACWY-CRM induced adequate immune response to all four serogroups. Concomitant administration of MenACWY-CRM with MMRV vaccinations at 12 months was associated with robust immune responses to all components of both vaccines were produced and all criteria for non-inferiority were met (68).

5.9.2 HZ vaccine administered with other vaccines given in adulthood

5.9.2.1 Evaluation of the incidence of HZ after concomitant administration of HZ vaccine and pneumococcal polysaccharide vaccine

In 2009, a revision to the HZ vaccine package insert was approved stating that the HZ vaccine and the pneumococcal vaccine should not be given concurrently, because concomitant use resulted in reduced immunogenicity of the HZ vaccine. The research to support this claim was a retrospective cohort observational study to evaluate if concomitant vaccination of Zostavax® and PPV-23 reduced the protective effect of the HZ vaccine. A subsequent study was conducted in Kaiser Permanente Southern California in people over 60 years of age. Incidence of HZ after vaccination with a HZ vaccine in the population receiving both vaccines on the same day was compared to that in the population receiving a pneumococcal vaccine within one year to 30 days prior to HZ vaccine. There were 56 incident HZ cases in the concomitant vaccination cohort and 58 in the non-concomitant vaccination cohort, yielding a HZ incidence of 4.54 (95% CI, 3.43-5.89) and 4.51 (95% CI, 3.42-5.83) per 1000 person-years, respectively. The hazard ratio comparing the incidence rate of HZ in the two cohorts was 1.19 (95% CI, 0.81-1.74) in the adjusted analysis. There was no evidence of an increased risk of HZ in the population receiving HZ vaccine and pneumococcal vaccine concomitantly. The authors concluded that revision of the product information needs to be carefully assessed to avoid introducing barriers to patients and providers using these vaccines (69).

5.10 Duration of protection of VZV vaccines

5.10.1 Duration of protection of VZV vaccine given in childhood

No recent publications on duration of protection of VZV vaccine were identified in our literature search.

5.10.2 Duration of protection of HZ vaccine given in adulthood

5.10.2.1 Persistence of the efficacy of HZ vaccine in the shingles prevention study and the short-term persistence sub study

The Shingles Prevention Study in the US (SPS; Department of Veterans Affairs Cooperative Study) demonstrated that HZ vaccine was efficacious through to at least four years after vaccination. This Short-Term Persistence Sub study (STPS) was initiated after the SPS to further assess the persistence of vaccine efficacy. The STPS re-enrolled 7320 vaccine and 6950 placebo recipients from the 38,546 participant SPS population. Methods of surveillance, case determination, and follow-up were analogous to those in the SPS. Vaccine efficacy for HZ burden of illness, incidence of PHN, and incidence of HZ were assessed for the STPS population, for the combined SPS and STPS populations, and for each year up to year seven post vaccination. In the STPS as compared to the SPS, vaccine efficacy for HZ burden of illness decreased from 61.1 to 50.1, vaccine efficacy for the incidence of PHN decreased from 66.5 to 60.1, and vaccine efficacy for the incidence of HZ decreased from 51.3 to 39.6, although the differences were not statistically significant. Analysis of vaccine efficacy for each year after vaccination for all three outcomes showed a decrease in efficacy after year one, with a further decline thereafter. Vaccine efficacy was still statistically significant for the incidence of HZ and the HZ burden of illness through year five. Vaccine efficacy for each study outcome was lower in the STPS than in the SPS indicating the persistence of vaccine efficacy through year five after vaccination (70).

5.11 Summary of effectiveness

The immunogenicity of VZV vaccine when given as MMRV is over 95% when given at 9, 11 or 12 months of age and two doses increased the seroconversion to over 99%. If MMRV is administered at nine months of age, a second dose is required three months later due to the decreased response to measles component possible when given at this age. The immunogenicity of MMRV is non-inferior to MMR +V administered concomitantly.

Single dose VZV programs have had a dramatic impact on the incidence of VZV infections, hospitalisations and serious outcomes, particularly when high coverage rates are achieved. Indirect effects are also apparent. However, single dose programmes are associated with outbreaks among highly vaccinated groups. The use of a second dose during outbreaks has been an effective strategy to prevent further cases and catch ups in non-immunised groups without previous history of VZV is important.

Two doses of VZV vaccine have been recommended by the ACIP as part of the routine schedule. There is a significant reduction in the odds of developing VZV breakthrough when two doses are given and outbreaks will continue to occur in the absence of a second dose.

In some populations, over 10% of women of childbearing age are seronegative for VZV. This has implications for antenatal screening and routine counselling. Immigrants from countries with a low prevalence of VZV, particularly from tropical countries, are at greater risk of infection during adulthood. In immigrant groups, such asylum seekers in housing facilities, routine vaccination against VZV was more effective at preventing cases than rapid response to outbreaks.

VZV vaccine is poorly immunogenic in people with HIV; a study is investigating the HZ vaccine for this group. VZV vaccination is immunogenic for paediatric transplant patients, patients undergoing alloHCT and kidney and liver transplant patients. However, serology should be monitored periodically to ensure protection is maintained in these groups.

VZV vaccine can be effective when given as post-exposure prophylaxis within five days. It also attenuated the illness. In situations such as outbreaks in institutions, the isolation of cases of exposure can further maximise the effectiveness of a vaccine intervention.

Several countries have published mathematical models of the potential impact of the childhood vaccination programme on the incidence of HZ. These models generally predict an increase in HZ over the next few decades, following the institution of a childhood programme, followed by a rapid decline. Vaccinated persons have a lower risk of developing HZ than unvaccinated persons. HZ vaccination has been demonstrated to be effective against HZ and PHN. However, it is still not known whether the introduction of childhood mass VZV vaccination does significantly alter the epidemiology of HZ. Studies that have investigated this issue have been unable to attribute any increase in incidence of HZ to the childhood VZV vaccine programme.

VZV vaccine can be concomitantly administered with other childhood vaccines. There are no recent publications reporting on the duration of protection for VZV vaccines. The persistence of immunity from HZ vaccination has been measure to year five. Recent evidence suggests that HZV can be concomitantly delivered with PPV23, despite earlier research to the contrary.

6. Age-specific considerations

6.1 Objective

The objective of this section is to review the most recent publications in relation to VZV vaccines at different age groups.

6.2 Review

6.2.1 Infants under 12 months

There has been an apparent reduction of congenital VZV and a significant reduction of neonatal VZV in Australia following the introduction of universal VZV vaccination in 2005 (33)

6.2.2 Children over 12 months

The most recent policy statement from the US Committee on Infectious Diseases, on the prevention of VZV, and recommendations for use of quadrivalent and monovalent VZV vaccines in children make recommendations based on the age of the child. It is estimated from post-licensure data that, after vaccination at 12 through 23 months of age, three - four febrile seizures occur per 10,000 children who receive the measles-mumps-rubella (MMR) and VZV vaccines administered concurrently but at separate sites, whereas seven - nine febrile seizures occur per 10,000 children who receive the MMRV. Thus, one additional febrile seizure is expected to occur per approximately 2300 to 2600 children aged 12 - 23 months old vaccinated with the MMRV, when compared with separate MMR and VZV vaccine administration (see 4.4.1 for further details on this issue) (71).

6.2.3 Adults

6.2.3.1 Adults 50 to 59 years

Efficacy, safety, and tolerability of HZ vaccine (zoster vaccine, ZV) in 22,439 persons aged 50 - 59 years has been assessed in a randomized, double-blind, placebo-controlled study conducted in North America and Europe. Subjects were given one dose of ZV (Zostavax®) and followed for occurrence of HZ for ≥one year (mean, 1.3 years) post-vaccination until accrual of ≥96 confirmed HZ cases (as determined by PCR). The ZV reduced the incidence of HZ (30 cases in vaccine group, 1.99/1000 person-years vs. 99 cases in placebo group, 6.57/1000 person-years). Vaccine efficacy for preventing HZ was 69.8% (95% confidence interval, 54.1-80.6). AEs were reported by 72.8% of subjects in the ZV group and 41.5% in the placebo group, with the difference primarily due to higher rates of injection-site AEs and headache. The proportion of subjects reporting SAEs occurring within 42 days post-vaccination (ZV, 0.6%; placebo, 0.5%) and 182 days post-vaccination (ZV, 2.1%; placebo, 1.9%) was similar between groups (72).

Although Zostavax® is approved by the US FDA for use in adults aged 50 years or older, the Advisory Committee for Immunization Practices (ACIP) of the CDC recommends that this vaccine be routinely administered only to patients aged 60 years or older. As more data regarding duration of immunity after vaccination become available, and as concerns regarding supply of this vaccine are adequately addressed, the ACIP plans to reconsider its recommendations regarding the use of the vaccine in patients aged 50 to 59 years. The author provides an overview of the ZV, focusing on the latest extension in use approved by the FDA and the recommendations of the ACIP (73).

6.2.3.2 Adults > 60 years of age

Zostavax® (Merck), the zoster vaccine to prevent HZ, is approved by US FDA and is recommended by the ACIP for people aged >60 years in 2006 (these recommendations were published in 2008).

A second dose of ZV was generally safe in adults aged ≥ 60 years, but did not boost VZV-specific immunity beyond levels achieved post dose one (19).

6.3 Summary of age-specific issues

The American Academy of Paediatrics recommends that either MMR and VZV vaccines separately or the MMRV be used for the first dose of measles, mumps, rubella and VZV vaccines administered at 12 through 47 months of age. For the first dose of measles, mumps, rubella, and VZV vaccines administered at ages 48 months and older, and for dose two at any age (15 months to 12 years), use of MMRV generally is preferred, over separate injections of MMR and VZV vaccines, as a first dose in this age group (71).

The ACIP of the CDC recommends that the HZ vaccine be routinely administered only to patients aged 60 years or older. Supply issues with the vaccine and lack of long-term data have led ACIP to not recommend that the HZ vaccine be given to a 50 – 60 year old age group at this time.

7. Vaccines and options for scheduling

7.1 Objectives

The objectives for this section are to summarise the available vaccines and present options of using VZV vaccines on the NZ Immunisation Schedule. It will also provide a summary of the information for consideration when debating options of a one-dose or two-dose schedule for NZ children. Considerations for options for HZ virus vaccine in the older adult population will be presented.

There are three key areas for consideration for the use VZV, HZ and MMRV vaccines and their placement on the schedule.

1. Age of target population for each dose
2. One or two dose schedule
3. Use of MMRV vaccine

7.2 Routine VZV vaccination

7.2.1 Vaccine options

VZV vaccine is available as a single V antigen, or combined with measles, mumps, and rubella as MMRV. The use of MMR + V vaccines given concomitantly, but separately, is generally preferred for children under 48 months of age in view of the lower incidence of febrile seizures for the first dose of measles, mumps, rubella, and VZV vaccines. MMRV is preferred if used at ages 48 months and older.

MMRV is the preferred choice as a second dose at any age, instead of MMR + V in view of the reduction in the number of injections required.

7.2.2 Considerations for one-dose or two-dose VZV schedules

There are several implications to consider when deciding whether a childhood VZV vaccine schedule should be one dose or two doses: effectiveness of the vaccine schedule in relation to outbreaks in children; the impact on VZV incidence in adults; and the impact on HZ incidence in adults. There are also practical considerations regarding the number of vaccines that would be required at the relevant milestone visits.

7.2.2.1 VZV outbreaks in children

The evidence is clear that a single dose of VZV vaccine will reduce the incidence of VZV disease considerably, but outbreaks and breakthrough cases are still to be expected. Modelling studies also reinforce that a single dose of VZV would be expected to result in a large number of breakthrough cases and that achieving high coverage is important. An eight-fold decrease in breakthrough cases of VZV infection has been predicted with the use of a two-dose compared with a one-dose schedule (62). A coverage level of 90% for the first dose and 70% for the second dose predicts a reduction in the incidence of VZV to "very low" (60). Assuming a 90% coverage other modelling has predicted that a one-dose vaccine programme will reduce overall VZV by 64% and adding a second dose will further reduce VZV by an additional 22% (61).

In population studies, the inclusion of a second dose on the childhood immunisation schedule has been reported to reduce the incidence of VZV outbreaks in schools and reduce transmission in institutional based outbreaks (41, 42). The odds of developing VZV have been calculated to be 95% lower with a two-dose regimen than a one-dose (40). In the last four years, there has been only one reported study which found that the effectiveness of the one-dose versus two-dose VZV vaccine was similar (44).

7.2.2.2 VZV infection in the adult population

Anticipated likely rates of coverage will be an important consideration with respect to the impact of a childhood VZV vaccination programme on incidence of VZV infection in adults. It has been predicted that if only moderate levels of coverage can be achieved for VZV vaccination, at 70% for the first dose and 60% for the second dose, then an increase in adult VZV incidence would be expected. However, this is predicted to be unlikely if high childhood programme coverage rates of 90% and 80% could be achieved. (60)

7.2.2.3 Schedule options

Suggestions for a two-dose schedule with a catch-up that avoids the use of MMRV as a first dose in children less than four years of age are presented below.

Table 1. Possible schedule option for NZ for a two-dose VZV regimen

	Over 9 months	12 – 15 months	4 years	Voluntary catch up for all persons > 4 years with no VZV history	Over 60 years
Monovalent VZV vaccine	Outbreak control	*		MMRV or V depending on vaccination history	
MMRV			*		

7.2.3 Special groups

Special considerations should be given to providing funded VZV vaccine for the following groups at any time:

- Immigrants from countries without VZV circulating
- Healthcare workers, and close contacts of immunocompromised or pregnant patients
- Teachers and people working in childcare facilities or primary schools
- Seronegative women of childbearing age (who are not pregnant - women should not get pregnant for one month after being vaccinated, if pregnant vaccinate immediately post-partum)
- Seronegative people prior to receiving immunosuppressive therapy for autoimmune disease, organ transplant or chemotherapy for cancer
- People working or living in overcrowded situations (such as students, staff and inmates of correctional institutions, military personnel)

7.2.4 Considerations for HZ vaccine in adults

7.2.4.1 Considerations of age of recommendation for HZ vaccine

As of early 2013, Zostavax® is indicated for immunisation of individuals 50 years of age or older, although internationally, Zostavax® is generally recommended for adults aged 60 years and above. This is mostly due to supply issues with the vaccine and the greater burden of severe disease in the more elderly.

If NZ was to introduce a VZV vaccine on the childhood immunisation schedule, this may have an impact on the incidence of HZ in adults. Mathematical models predict an increase in the incidence of HZ infection in the middle-aged group for a period of 30-50 years after the introduction of the childhood VZV immunisation. Therefore, once supply issues of Zostavax® have been resolved, the future considerations for NZ would be to consider the introduction of the HZ vaccine and at what age is HZ virus vaccine should be recommended for adults. Whilst the age of 65 years would fit with the current immunisation schedule, it may be prudent to consider a HZ vaccine at the age of 50 years age if VZV vaccine is added to the childhood immunisation schedule. As more countries add VZV vaccine to the childhood immunisation schedule, the modelling data will be replaced with more real epidemiology data and the actual burden of HZ for each age group may influence where the vaccine should be best placed on adult immunisation schedules.

One further consideration would be whether the HZ vaccine requires a booster dose at some time in adulthood, especially if given in mid-age adults as opposed to old-age adults. Data indicate the persistence of vaccine efficacy up to year five after vaccination, longer term data is unavailable to date (70).

7.2.4.2 Concomitant administration with other adult vaccines on NZ schedule

A study has been published on the concomitant administration of HZ vaccine with inactivated influenza vaccine in adults aged 50 years and older. ZOSTAVAX® and influenza vaccine given concomitantly were generally well tolerated and antibody responses were similar whether ZOSTAVAX® and influenza vaccine were given concomitantly or sequentially (74).

No publications have been found evaluating the immunogenicity or safety of adult booster doses of dT or Tdap adult given concomitantly with HZ vaccine.

7.3 Special groups

The groups most at risk for complications of infection from VZV are immunocompromised persons. VZV vaccination in leukaemic children, children undergoing renal transplantation and HIV infection children has been intensively studied during pre-licensure trials (5).

7.3.1 Use of VZV vaccine in children with HIV

There were approximately 55 cases of HIV notified in children in NZ in 2010 (Starship Children's Hospital) (75).

Recently, guidelines have been published on vaccinating HIV-positive children across Europe. The guidelines are detailed; the recommended schedule for primary immunisation and booster doses for children infected with HIV is presented below, and is based on vaccines available in the UK as of early 2013. The schedule can be modified according to local schedules and availability.

Table 2. Recommended schedule of primary immunisation and booster doses for HIV-infected children, taken from the European guidelines 2012.

Age	Vaccine
Birth	HBV
1 month	HBV
2-3 months	DTaP/IPV/Hib + PCV13 +HBV (+ Rota)
3-5 months	DTaP/IPV/Hib + MenC (+ PCV13 + Rota)
4-7 months	DTaP/IPV/Hib + MenC + PCV13 (+ Rota)
Every autumn after 6 months of age	Flu; a 2nd dose 1 month later if <13 years and no previous doses
12 months	HBV (+HAV)
13 months	Hib/MenC conjugate + PCV13 +MMR
15 months	VZV
18 months	VZV (+HAV)
3 year 4 months or soon after	DTaP/IPV/Hib or dTaP/IPV + MMR
12 to 18 years	Td/IPV (or dTaP) + MenC conjugate For girls: HPV x3

7.4 Summary of vaccines and schedule options for NZ

In countries where VZV vaccine is on the childhood immunisation schedule, the first dose is generally given between 11 and 18 months. For countries that have moved to a two-dose schedule, the second dose is administered between 15 and 23 months or between four and six years, usually, in combination with the MMR vaccine. It is clear that if a single dose schedule be adopted breakthrough cases and outbreaks will occur, as well as a possible shift in age for disease to an older age group, particularly if coverage is not high. MMR + V is likely to be the preferred, if used in children under 48 months of age as a first dose, whereas MMRV is appropriate at any age for the second dose.

If NZ were to follow international practice, the options for inclusion of a VZV vaccine on the current immunisation schedule, with the least disruption, could be two doses administered at 15 months and four years of age as MMR + V followed by MMRV. There are some special groups for consideration, particularly immunocompromised. VZV vaccination in these groups has demonstrated to reduce risk for HZ significantly.

Internationally, HZ vaccine for adults is licensed for adults over 50 years of age and, mainly due to vaccine supply constraints, recommended for over 60 years of age. With the high burden of disease with HZ, particularly in the elderly, and also with the institution of a childhood programme, consideration also needs to be given to the use of the ZV in the older age groups, initially from age 60 years but possibly from lower ages. It can be concomitantly administered with influenza vaccine. International epidemiology needs to be watched and reviewed regularly as further knowledge in this area progresses.

8. Implementation considerations

8.1 Implementation of VZV onto childhood schedule

There were no recent publications identified addressing implementation issues for VZV vaccine in children.

8.2 Implementation of HZ vaccine for older adults

8.2.1 Low coverage of HZ vaccine in healthy older adults

Data from the US 2008 National Health Interview Survey, among people aged >60 years, were analysed to examine HZ vaccination among this age group. By 2008, only 6.7% (95% CI=5.9%, 7.6%) of adults aged >60 years reported having had HZ vaccination. The level of HZ vaccination coverage was lower among people aged 60 to 64 years (4.7%) compared to people aged 65 to 74 years (7.4%); 75 to 84 years (7.6%); and >85 years (8.2%). There were racial differences in uptake of the vaccine. Coverage was statistically higher for non-Hispanic whites (7.6%) compared with non-Hispanic blacks (2.5%) and Hispanics (2.1%). Among people aged >60 years who reported never receiving HZ vaccination, 95.1% reported at least one missed opportunity to be vaccinated. People more likely to report ever having been vaccinated were older, female, non-Hispanic white, married, more educated, and reporting received influenza vaccination in the past year. The coverage level was low among all groups and lowest among minority groups (76).

A study in immunocompetent, community dwelling adults aged ≥ 60 years, who were members of the Kaiser Permanente Southern California integrated health care system (KPSC) between 1 Jan 2007 and 31 Dec 2009, confirmed the findings above and identified some additional factors associated with HZ vaccine uptake. White persons, female patients and individuals who had more outpatient visits, but fewer chronic diseases, were more likely to receive the HZ vaccine (77).

9. International policy and practice

9.1 Objective

To provide a review of international vaccine schedules for the prevention of VZV in childhood and the prevention of HZ in adulthood.

9.2 Review

This review has been restricted to immunisation schedules in US, Canada, UK, Europe and Australia.

9.2.1 United States

VZV vaccine was licensed in the US in 1995 and was the first country to start a universal vaccination programme for VZV. Initially, as a single dose schedule, however, since 2006, the ACIP has recommended a two-dose schedule.

The ACIP recommends that all healthy people who do not have evidence of immunity to VZV should be vaccinated against this disease.

Routine two-dose vaccination

First dose at 12 to 15 months old

Second dose at four to six years old

Second dose catch-up vaccination

Given ≥three months after first dose for children <13 years of age

Adolescents and Adults (≥13 years old)

Given two doses four to eight weeks apart

If it has been more than eight weeks since the first dose, the second dose may be given without restarting the schedule

VZV vaccination is especially important for

- Healthcare professionals
- People who care for or are around immunocompromised people
- Teachers
- Childcare workers
- Residents and staff in nursing homes and residential settings
- College students
- Inmates and staff of correctional institutions
- Military personnel
- Women of childbearing age who are not pregnant (women should not get pregnant for one month after being vaccinated.)
- Adolescents and adults living with children
- International travellers

HZ vaccine (Zostavax®, Merck & Co.) was licensed and recommended in 2006 for prevention of HZ among adults aged 60 years and older. In March 2011, the US FDA approved the use of Zostavax® in adults aged 50 to 59 years. In June 2011, the ACIP declined to recommend the vaccine for adults aged 50 to 59 years and reaffirmed its current recommendation that HZ vaccine be routinely recommended for adults aged 60 years and older (78).

9.2.2 Canada

All Canadian provinces and territories have had routine immunization programs for one dose of VZV vaccine since 2007, a strategy that has reduced VZV disease rates dramatically. However, breakthrough cases still occur, and some cases are severe. There is increasing evidence that immunity to one dose of the vaccine can wane in a vaccinated population, and the disease may be shifting to an older age group that can experience more severe disease and more complications. This statement presents the rationale for a two-dose immunization strategy in Canada, as well as recommendations for a routine two-dose VZV vaccine schedule for all Canadian children. Children who have had one dose of VZV vaccine and have not had breakthrough infection should receive another dose of VZV vaccine. This document replaces the Canadian Paediatric Society's 2005 position statement on VZV prevention (79)

As part of the Canadian immunisation schedule, as of early 2013, children aged 12 months to 12 years receive one dose of VZV vaccine. Susceptible individuals ≥ 13 years of age receive two doses at least 28 days apart (80).

In August 2008, a live, injectable, attenuated HZ vaccine (Zostavax® ™, Merck Frosst Canada, Inc.) was authorized for use in Canada for the prevention of HZ infection in adults aged 60 years and older.

HZ vaccine is recommended for the prevention of HZ and its complications in adults 60 years of age and older. This vaccine is given in one dose, and as of early 2013, is not publicly funded (81).

9.2.3 Australia

The national immunisation programme schedule of Australia includes VZV vaccination. This programme commenced on 1 November 2005. It provides free VZV vaccine for all children at 18 months of age and a catch-up programme for children aged 10 to 13 years who have not received VZV vaccine or who have not had the disease (82)

In the latest fact sheet (Nov 2009) on HZ from the NCIRS, their statement about HZ vaccination for adults is "The vaccine is registered for use in people aged >50 years as a single dose. The HZ vaccine has been recommended for use in adults aged 60 to 79 years on the National Immunisation Program but a government decision is pending"(83).

9.2.4 United Kingdom

The VZV vaccine is not on the standard immunisation schedule in the UK, but is available privately, and there is a policy for at-risk groups. These include people who have weakened immune systems through illness, such as HIV, or through treatment, such as chemotherapy (84).

At present, a vaccine for HZ immunisation is not routinely offered on the NHS to people in the UK. However, the Joint Committee on Vaccination and Immunisation (JCVI) that advises the UK government made a statement in 2010. The statement recommended that a universal HZ vaccination programme for adults aged 70 up to and including 79 years should be introduced provided that a licensed vaccine was available at a cost effective price (85).

9.2.5 European Union

In 1998, the WHO recommended that routine childhood VZV vaccination be considered in countries where the disease is a relatively important public health and socioeconomic problem, where the vaccine is affordable, and where high (85 - 90%) and sustained vaccine coverage can be achieved. Recommendations for VZV vaccination in Europe vary, with the majority of countries not following the WHO recommendations for universal routine vaccination, instead recommending vaccination of susceptible adolescents or high-risk groups.

Germany has the widest experience with universal VZV vaccination in Europe, since use of the monovalent vaccine was recommended in 2004. From 2006, the combined MMRV vaccine, to be used in place of MMR and VZV vaccines at the physician's discretion, was included in the German childhood immunisation schedule as a two-dose regimen (86).

The majority of European countries with a national recommendations for VZV vaccination suggest targeted vaccination in susceptible adolescents or high-risk groups, such as seronegative women of childbearing age, healthcare workers, susceptible individuals with immunosuppressed close contacts, childcare personnel and teachers (86).

The European countries with VZV vaccine on their national immunisation schedule are: Austria, Cyprus, Germany, Greece, Italy, Latvia, Spain and Switzerland.

VZV vaccine is not currently listed on the national childhood immunisation schedule in the following European countries: Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Hungary, Iceland, Ireland, Lithuania, Luxembourg, Malta, The Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia and Sweden (87).

9.3 Summary of international policy and practice

9.3.1 VZV vaccine

The US has a two-dose VZV vaccine schedule for children at 12 - 15 months and four - six years.

As of early 2013, Canada had a single dose VZV vaccine schedule for children but is considering moving to a two-dose schedule.

Australia provides a single dose VZV vaccine for all children at 18 months of age and a catch-up programme for children aged 10 - 13 years who have not received VZV vaccine or who have not had the disease.

The VZV vaccine is not on the standard immunisation schedule in the UK, but is available privately, and there is a policy for at-risk groups. HZ vaccine is being considered for the 70-79 year age group.

Germany has the widest experience with VZV vaccine in Europe since use of the monovalent vaccine was recommended in 2004. From 2006, the combined

MMRV vaccine was included in the German childhood immunisation calendar as a two-dose schedule (11 - 14 months and 15 - 23 months) with a catch-up dose at nine to 17 years recommended for those not previously vaccinated against or contracted VZV. Use of combined vaccines is generally recommended.

The majority of European countries with a national recommendation for VZV vaccination suggest targeted vaccination in susceptible adolescents or high-risk groups.

See table 4 for summary of international VZV vaccine schedules.

Table 3. Summary of childhood national immunisation schedules which include VZV vaccine as of 2012 (adapted from ECDC) (87)

Country	Age of VZV vaccination	Number of doses	Special recommendations
USA	12 – 15 months + 4 – 6 years	Two	
	Catch up: in children < 13 years	Two, 2nd >3 months after first	
	Adults/adolescents ≥13 years	Two, 4 - 8 weeks apart	
Canada	12 months – 12 years	One	
	≥13 years	Two, 28 days apart	In susceptible adolescents/adults
Australia	18 months	One	If unvaccinated & no history of varicella.
	10 – 13 years (catch-up)		
NZ	12 months – 12 years	Two	Not funded
Austria	9 – 17 years	Two	No history of varicella or negative serology. Payment required
Cyprus	13 -18 months	One	Universally in private sector
	11- 12 years (if missed)		Public sector to high risk groups
Germany	11 - 24 months	Two, 4 - 6 weeks apart	Catch-up if unvaccinated & no history of varicella
	9 – 17 years (catch-up)		
Greece	12 – 18 months	Two, 4 - 8 weeks apart	All ages if unvaccinated & no history of varicella
Italy	13 – 24 months	One	In adolescents if susceptible
	9 – 15 years		
Latvia	12 – 15 month	One	
Sweden	9 – 15 years	One at 10 – 12 years	Unvaccinated & no history of varicella
		Two at ≥13 years, 28 days apart.	
Switzerland	11 – 15 months (at risk)		At risk of complications
	Adolescents (catch-up)		Adolescents with no history of varicella.

9.3.2 HZ vaccine (shingles prevention)

In the US it is recommended that all people over the age of 60 years should receive HZ vaccine.

In Canada, HZ vaccine is approved in adults ≥60 years of age as one-dose, but as of early 2013, is not publicly funded.

The HZ vaccine has been recommended for use in adults aged 60–79 years on the National Immunisation Program of Australia but a government decision is pending.

In the UK, a recommendation has been made that a universal HZ vaccination programme for adults aged 70 up to and including 79 years should be introduced, provided that a licensed vaccine is available at a cost effective price.

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