Antigen Review for the New Zealand National Immunisation Schedule, 2016: Varicella-zoster virus (chickenpox)

May 2016

Executive summary

This review summarises selected literature on the use of varicella-zoster virus vaccines published from 2013 to May 2016.

Varicella-zoster virus (VZV) infection causes a primary infection known as chickenpox (varicella), usually in childhood. VZV remains dormant in the dorsal and trigeminal root ganglia, and may reactivate later in life, when cell-mediated immunity wanes or is suppressed, resulting in herpes zoster (HZ; shingles). Varicella is commonly seen as a mild to moderate, self-limiting disease, however, serious complications can occur in previously healthy individuals. The risk of complications increases in adolescents and adults. Secondary bacterial infections of the skin and respiratory system are the most common morbidities and more rarely VZV encephalitis.

New Zealand (NZ) experiences approximately 50,000 cases of chickenpox each year, which is approximately equivalent to number in the birth cohort each year, and results in around 400 hospitalisations each year.

Varicella vaccines available in New Zealand contain a live attenuated strain of VZV - the Oka strain. There are two types of vaccine available, namely, monovalent varicella vaccine (V) and combined measles-mumps-rubella-varicella (MMRV) vaccine.

Safety of varicella vaccines

No serious adverse events have been identified for varicella vaccines. Safety concerns are restricted to immunocompromised individuals, for whom live vaccines are usually contraindicated. However, case-by-case evaluation of patients who are mildly or moderately immunocompromised may be conducted to consider balance of the risk from wild-type varicella disease versus the risk of vaccine-associated varicella or subsequent breakthrough disease. In such cases, the clinical experience of vaccine-associated or breakthrough varicella is usually milder than disease seen in patients who are unvaccinated with wild-type disease and can be controlled by antiviral treatment.

The use of the quadrivalent MMRV in young children has been associated with an increase in febrile convulsions. The risk is around 7-9 cases per 10,000 children aged 12-23 months, compared with 3-4 cases per 10,000 children who received MMR alone or MMR+V (as two injections at same visit). Children aged 16 – 23 months receiving the first dose of MMRV are at higher risk from fever than those aged 12-15 months. Many countries have opted to administer MMR+V as separate vaccines for the first dose at 12-23 months of age rather than MMRV. However, this entails two injections and has been suggested to affect the coverage.

Immunogenicity and effectiveness

Seroconversion rates in immunocompetent children are 95-100% following two doses of MMR+V or MMRV. There do not appear to be differences in immunogenicity between varicella vaccine alone, MMR+V or combined MMRV in protection against varicella. The efficacy of MMRV was shown to be around 95% against all varicella and 99.5% against moderate-severe disease.

The duration of protection from one dose of varicella vaccine is shorter than for a two-dose schedule and less effective against all cases of varicella (around 80% compared with 93% for two doses). Breakthrough cases in vaccinated persons are usually attenuated and

severity does not increase with time post-vaccination. Two-dose schedules provide long lasting protection, however, the duration of protection has not yet been evaluated fully. One study found no breakthrough cases in children 14 years since vaccination. However, in programmes where the time between the first and second dose is long, breakthrough cases may occur before the second dose is administered.

Effectiveness of the vaccine when given to immunodeficient individuals is unclear. The immune response may not fully develop following one or even two doses of vaccine in these patients and breakthrough disease may occur. There is evidence that disease severity is reduced by vaccination and that seroconversion is possible in those who are mildly immunosuppressed. Herd immunity, particularly provided by vaccinating close contacts, can help to reduce circulating disease and thereby convey protection to those who cannot be immunised or do not adequately respond to vaccination.

Impact of varicella immunisation programmes

Significant declines in varicella cases and hospitalisations have been observed in regions where universal varicella vaccination has been implemented. Herd immunity is being provided through the decline in circulating VZV, particularly for infants under one year of age and immunocompromised persons.

It is unclear what impact adolescent catch-up doses have had on disease. The greatest impact has been seen in children aged 12 months to 5 years, because these age groups are most likely to develop the disease in temperate climates. However, where VZV remains in circulation, there is some suggestion that with a reduction of disease in younger age groups, disease incidence is pushed to the older children and therefore vaccination of non-immune adolescents is warranted.

Available vaccines and options for scheduling

Options for varicella immunisation programmes include one or two-dose strategies, concomitant use with MMR, consideration is required around timing between two doses, and the role of catch-up campaigns for non-immune adolescents and adults.

High coverage with a single dose regimen may be sufficient to reduce circulating disease rapidly. However, most countries have ultimately opted for a two-dose schedule even where a single dose was introduced initially. In Germany, improvements in vaccine effectiveness were noted following the introduction of a two-dose schedule due to improvements in coverage.

Australia opted for a single varicella dose at 18 months of age. To mitigate the increased risk of febrile convulsion in this age group, MMR alone is given as the first dose at 12-15 months and MMRV is administered as the second MMR dose at 18 months. A catch-up varicella dose was initially introduced for adolescents as part of a school-based programme but has been discontinued.

The timing between doses has an impact on the incidence of breakthrough disease. Individuals who may not have mounted a sufficient immune response against the first dose of vaccine, are at risk of breakthrough disease if VZV remains in circulation. To be fully immunised, these individuals would benefit from a second dose close to the first dose (i.e. a minimum of four weeks between doses). Alternatively, higher coverage may be achieved by giving the second dose at age 4-6 years as MMRV as part of the established MMR schedule. High coverage is critical for the development of effective herd immunity to protect those unable to be vaccinated.

There are variable approaches to the use of catch up campaigns alongside the introduction of a universal vaccination programme. The greatest gain appears to be in enabling the reduction in circulating disease, thus obtaining less breakthrough disease and good herd immunity. Programmes that have started with a two-dose regimen and/or included a catch up programme appear to have greater gains and more quickly.

Impact of varicella vaccination on herpes zoster incidence

There is insufficient data to determine whether childhood varicella vaccination has an effect on HZ incidence. No definitive increase has been demonstrated in countries that have introduced varicella vaccination. Most modelling studies have been based on the exogenous boosting hypothesis that requires exposure to circulating VZV to maintain latency of the VZV virus. There is insufficient evidence to support this hypothesis.

No data so far have been able to determine what, if any, risk there is of vaccine-type HZ as those who have been vaccinated grow older. A US-based study has shown a lower incidence of HZ in vaccinated children than unvaccinated children up to the age of 18 years.

International policy and practice

Most countries that recommend varicella vaccines have implemented a two-dose varicella schedule for young children aged 12-24 months, with catch-up available for adolescents without evidence of VZV immunity. In children, the first dose is generally MMR+V or a choice of MMR+V or MMRV. The second dose is generally MMRV. Australia has introduced MMRV to be given at 18 months of age as a second dose of MMR.

Options for New Zealand

Careful consideration should be given to the timing of varicella vaccination programmes, particularly, if two doses are given. High coverage of varicella and MMR vaccines need to be maintained to effectively prevent disease.

Improvements in varicella surveillance are necessary to monitor VZV circulation, the incidence of breakthrough disease and possible vaccine-strain varicella disease. Also to monitor the incidence of HZ.

As circulation of wild-type disease declines, the incidence of varicella is expected to move to older age groups, resulting in an increased burden of more severe disease, due a greater risk of complications and the risk of varicella infection during pregnancy. A catch-up campaign, particularly for adolescents, is recommended to help to protect non-immune individuals and contribute to herd immunity.

Contents

Figures and tables

Acknowledgements

Abbreviations

ACIP	Advisory Committee on Immunization Practices
AE	Adverse events
AEFI	Adverse Events Following Immunisation
CDC	Center for Disease Control and Prevention
CI	Confidence interval
CVS	Congenital Varicella Syndrome
DGS	DiGeorge Syndrome
DTaP-IPV-HepB/Hib	Combined diphtheria, tetanus, acellular pertussis, inactivated poliovirus, hepatitis B and *Haemophilus influenzae* type b vaccines.
ESR	Institute for Environmental and Scientific Research
EU	European Union
GAS	Group A Streptococcus
GSK	GlaxoSmithKline Ltd
Hib	*Haemophilus influenzae* type b
HibMenCY-TT	Combined *Haemophilus influenzae* type b, meningococcal C and Y conjugated to tetanus toxoid vaccine
HIV	Human immunodeficiency virus
HSCT	Haematopoietic stem cell transplant
HSV	Herpes simplex virus
HZ	Herpes zoster
IDSA	Infectious Disease Society of America
IRR	Incidence risk ratio
ITP	Idiopathic thrombocytopenic purpura
MMR	Combined measles, mumps, rubella vaccine
MMR+V	Concomitant MMR and varicella vaccines – given in separate limbs
MMRV	Combined measles mumps rubella varicella vaccine
MMR/V	MMR and varicella vaccines given as separately on different occasions.
MSD	Merck Sharp & Dohme Ltd (Merck & Co in US and Canada)

NZ	New Zealand
RCT	Randomised clinical trial
RR	Relative risk
SAE	Serious adverse events
SAGE	Strategic Advisory Group of Experts on Immunization
UK	United Kingdom
US	United States of America
VAERS	Vaccine Adverse Event Reporting System
VZV	Varicella zoster virus
WHO	World Health Organization

1 Background – varicella infection and vaccination

Varicella-zoster virus (VZV) is a highly contagious pathogen that occurs worldwide and is exclusive to humans. The primary infection with VZV causes varicella disease (commonly known as chickenpox), and subsequently establishes life-long persistence in sensory nerve ganglia: reactivation from latency produces the clinical syndrome referred to as herpes zoster (HZ, shingles). VZV is a human alpha-herpesvirus most closely related to herpes simplex virus-1 (HSV1) and HSV2. It is typically acquired through inhalation of aerosolised virus, although the virus may rarely be spread by direct contact with the skin blisters.[1]

The global burden of VZV-specific mortality is lower than some other major infectious diseases such as measles, pertussis, rotavirus or invasive pneumococcal disease. Although varicella is usually a self-limiting disease, it can cause significant morbidity for some, and particularly for certain high risk groups, such as individuals who are immunosuppressed, the severity of the disease and outcomes increases the societal burden.[2]

In the majority of children, infection with VZV results in a mild to moderate illness with a typical case having 200-500 skin lesions. However, complications requiring hospitalisation and fatalities do occur in both adults and children who were previously healthy. The most common and serious complications in children include central nervous system involvement (encephalitis) and secondary invasive bacterial infections, which rarely are fatal. Primary infection in adults is rare in New Zealand but has a higher rate of complications than for children. Adults with varicella are several times more likely to develop severe disease than children. Viral pneumonia is the most common complication in adults, often requiring mechanical ventilation, and carries an overall mortality rate of 10–30% despite appropriate antiviral therapy.[1]

Pregnant women and their unborn babies are particularly vulnerable to VZV infection. Maternal varicella occurring in the first half of pregnancy can cause the rare but devastating congenital varicella syndrome, whereas maternal infection in the last weeks of pregnancy or just after delivery results in neonatal VZV infection. This has a high case-fatality rate due to a lack of opportunity for the development and transfer of antibody from mother to infant and the immaturity of the infant's cellular immune response. Non-immune women who contract VZV while pregnant have an estimated 10-20% risk of developing VZV pneumonitis, which is a higher rate than observed in non-pregnant women.

People who are immunocompromised are most vulnerable to both VZV and HZ; these individuals include those taking immunosuppressive medications, such as cancer treatment, certain anti-inflammatory therapeutics or organ transplant patients, and those with human immunodeficiency virus (HIV) infection. In otherwise healthy children receiving courses of high-dose corticosteroids for treatment of asthma and other illnesses, cases of severe and even fatal varicella have been reported[3].

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. As VZV-specific T cell-mediated immunity declines with age, latency of the virus is less well maintained, increasing the incidence of HZ.[4]

Varicella vaccines have been available since 1974 when the live attenuated (Oka strain) varicella vaccine was developed, which was first licensed in 1986 in Japan. It was first licensed for routine use in the United States (US) in 1995. The Oka strain of VZV has been cold-adapted through repeat passage in cell culture to grow optimally at 34°C and grows less well at 39°C than wild-type VZV. When administered subcutaneously, the incidence of rash is less than for natural infection and inadvertent transmission usually results in mild or subclinical disease. In contrast to wild-type infection, vaccine-strain VZV rarely induces viraemia after immunisation.[1] Varicella vaccines have shown excellent safety profiles and effectiveness in controlling disease. The vaccine-strain VZV is also susceptible to treatment with antivirals.

This review evaluates the literature on vaccination against varicella published from 2013 to 2016 since the previous review of this antigen (2012).[5] The focus of this review is on the varicella vaccines to protect against chickenpox, including monovalent varicella vaccines and combined measles, mumps, rubella and varicella (MMRV) vaccines. A separate review will be conducted on HZ.

2 Methodology for review

2.1 Objectives

The objectives for this review have been informed by the general specifications for the 2016 New Zealand (NZ) academic review and the specific specifications for varicella vaccines. These are listed below. The dates for eligible publications are between January 2013 and May 2016. This is neither a systematic review nor 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 varicella vaccines, but not herpes zoster vaccines, for NZ.

- General specifications
    - Safety
    - Effectiveness
    - Impact of varicella vaccination programmes
    - Different vaccine options and comparisons
    - Duration of protection
    - Herd immunity
- Service specifications for varicella vaccines
    - Schedule options as described in the literature
    - Implications for burden of disease on health service
    - Implications for older age groups as circulating VZV declines.
    - Timing of two-dose schedule
    - Effectiveness of one-dose schedule
    - Use in special groups
    - International evidence regarding the use of MMR+V versus MMRV in infants
    - Consideration of international practice for timing of schedule and eligibility

2.2 Literature search strategy

Medline search terms and strategy
MeSH term Chickenpox vaccine: 1706
Limit to Humans, English, 2013 – current: 177

NOT Cost and Cost analysis: 112

Cochrane Library search terms and strategy
MeSH term: Chickenpox Vaccine
Limit to Cochrane reviews, other reviews, trials 2013-2016: 2 results (keep and view)
NOT herpes zoster: 1

Scopus search terms and strategy

Varicella vaccine* 2013-present; excluding social science and physical science: 1099
Limit to: Medicine, humans, articles, reviews, articles in press, conference papers
Exclude letter, short survey, editorial and erratum: 682
Exclude herpes zoster: 360
Limit to chickenpox vaccine; deleted duplicates: 133

2.2.1   Grey literature

Conference abstracts were sought to include data that has not yet been published, particularly from the key infectious diseases conferences for 2013 and 2016. One abstract was accessed.

2.2.2   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. All duplicates were removed from the final library.

2.2.3   Final Endnote Library 172 Articles

Where systematic reviews and/or meta-analysis were available the preceding literature has been excluded from the review. Twelve review articles have been included and 18 articles were excluded.

2.3 Participants/populations

The population for a universal programme are infants and targeted vaccination for all ages susceptible to varicella with no contraindications.

High risk persons, or contacts of high risk, that could particularly benefit from varicella vaccine identified from the literature include:

- Non-immune immunocompetent individuals
    - Healthcare workers
    - Childcare workers
    - Other residential care workers
    - Correctional facility workers and inmates
    - Household contacts of immunocompromised individuals
    - Post-exposure prophylaxis for immunocompetent in-patients
- Non-immune, prior to immunosuppression
    - Solid organ (liver) transplant candidates
    - Elective immunosuppression for more than 28 days
    - Haematopoietic stem cells transplant candidates
    - Prior to planned pregnancy
- Non-immune, mild-moderate immunosuppression or post immunosuppression:
    - Inflammatory bowel disease
    - Juvenile Rheumatoid arthritis

- o Post haematopoietic stem cells transplant
- o Post cancer therapies.
- o DiGeorge syndrome
- o Postnatal women
- o HIV infected with high CD4 cells counts
- Patients with, or with a history of, lymphoma and leukaemia

2.4 Interventions

2.4.1 Varivax®

Varivax® is a live attenuated virus vaccine against VZV produced by Merck Sharp and Dohme (MSD) Ltd. Each 0.5mL dose of Varivax® contains a minimum of 1350 PFU (plaque forming units) of Oka/Merck varicella virus. Each dose also contains approximately 18mg of sucrose, 8.9mg of hydrolysed gelatin, 3.6mg of urea, 2.3mg of sodium chloride, 0.36mg of monosodium L-glutamate, 0.33mg of sodium phosphate dibasic, 57µg of potassium phosphate monobasic, 57µg 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.

2.4.2 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.

2.4.3 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 $10^{3.0}$ CCID50 of the Schwarz measles, not less than $10^{4.4}$ CCID50 of the RIT 4385 mumps, not less than $10^{3.0}$ CCID50 of the Wistar RA 27/3 rubella and not less than $10^{3.3}$ PFU of the varicella virus strains.

2.4.4 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 Study designs

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

3 Epidemiology of VZV

Varicella-zoster virus circulates as five distinct genotypes, known as 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, migration has redistributed European, African and Asian clades. Clade 1 and clade 3 are commonly isolated in temperate climates and have been seen in Europe and New Zealand.[1] The Oka virus used to derive varicella and HZ vaccines is a clade 2 strain.[6]

In temperate climates the incidence of varicella is highest in preschool children (age 1 – 4 years) or early primary school age (5 – 9 years). Around 90% of individuals have been infected by adolescence and fewer than 5% of adults are susceptible. On average, the annual number of infections has been estimated to be approximate in number to the birth cohort. Crude hospitalisation admission rates in developed countries range from around 2 to 6 per 100,000 population-year. Most of these admissions are children, consistent with the high incidence of varicella in children. Crude mortality rates ranged from 0.3-0.5 per million population-year with overall case fatality ratios of around 2-4 per 100,000 cases. Almost 90% of hospital admission cases with varicella were otherwise health or immunocompetent.[7, 8]

In tropical climates, varicella is acquired later in childhood or adolescence and there is high susceptibility amongst adults. For example, surveillance data in Sri Lanka found that around 30% of cases were reported in the 20-29 year age group during 2011 and 2012. Since the mean age of varicella infection is older there is an associated increase in morbidity. Overcrowding in urban households may overcome the normally diminished ability for VZV to spread in tropical climates. Population-based data on severe disease burden in developing countries with tropical climates is sparse. One study in Sri Lanka found that varicella was a significant cause of morbidity and mortality of adults and the most common disease in adults treated at the main infectious diseases hospital; during 2000-2001, 58% of the 1690 hospitalisations were due to varicella.[7]

Live attenuated varicella vaccines were developed over forty years ago, and although they are available throughout the world, they are only recommended in a small number of countries for routine immunisation. However, where high coverage rates have been achieved important declines in varicella-associated incidence, morbidity and mortality have been seen. By 2005 in the US, a decade after the introduction of routine varicella vaccination, vaccine coverage was approximately 90% and varicella incidence had declined by more than 90%. Herd immunity was also observed outside of age groups targeted for vaccination.[7]

3.1 New Zealand epidemiology

A total of 1001 samples were positive for VZV during 2014, based on weekly data collated from virology laboratories at Auckland Labplus, Waikato hospital, Canterbury Health, Wellington Hospital, Middlemore Hospital, Tauranga Labplus and the ESR.[9] These data are mainly passive surveillance data for hospital inpatients and outpatients during routine viral diagnosis. In 2014, two outbreaks were reported to ESR which included 45 cases.[10] However, as varicella is not a notifiable disease in New Zealand and the need for viral diagnosis is uncommon due to its identifiable clinical symptoms, these data do not in any way reflect actual numbers of cases per year. It is estimated in a typical year, there are around 50,000 chickenpox infections in New Zealand and the incidence, as for other temperate countries, is assumed to be approximate in number to the birth cohort each year. The majority of the burden is in otherwise healthy children.[11]

Hospital discharge data is reliant on accurate coding of complications to include preceding varicella infection, thus will underestimate admission attributable to varicella. Figure 1 gives the annual hospitalisations ICD-9 coded for chickenpox and associated complications (052) in New Zealand from 1993-2015. The data exclude short stay emergency department cases. (Source: Ministry of Health).
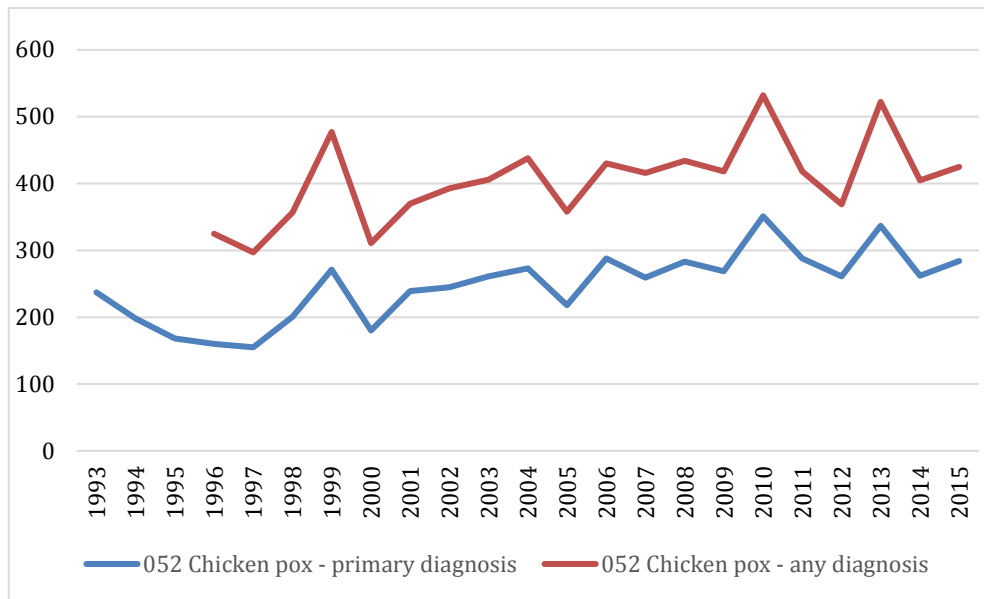
Figure 1. Number of annual chickenpox hospitalisations in New Zealand 1993-2015 (source: Ministry of Health)

The number of annual admissions to hospital with chickenpox diagnosis has trended upwards since the 1990s and is associated with serious complications and sequelae. A retrospective chart review, conducted over a 10 year period from July 2001- July 2011 of children admitted to paediatric intensive care unit (PICU) at Starship Children's Hospital, Auckland, identified 34 cases with primary or secondary varicella diagnosis; 26 were included in the study, the 8 excluded had been exposed to varicella without acquiring disease. These admissions represented 0.27% of the total PICU admissions over ten years. Of these 26, 84.6% were of Māori or Pacific ethnicity, 54% were previously healthy, 46% had pre-existing medical conditions and 23% were immunocompromised. Although all the children were up-to-date with their routine immunisations, only one had received a single dose of varicella vaccine. Secondary bacterial infection is recognised as a common complication of varicella. In this study, 65% of cases developed secondary bacterial infections and 59% of these were due to invasive group A streptococcal (GAS) and/or staphylococcal infections. The reasons for PICU admission were neurological complications (38.5%), secondary bacterial sepsis (26.9%), respiratory complications including bacterial pneumonia (15.4%), disseminated varicella (11.5%) or other causes (7%). Twenty-one children required mechanical ventilation. Four children died (15%), one who was a previously healthy 5-year-old and three who were immunocompromised (two on immunosuppressive therapy following organ transplantation, one with leukaemia receiving chemotherapy). The relative risk of death was higher for those children with varicella who were immunocompromised (risk ratio 13.3, 95% CI 1.82-97.8, $p<0.005$). A further eight children (31%) had ongoing disability at discharge, predominantly due to neurological impairment. The authors note that varicella, and its secondary complications requiring intensive care admission, results in high mortality for immunocompromised patients, in particular, and long-term morbidities in previously healthy children. They conclude that

these data support the inclusion of varicella immunisation to the childhood schedule to help to limit the uncommon but severe consequences of varicella.[12]

Further NZ data support that serious varicella disease is not limited to immune compromised children and also highlight the disparate burden in children with Māori and Pacific ethnicity. A prospective surveillance study investigated varicella and post varicella complications

Figure 2. Complications resulting in varicella-associated hospitalisation of children (adapted from Wen et al 2015)
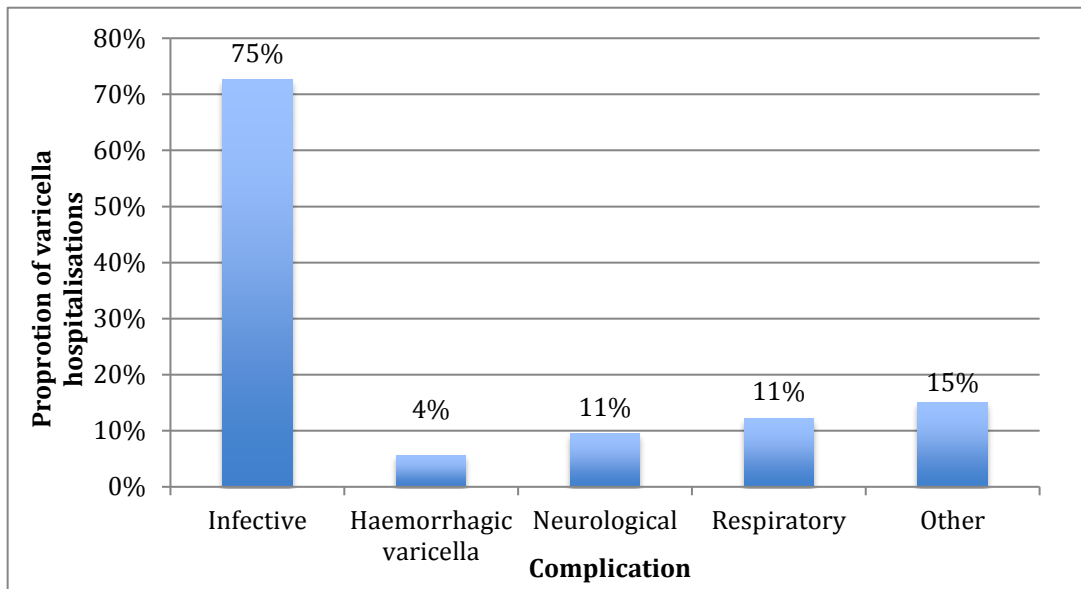
(excluding HZ) requiring hospitalisation in New Zealand as reported to the NZ Paediatric Surveillance Unit (NZPSU) from November 2011 to October 2013. Out of 178 notifications, 144 were confirmed varicella cases; 74% were Māori and Pacific Island children. The median age was 2.4 years (range 14 days–14.7 years; including 3 cases of neonatal varicella). The overall incidence of varicella-associated hospitalisations was 8.3/100,000 children per year. Incidence ratios were significantly higher for Māori (2.8) and Pacific children (3.9) compared with European children (p<0.01 for both). Only 9% of those hospitalised were immunocompromised. There were no reported deaths, however, 19% had ongoing issues following discharge. The most common complications were secondary infections (75%) as shown in Figure 2. Multiple complications were reported in 42 patients (29%). Other complications included electrolyte disturbance and dehydration, abnormal blood counts and severe pain. The authors conclude that varicella morbidity is higher in immunocompetent children than commonly perceived, particularly in children of Māori and Pacific ethnicities.[13]

4 Safety

4.1 Objective

The objective of this section is to review the most recent safety data for currently licenced vaccines. The main focus is on adverse events in children following combined MMRV or MMR+V and varicella vaccine recipients with some degree of immunosuppression. Only Adverse Events Following Immunisation (AEFI) that have been considered subsequent to the pivotal clinical efficacy trials will be reviewed here.

4.2 Outcomes

Outcomes include AEFI and serious adverse events (SAE). Excluded is the reactogenicity profile for injection site reactions and minor systemic reactions as these reactions are thoroughly considered in the pivotal studies for licensure. Adverse Events are not necessarily caused by the vaccine but are events that occur in temporal association with the immunisation event.

4.3 Safety of varicella vaccination

As varicella is a live attenuated vaccine it is contraindicated for use during pregnancy and in immunocompromised individuals. However, for some immunocompromised patients with less severe immunosuppression such as those with HIV controlled by treatment and organ transplant recipients on maintenance immunosuppression, the benefit of the vaccine can outweigh the risk as the vaccine strain VZV has limited capacity for virulence or replication. In some children with undiagnosed immune deficiencies, disseminated vaccine strain varicella has been reported. MMRV is associated with a greater risk of febrile convulsion in younger children, but this risk is balanced with the discomfort of receiving two injections at one time. Concomitant use of varicella vaccines with other childhood schedule vaccines has been found to be safe.

A systematic review, conducted by the WHO Strategic Advisory Group of Experts on Immunization (SAGE), noted that the most frequently reported reactions and AEFI during clinical trials were mild and primarily restricted to injection site reactions such as pain, swelling and redness, which occurred in up to 28% of recipients. Localised or generalised rash was also found to be common. No increased risk of cerebellar ataxia, encephalitis or ischaemic stroke was found following vaccination. A 2008 review found the rate of AEFI to be 3.4 per 10,000 doses based on approximately 55.7 million doses distributed during 1995-2005 worldwide. Further post-market surveillance in the US found the rate of AEFI to be 30 per 100,000 doses of varicella-only vaccine and the rate of serious adverse events (SAE) was less than four per 100,000 doses.[14] Since 2012 there has been little new literature around monovalent varicella vaccine safety; most of the recently published data are around the safety of MMRV.

4.4 Immunocompetent vaccine recipients

4.4.1 Infants and children aged older than 12 months

An AEFI passive surveillance study in Victoria, Australia, identified 27 cases of anaphylaxis associated with paediatric vaccination from 2007-2013. Only one of these cases was following administration of varicella vaccine (Varilrix®) in a 16 month old boy.[15]

An Australian retrospective study analysed the risk of febrile seizure following MMR dose one at 12 months of age and varicella vaccine given at 18 months of age from sentinel surveillance data from paediatric hospitals (Paediatric Active Enhanced Disease Surveillance network; PAEDS). Since the first dose of MMR and varicella vaccines were not given concurrently, this study was able to demonstrate that there was no increased risk of febrile seizure associated with monovalent varicella vaccine alone at 18 months of age (relative incidence [RI]=0.6; 95% CI 0.3-1.2). The risk of febrile seizure was significantly increased following the first MMR dose at 12 months of age (RI=1.9; 95% CI 1.3-2.9).[16]

4.4.2   Concomitant use in children

Concomitant administration of varicella vaccine with other childhood vaccines, including HibMenCY-TT, influenza, Hib and MMR, is considered safe.[14]

4.4.3   Use in adolescents

A post-licensure study of more than 1.8 million varicella vaccine recipients identified idiopathic thrombocytopenic purpura (ITP) as being moderately associated with varicella vaccination in adolescents aged 11-17 years (incidence rate ratio R 12.14, 95% CI 1.10–133.96; p=0.04). However, the very small number of reported cases (197 chart-confirmed cases across all age groups) were mild and acute. Further investigation was considered warranted for older children.[17-19]

4.4.4   Use as post-exposure prophylaxis in children

A systematic review, which assessed the efficacy and safety of vaccines for use as post-exposure prophylaxis (PEP) for the prevention of varicella in children and adults, found no AEFI were reported in three trials in which varicella vaccine or placebo was given following household varicella exposure of 110 healthy non-immune siblings. However, these trials were small and the authors concluded that safety was not adequately addressed since the trials did not comment on AEFI, such as fever or injection site reactions. No randomised clinical trials (RCT) were identified for the use of varicella vaccine as PEP in adults or adolescents.[20]

4.5   Use in immunocompromised individuals

People with compromised immune systems are at the greatest risk from serious complications of varicella. Children undergoing cancer treatment, for example, may not have gained immunity against the disease or have lost immunity to prior varicella infection due to chemotherapy or bone marrow transplant. It is therefore important to assess vaccine safety in these groups.

The WHO Global Advisory Committee on Vaccine Safety reported in July 2013 that varicella vaccine is associated with higher risk of adverse reactions in selected populations of children with cell-mediated immunity deficiencies when compared with healthy children. Case reports of adverse outcomes following varicella vaccination highlight incidents where children have previously had undiagnosed immunocompromise, such as dissemination, pneumonitis or fatal outcomes. Varicella vaccine is contraindicated or used with extreme caution in individuals with leukaemia or HIV. The WHO states that introducing risks of varicella vaccination should be balanced against the benefits of reducing severe wild-type varicella disease in the numerous immunocompromised subpopulations.[21]

A systematic review of safety of vaccines in children in the US found evidence of a causal relationship between varicella vaccine and disseminated Oka VZV with and without other organ involvement and subsequent infection causing pneumonia, meningitis or hepatitis in

individuals with immunodeficiencies. There was evidence of vaccine strain viral reactivation and subsequent infections, such as meningitis and encephalitis. Anaphylaxis was also associated with varicella vaccination. All the studies used in this systemic review were published prior to 2013.[17]

4.5.1   Use in children with cancer

Studies have been conducted in patients with cancer receiving varicella vaccine, particularly children with leukaemia. During a clinical trial of 548 children with leukaemia, a significantly increased risk of adverse events was seen up to six weeks following receipt of varicella vaccine. In this trial, a rash developed in 50% of children receiving chemotherapy compared with 5% of children no longer receiving chemotherapy. In another study of 437 children, 40% of vaccinated children in remission from leukaemia developed a rash following the first dose of vaccine. No SAE were reported for 29 vaccinated children in remission from various other cancers in a small study, although some children experienced mild to moderate rash.[14]

A prospective cohort study in the Netherlands demonstrated safe administration of varicella vaccine to closely monitored paediatric oncology patients without interrupted chemotherapy. Of these varicella seronegative children, 24 were being treated for haematological malignancies and seven for solid tumours. Out of 31 children, seven had mild (<50 vesicles) varicella rashes within 10 days of vaccination. Four were treated with oral acyclovir, two did not receive antiviral treatment and one required intravenous acyclovir due to mucositis. All seven patients recovered without interruption or delay to chemotherapy regimens.[22]

4.5.2   Use in children on treatment for juvenile idiopathic arthritis

No SAE were seen following two doses of varicella vaccine in a prospective study of six children (aged 2.5-7 years) with stable juvenile idiopathic arthritis being treated with biological therapy (etanercept, tocilizumab or infliximab) in Slovenia. No clinical varicella infection occurred within three months of vaccination and none of the children experienced a flare in their arthritis following vaccination. [23]

4.5.3   Use during pregnancy

Vaccines containing live attenuated VZV are contraindicated for administration during pregnancy. A review of 17 years of pregnancy register data (Merck & Co/CDC Pregnancy Registry) for inadvertent exposure to VZV-containing vaccines showed that no congenital varicella syndrome (CVS) and no increased birth defects were associated with varicella vaccine given within 3 months before or during pregnancy. The number of exposures being registered annually was very low (around two seronegative women exposed during high risk period per year). The registry received 860 prospective reports and 68 retrospective reports during 1995-2012. Ninety-five infants were born to mothers who were varicella-susceptible and exposed to vaccine during the high risk period. Based on these, the 95% confidence interval for risk for CVS ranged from 0% to 3.8%, however, these numbers are insufficient to estimate the theoretical risk of CVS following inadvertent vaccination during pregnancy as being lower than wild-type disease. The overall prevalence for major birth defects in the registry was 2.2% among live-born infants (95% CI 1.3–3.5), which is similar to the prevalence in the general population. The estimated risk of CVS after wild-type infection during the first two trimesters of pregnancy is around 1% of live births. This registry was closed in 2013 due to falling numbers of exposures and wild-type disease. VAERS and Merck continue to monitor inadvertent exposure to varicella vaccines during pregnancy and adverse events. [24]

4.5.4 Use in adults following autologous haematopoietic stem cell transplantation

Varicella vaccine (Varilrix®) was shown to be safe when given to 29 adults up to six months post autologous haematopoietic stem cells transplant (HSCT). Adverse events were reported by 13 (44.8%) vaccine recipients (95% CI: 26.4-64.3) and Grade 3 AE causally related to vaccination were reported for 3 (10.3%) participants (95% CI: 2.2-27.4). Varicella rash was reported in three patients – one case was a breakthrough wild-type virus infection. No SAE were causally associated to the vaccine.[25]

A fatal case of persistent disseminated vaccine-virus zoster was reported in the US in a 47-year-old immunocompromised man following MMR, hepatitis and varicella vaccines. The man, who was clinically healthy despite a localised recurrence of diffuse large B cell lymphoma, had received chemotherapy and an autologous HSCT four years prior to the vaccinations. Three months following the vaccination with varicella vaccine, he developed a HZ rash on his forehead and although he was repeatedly treated with antiviral medication, the HZ became disseminated with multiorgan involvement. The VZV was identified as a vaccine strain of Oka varicella virus and was found to have become acyclovir resistant.[26]

4.5.5 Use in patients with Human Immunodeficiency Virus (HIV)

Cases of disseminated vaccine varicella have been reported in patients with undiagnosed HIV infection. A South Asian man in a US military base in Afghanistan developed varicella two days following the second dose of varicella vaccine, given one month after the first. The patient required mechanical ventilation. Although a previous HIV test was negative, subsequent viral tests conducted found him to be HIV positive.[27]

4.5.6 Use in patients with DiGeorge Syndrome

DiGeorge syndrome (DGS) is a congenital disorder characterised by cellular immune deficiency. In a US-based retrospective cohort study of 194 patients (age between 0 – 31.5 years) with DGS, 75% received varicella vaccine as part of routine immunisations despite recommendations to the contrary. Adverse events were seen in 20% of those vaccinated, but no SAE were causally associated with live varicella vaccine. The study concluded that live vaccines may be given to some patients with DGS with mild-to-moderate immunosuppression and that receipt of MMR and varicella vaccines may outweigh the risk of wild-type disease. MMRV vaccine was not investigated.[28]

4.5.7 Use in children following liver transplantation

A Japanese study in 39 paediatric living donor liver transplant recipients (median age of transplant 17 months, range 3-202 months) found varicella vaccine to be safe when given at least a year post-transplant (median 18 months) to children who were not severely immunosuppressed. The children received both live measles-rubella, mumps and varicella vaccines, and inactivated hepatitis B, DTaP-IPV and Japanese encephalitis vaccines. No serious adverse events were associated with immunisation. One patient, who had not been immunised pretransplant, developed varicella 30 days after receiving post-transplant vaccination; it was not determined if this was vaccine or wild type virus.[29]

4.5.8 Vaccine-related herpes zoster

Herpes zoster following receipt of varicella vaccines is documented to occur, although it is important that the vaccine-virus is proven to be causative as acquisition of asymptomatic wild type VZV prior to vaccination is also possible and may be more likely to be precedent to HZ.

Since 2013, two cases reports describe HZ following receipt of varicella vaccine in the US. One was a 17 month-old, previously healthy child who developed HZ due to vaccine-type VZV 37 days after vaccination on the leg where the vaccine was administered.[30]

A six year-old child developed HZ ophthalmicus and stromal keratitis one year after a two-dose course of varicella vaccine in the US. However, the strain of VZV was not determined.[31]

A study, which enrolled 322 subjects through electronic medical records during 2005-2009 in the US, found that the incidence of HZ was 79% lower in vaccinated children (aged 0-17 years) than unvaccinated children, and that around half of the HZ cases in 118 vaccinated children was due to wild-type VZV. The incidence of laboratory-confirmed HZ was 48 per 100,000 person-years in vaccinated children (vaccine and wild-type VZV) and 230 per 100,000 person years in unvaccinated children (wild-type only). Of the specimens collected, 84% were wild-type VZV, 15% were vaccine strain and 1% was a possible vaccine-wild-type recombinant.[32]

4.6   Safety of MMRV and MMR+V

Most of the recent safety studies of varicella vaccines have focused on the combined measles-mumps-rubella-varicella vaccine (MMRV) and concomitant use of MMR and varicella vaccines (MMR+V).

4.6.1   Use of MMRV or MMR+ V in children aged 9-24 months

A systematic review was conducted by SAGE to inform a WHO position statement on varicella vaccination. Several clinical trials, comparing MMRV and MMR+V (the two vaccines given concomitantly but in separate limbs), found significantly higher rates of fever after the first dose of MMRV. The incidence of fever was lower and comparable following the second dose. No SAE were observed following MMRV administration in ten small and one large clinical trials (<2,620 participants in total). However, in two larger trials (with 5,833 and 3,927 participants) increased incidence of fever was reported. Other SAE included febrile seizure, cough and bronchiolitis in the MMRV groups. Febrile seizures have been reported in a range of clinical trials. A review of MMRV safety reported that the risk of febrile seizures in children aged from 12 to 23 months receiving MMRV was 7-9 per 10,000 recipients compared with 3-4 per 10,000 children following delivery of separate simultaneous MMR+V vaccines. The peak time for the risk of febrile seizures was found to be 5 to 12 days after vaccination. Through a large retrospective cohort study and post-market surveillance, no increased risk of febrile seizures was seen for children aged 4-6 years with MMRV. The increase in risk of febrile seizure for children aged 12-23 months was determined to be one additional febrile seizure for every 2,300 MMRV doses.[14]

An open-label RCT compared the safety of MMRV (Priorix-Tetra®) vaccine with MMR+V (Priorix® plus Varilrix®) in 458 Korean children aged 11-23 months. Fever was observed on days 0-14 for 59% of the MMRV recipients (95% CI 53.3-64.6, n=310) and 39% of MMR+V group (95% CI 31.4-47.0, n=159), and fever of 39.5°C or higher was seen in 12.3% of MMRV and 6.9% of MMR+V group (95%CI 8.8-16.4 and 3.5-12.0, respectively). The incidence of rash was comparable between the groups (MMRV 10.6%, MMR+V 10.1%). One child in the MMRV group was hospitalised with a fever four days after vaccination; this was the only SAE related to vaccination. Other SAE, reported in 37 participants (25 in MMRV group, 12 in MMR+V group), included gastroenteritis and bronchopneumonia.[33]

A retrospective cohort study of Vaccine Safety Datalink data examined the incidence of fever and febrile seizures in 840,348 children aged 12 to 23 months who received a measles containing (MMR, MMR+V and MMRV) vaccine during 2001-2011. The study found that

incidence of fever declined steadily from 12-13 months to 19-23 months of age, and the incidence of seizures was highest in children age 16-18 months. The relative risk of seizures during days 7-10 after vaccination was significantly greater in children age 16-23 months than those aged 12-15 months. The findings were consistent with other studies in showing that the incidence of fever and seizures was significantly greater following MMRV administration when compared to MMR+V. The number of excess cases of seizures was 4.2/10,000 doses of MMRV in the 12-15 month age group and 9.0/10,000 doses in the 16-23 month olds; however this difference was not significant (p=0.2). The authors conclude that this study highlights gains in the timely immunisation of children with the first dose of a measles-containing vaccine in accordance with the US schedule at 12-15 months.[34]

Another Vaccine Safety Datalink data study, which included a 323,247 cohort of children born in the US during 2004-2008, showed that a delay in first MMR vaccine dose until 16 months or older increased the relative risk for seizures by three times compared with on-time immunisation. For the first MMR dose, the incidence risk ratio for seizures (IRR) at 12-15 months was 2.65 (95% CI 1.99-3.55); at 16-23 months IRR = 6.53 (95% CI 3.15-13.53). However, use of MMRV doubles the risk of seizures compared with MMR at both 12-15 months (IRR = 4.95; 95% CI 6.68-6.66) and 16-23 months (IRR = 9.80; 95% CI 4.35-22.06). The authors concluded that later vaccination results in more post-vaccination seizures than the scheduled on-time vaccination in the second year of life.[35]

A meta-analysis of 19 RCTs found comparable overall safety profiles for single doses of MMRV and MMR+V in healthy children, although higher incidence of fever and measles or rubella-like rashes were seen in the MMRV groups. Pooled incidences of fever were observed in around 60% of MMRV groups and 50% of MMR or MMR+V groups; half of the events were considered to be vaccine related (pooled relative risk [RR] 1.12 – 1.60). Pooled incidence of rash ranged from 11% - 20% in all groups, and around one third of rash events were vaccine-related. The incidence of measles/rubella rash was only found to be significant following Merck MMRV vaccine compared with MMR+V (RR=1.61; 95% CI 1.16-2.22, p=0.004). For varicella-like rash, a significant increase in incidence was only seen following GSK-MMRV compared with MMR+V (RR=1.86; %95% CI 1.12-3.30; p=0.020). The incidence of any SAE was around 1% across all groups, one-tenth were considered vaccine related. Febrile seizures represented around half of the vaccine-related SAE (<0.8 per thousand in MMRV and <0.5 per thousand MMR or MMR+V groups). No vaccine-related SAE were reported in any of the studies.[36]

4.6.2   Use of MMRV in combination with hexavalent vaccine (DTaP-IPV-HepB/Hib)

In an RCT of 960 children aged 12-23 months conducted in Germany and Italy, the safety of concomitant administration of MMRV (ProQuad®) and hexavalent DTaP-IPV-HepB/Hib vaccine (Infanrix-hexa®) was examined. The children randomised to three groups: group 1 received ProQuad and Infanrix-hexa concomitantly at different injection sites (n=474); group 2 received ProQuad alone (n=234), and group 3 received Infanrix-hexa alone (n=239). The study found that the safety profile of MMRV was comparable for all groups and in line with the known safety profile for ProQuad when given as a first dose (as given in Summary of Product Characteristics). The frequency of systemic AE related to MMRV was similar for both MMRV groups (70% of group 1 vs 65% of group 2), these included fever (24.1% vs 21.4%), vaccine-associated rashes (measles 4.6 vs 5.6%, rubella 2.5 vs 2.1% and varicella 1.5 vs 0.4%) and irritability (5% vs 3%). The highest incidence of fever following MMRV administration occurred on days 7-9: on day 8, almost 35% of children in group 1 and approximately 33% in group 2 had experience a fever (≥38°C). Two cases of febrile convulsion were reported for group 1. No children were withdrawn from the trial or

died as a result of an adverse event. The authors reported that there was a lower incidence than expected of some vaccine-related systemic adverse events (rash, upper respiratory tract infection, vomiting and diarrhoea) in those who received MMRV vaccine.[37]

4.6.3 Use of two doses of MMRV in children in the second year of life

Data was analysed from five RCTs, consisting over 11,800 children aged from 12 months to 6 years, to examine the safety of two doses of MMRV (ProQuad®) given in the second year of life. A second dose of MMRV was administered to 2780 out of 3112 children who had receive a dose of MMRV 3-6 months previously. At least one AEFI, including injection site reactions, was reported for 70.5% of these children after the first MMRV dose and for 57.7% following the second dose. Of the 22 subjects who reported SAE after dose one, nine had received MMRV alone. The only SAE report that was considered MMRV vaccine related was of a child who had fever and febrile seizure 7 days after vaccination. Three of the remaining 13 SAE were deemed related to other vaccines given with MMRV. SAE were reported for six children following the second MMRV dose, none were considered vaccine related. Measles-type rash was the most commonly reported vaccine-related rash. In these studies, no mumps-like symptoms or HZ-like rashes were reported. Out of ten reported febrile seizure cases, only three were possibly vaccine-related following MMRV administration, with or without other vaccines. The rate of febrile seizure incidence was 0.26% (8/3019) post dose one and 0.07% (2/2695) post dose two of MMRV. All cases of febrile seizure, vaccine related or unrelated, resolved without sequelae. The authors conclude that the risk of febrile seizure is relatively low for any individual child, even though there is a small increase in risk of febrile seizure following dose one MMRV compared with giving the component vaccines separately.[38]

Further meta-analysis, as reported by Ma et al, investigated the safety of MMRV administered as a second dose following MMR, MMR+V or MMRV in healthy children. In nine RCT, children aged 9-24 months received two doses of MMRV vaccines with an interval of 4 weeks to 6 months between doses. The second doses were well tolerated, although local injection site symptoms were more frequently reported following the second dose than the first dose of MMRV in most studies.[36]

No new safety concerns were identified in a study comparing MMRV and MMR+V when given to children aged 12 – 23 months in the US Vaccine Safety Datalink from 2000-2012. The study evaluated 123,200 doses of MMRV and 584,987 doses of MMR+V and found for seven main adverse outcomes (considered theoretical/ biologically plausible for MMR and varicella vaccines) that the risks were low (few or zero events) and were not significantly different. For data limited to October 2008 – June 2012, this study confirmed an increased risk of seizure and fever 7 -10 days post vaccination following MMRV compared with MMR+V (fever RR=1.16, [95% CI 0.96-1.39]; seizure RR=1.99 [95% CI 1.08-3.53]).[39]

No recent studies were found investigating the safety of MMRV following the second dose given at 4-6 years of age. The incidence of febrile seizure is lower in general for older children than at 12-15 months and previous studies have found that a second dose of MMRV is less likely to cause fever than the first dose at any age, so is not considered a concern for this age group. No other adverse events were identified in the literature for this age group.

4.7 Summary of vaccine safety

The WHO SAGE systematic review of RCT, observational studies and post-licensure studies, identified no serious AEFI associated with the use of varicella vaccines.

As previously reported, there is an increased risk of febrile seizures following administration of MMRV in children age 12-23 months, at around 7-9 cases per 10,000 recipients compared with 3-4 per 10,000 children following delivery of concomitant MMR+V or MMR alone. This increase in risk is relatively low for each individual. Febrile events are significantly associated with the first dose of MMRV in young children, however, for the second dose the risks of fever and febrile convulsion are lower and equivalent to MMR+V. It appears that the risk of febrile seizure is higher in the 16-23 month age groups than for the younger 12-15 month infants, therefore timely administration at a schedule of 12-15 months would be important if MMRV is given as the first dose to this age group rather than MMR+V.

Most of the safety concerns are restricted to immunocompromised individuals. A summary of these concerns are listed below:

- The risks of complications from varicella disease are greater than the risk from the vaccine VZV.
- Cases of disseminated vaccine-associated varicella infections have been reported in immunocompromised children and adults.
- Immunocompromised individual may not mount an adequate primary immune response to prevent breakthrough disease.
- Hospitalised cases risk transmitting vaccine-type varicella to other immunocompromised patients.
- Antiviral treatment is recommended in cases of breakthrough disease or vaccine-associated varicella.

Case by case decisions should be made about administering varicella vaccine to those with mild-moderate immunosuppression or deficiencies.

5 Immunogenicity and effectiveness in disease control

5.1 Objective

The objective of this section is to review the most recent immunogenicity and effectiveness data for currently licensed varicella vaccines. The focus will be on the effectiveness and duration of protection in reducing the incidence of varicella and disease severity in children and immunocompromised recipients. Consideration is to be given to relevant immunogenicity data, efficacy and effectiveness studies that contribute to the current understanding of the effectiveness of varicella vaccines, evidence for the non-inferiority of alternative schedules and the implications of a two-dose schedule.

5.2 Outcomes

The outcomes considered for this review are a summary of the results of studies and reviews on the immunogenicity, and effectiveness and efficacy of one or two doses of varicella vaccines in preventing varicella, VZV associated morbidity and mortality.

5.3 Immunogenicity

5.3.1 Immunogenicity of MMRV vaccine in children

A meta-analysis of 19 RCTs found comparable immunogenicity following single doses of MMRV and MMR+V in healthy children, with similar seroconversion or seroprotection rates and comparable geometric mean titres (GMT) for the four viruses.

Seroprotection rate for varicella was used in the Merck-MMRV studies (% of subjects who were seronegative at baseline with post vaccination antibody titre ≥5 units/ml) and seroconversion rate was used by GSK (% of initially seronegative subjects with post vaccination titres above assay cut-off). The rates of both were above 91% in all groups in 15 RCTs (total numbers: Merck-MMRV = 3874, MMR+V = 1578; GSK-MMRV = 3909, MMR+V = 1571). No significant difference in varicella seroconversion between GSK-MMRV and MMR+V was seen. The varicella seroprotection rate for Merck-MMRV was found to be lower than that of MMR+V (RR=0.96; 95% CI 0.91-1.0; p=0.05) – this difference may be related to the use of a lower VZV titre vaccine formulation used in early prelicensure studies. No significant difference in anti-varicella antibody GMT was seen between MMRV and MMR+V groups in eight RCTs.

Nine RCTs investigated the immunogenicity of MMRV when given as second dose following MMR, MMR+V or MMRV vaccines to healthy children aged 9 to 24 months. Meta-analysis found that MMRV given as a second dose 4 weeks to 6 months after the first dose elicited strong immunogenicity against the four vaccine diseases and 95-100% seroconversion rates with up to 41.6-fold higher anti-varicella GMTs than compared with a single vaccine dose. A second dose of MMRV, given 4 weeks to 6 months after the first, increased anti-varicella GMT by 10.4 fold (95% CI 8.65-12.41) compared with a 5.2-fold increase for two doses of MMR+V (95% CI 4.14-6.53), and compared with 2.2-fold increases for the GMTs of the other 3 MMR viruses after the second dose in both groups. Five RCTs, not included in the meta-analysis, also indicated that MMRV vaccine was more immunogenic as a second dose after MMR or MMR+V in children aged 15 months to 6 years.[36]

An open-label RCT compared the immunogenicity of MMRV (Priorix-Tetra®) vaccine with MMR+V (Priorix® plus Varilrix®) in 458 Korean children aged 11-24 months. Based on seroconversion rates MMRV was found to be non-inferior to MMR+V for measles (98.0% vs 99.4%), rubella (99.7% vs 100%) and varicella (98.9% vs 100%, respectively), but not mumps (88.8% vs 94.2%), based on a lower 95% CI group difference of greater than -10%. However, the anti-mumps GMTs were comparable between the two vaccines groups and post hoc assay analysis showed non-inferiority.[33]

5.3.2 Immunogenicity of MMRV in combination with hexavalent (DTaP-IPV-HepB/Hib) vaccine

In a RCT conducted in Germany and Italy of 960 children aged 12-23 months, the immunogenicity of concomitant administration of MMRV (ProQuad®) and hexavalent DTaP-IPV-HepB/Hib vaccine (Infanrix-hexa®) was examined. The children were randomised to three groups: group 1 received ProQuad and Infanrix-hexa concomitantly at different injection sites (n=474); group 2 received ProQuad alone (n=234), and group 3 received Infanrix-hexa alone (n=239). The study found that concomitant administration was non-inferior to that of the individual vaccines. The antibody response rates six weeks after vaccination were non-inferior for both MMRV groups (group 1: measles 97.4% [95% CI 95.4-98.7], mumps 96.7% [94.6-98.2], rubella 97.9% [96.1-99.0] and varicella 97.7% [95.7 - 99.0]; group 2: measles 96.3% [95% CI 92.8-98.4], mumps 98.6% [95.9-99.7], rubella 99.1% [96.7-99.9] and varicella 95.1% [91.2-97.6]). The immunogenicity was not

affected by differences in hexavalent schedules (two or three doses) in the different countries and were comparable.[37]

5.3.3   Varicella immunity in healthcare workers

A prospective study in the US investigated the serology of 101 healthcare workers (median age 30 years [range 18-70]) who had received two doses of varicella vaccine administered 4-8 weeks apart. The study found that 12% of participants were varicella-antibody seronegative a median of 4 years after immunisation. The most recently vaccinated (<5 years) were twice as likely to be VZV seropositive than those vaccinated more than 5 years previously. Healthcare workers with direct patient contact were three times more likely to be seropositive. Antibody avidity was moderate to high in 88.5% of participants and low in 11.5%. All sera from control adults (n=142) with previous wild-type VZV infection had higher VZV IgG antibody levels, and 93% had high and 7% had moderate antibody avidity. The authors suggest that inadequate priming of cell-mediated immunity and antibody maturation may play a role in breakthrough varicella infections following vaccination.[40]

5.3.4   Immunogenicity in special groups

5.3.4.1 Immunogenicity of varicella vaccine in liver transplant recipients

A Japanese study showed that 70% (23/33) of paediatric living-donor liver transplant patients were able to seroconvert following receipt of one dose of varicella vaccine an average of 99 months after transplant. A total seroconversion rate of 81% (43 seroconverted out of 53 immunisations) was achieved by repeated immunisation of those who did not seroconvert after the first dose (30%, 10/33). Three mild breakthrough varicella cases were reported.[41]

5.3.4.2 Immunogenicity in autologous haematopoietic stem cells transplant (HSCT) recipients

Two doses of varicella vaccine (Varilrix®) were shown to be poorly immunogenic when given to 45 Australian adults at 4.5 and 6.5 months post autologous HSCT. Anti-VZV IgG antibodies and cell-mediated immunity were assessed in 19/45 patients. The mean age was 50.1 ± 8.4 years. All patients were seropositive for anti-VZV antibodies prior to vaccination (GMT 1024.0; 95% CI 481.8 -2176.2), however, these waned over time. Two out of 10 patients elicited a vaccine response two months after dose 1 (GMT 675.6; 95% CI 179.3-2545.2), and 1 out of 15 patients responded 1.5 months after dose 2 (GMT 707.5; 95% CI 308.0-1625.5). All nine patients for whom samples were obtained had VZV-specific $CD4^+$ T cells, and for an undetermined reason given the decline in GMT following vaccination, these cells expressed cytokine activation markers following stimulation with VZV antigens (gE_125 and VZV_100) at all time points; antigenic stimulation did not induce any $CD8^+$ T cell responses. This study found that up to six months after HSCT, the immune system of most of these patients was not sufficiently mature to generate an effective response to varicella vaccination, and that administering varicella vaccine within six months of HSCT was ineffective. This theory was supported by the lack of VZV-specific CD8 T cell responsiveness and the observation that two patients developed wild-type varicella after completing the vaccination course.[25]

5.3.4.3 Immunogenicity and effectiveness in children with juvenile idiopathic arthritis

Specific antibody production after varicella vaccination was determined in a prospective study of six children aged 2.5 - 7 years with stable juvenile idiopathic arthritis receiving biological therapy (etanercept, tocilizumab or infliximab) in Slovenia. Following two doses of varicella vaccine, five (83%) of patients had protective varicella antibodies after six weeks.

Two patients being treated with tocilizumab had low antibodies after the first dose (220 and 150 mIU/ml, respectively) and very high levels after dose 2 (1800 and 2500 mIU/ml), whereas two patients who received etanercept had low protective antibody levels after two doses (460 and 170 mIU/ml; cut-off for protection 106 mIU/ml). Antibody levels declined in all patients within two years of immunisation, although during long term follow-up only one patient receiving etanercept developed varicella 4 months after the second dose. The authors concluded that production of specific antibodies was not always at protective levels following varicella vaccination and was heterogeneous between patients, hence, case-by-case considerations are needed as to whether to vaccinate children on biological therapy at risk of exposure.[23]

5.3.4.4 Immunogenicity in children on chemotherapy for cancers

A prospective cohort study in the Netherlands demonstrated immunogenicity to VZV when varicella vaccine was given to closely monitored paediatric oncology patients without interruption to chemotherapy. Of these varicella-seronegative children, 24 were being treated for haematological malignancies (mean age 4.1 years [range 2.9-16.9]) and 7 for solid tumours (mean age 2.9 years [1.8-5.3]). Following one dose of vaccine, 14 out of 31 patients (45%) seroconverted with VZV IgG (41.5% of those with haematological malignancies, 57.2% with solid tumours). Twenty patients were revaccinated after 3 months because they did not seroconvert or did not have sustained seropositivity (5 and 15 patients, respectively); the final seroconversion rate was 70% after a second dose (10/15 [67%] of the patients with haematological malignancy and 4/5 [80%] of those with solid tumours). VZV-specific CD4+ T cells were detected in 20 out of 26 patients available for testing and seven of these remained VZV-seronegative. All the patients tested (11/11) who received a second dose of vaccine showed VZV-specific CD4+ T cells, four of whom remained VZV-seronegative. The authors concluded that VZV vaccination of paediatric oncology patients without interruption of chemotherapy induced adaptive immunity despite incomplete seroconversion.[22]

5.4   Review of Efficacy and Effectiveness

The effectiveness of single doses of varicella vaccines are around 80% for all varicella cases. Breakthrough cases do occasionally occur, although these are less severe in vaccine recipients than varicella in those are unvaccinated. Against severe disease, the effectiveness of a single dose increases to up to 99%. Two doses provide the greatest effectiveness against all varicella and severe disease.

5.4.1   Efficacy of two doses of MMRV compared with one dose of MMR and Varicella

A clinical trial conducted in ten European countries compared the efficacy of one dose of monovalent varicella vaccine and MMR with two doses of MMRV in varicella naïve children. A total of 5285 children, aged 12-22 months, were randomised 3:3:1 to receive vaccinations given 42 days apart, either a) two doses of MMRV, b) MMR dose 1 and monovalent varicella at dose 2 (MMR/V), or c) two doses of MMR alone. During a mean follow-up period of 36 months, 37 varicella cases were reported (of which two were moderate-severe) in the MMRV group, 243 (37 moderate-severe) cases in MMR/V and 201 (117 moderate-severe) cases in MMR group. Vaccine efficacy following two-dose MMRV was calculated to be 94.9% (97.5% CI: 92.4-96.6; p<0.0001) against all varicella and 99.5% against moderate-severe disease (97.5-99.9; p<0.0001). Vaccine efficacy for one-dose MMR/V against all varicella disease was 65.4% (57.2-72.1; p=0.126), which was not significantly different from MMR alone

controls, and 90.7% for moderate-severe (85.9-93.9, post hoc).[42] Note that this trial did not administer MMR and V concomitantly, rather 42 days apart.

5.4.2   WHO systematic review of varicella vaccine effectiveness

The WHO Strategic Advisory Group of Experts on Immunisation (SAGE) conducted a systematic review to assess the effectiveness of varicella vaccines, including combinations such as MMRV, the duration of protection and the impact of varicella vaccines on vulnerable populations. A total of 40 post-licensure studies and review articles were used. This review concluded that varicella vaccine is effective in preventing varicella in immunocompetent individuals, although the duration of protection has not been defined, and that a two-dose regimen is better than a single dose.[43]

5.4.2.1 WHO systematic review: Effectiveness and duration of protection of a single dose

Most studies reviewed by SAGE were conducted in the US and evaluated Varivax®; studies conducted elsewhere assessed Varilrix®, Okavax® and other varicella vaccines. Overall, the review found a single dose of varicella vaccine to be moderately effective for preventing any severity of varicella (around 80%) in immunocompetent individuals, highly effective for preventing moderate-severe disease (around 95%) and highly effective in preventing severe disease only (approximately 99%).

The duration of protection data following a single dose of varicella vaccine is conflicting. Some studies suggest that there is a waning of immunity whereas others indicate long–term protection. Differences in cohort and time definitions make comparisons between studies difficult. However, the overall conclusion is that breakthrough disease does not become more severe with time and is generally milder for vaccinated individuals compared with unvaccinated, who are more likely to develop moderate to severe disease. The circulation of wild-type varicella and possible natural boosting of immunity confounded these studies.[43]

5.4.2.2 WHO systematic review: Effectiveness and duration of protection of two doses

Few studies were available at the time of SAGE systematic review to evaluate the effectiveness of two doses of varicella vaccines. Overall, the review concluded that better protection was afforded by two doses of any varicella vaccine than one dose of any varicella vaccine (93% compared with 80%, respectively). Estimates for vaccine effectiveness (VE) against severe disease in one study were 100% following two doses of Varivax®.

At the time of this systematic review, the duration of protection of two doses of varicella vaccine was difficult to determine since there were few studies directly comparing one dose with two doses and the timing of the second dose was not consistent between studies. One ten year follow-up study found that children who received two doses of varicella vaccine did not develop breakthrough infection seven to ten years post vaccination, whereas within the same timeframe, breakthrough cases were reported for those who only received one dose. In this study, no severe disease was reported for children who received two doses of varicella vaccine and these children were 3.3 times less likely to develop breakthrough disease of any severity than those who received a single dose. Similarly, no breakthrough cases were seen in a 14 year study in children who had received two doses of varicella vaccine.

Only two studies were identified that looked at the VE of varicella vaccines in adults. Although these studies did not distinguish between one, two or three doses of vaccine, both studies reported if there was breakthrough disease it was mild, as seen in children, and breakthrough disease did not increase in severity with time.

SAGE concluded that the majority of studies reviewed support the introduction of a second dose into routine immunisation schedules. [43] These findings are in line with our previous antigen review conducted between 2009 and 2012.[5]

5.4.3   Effectiveness of one dose of varicella vaccine in children.

A global meta-analysis was conducted to assess varicella VE amongst healthy children. The study found that the pooled VE for one dose was 81% (95% CI 78-84%) against all varicella and 98% (95% CI 97-99%) against moderate-severe varicella, and had a median VE 100% (mean 99.4%) against severe varicella. The VE against all varicella was improved by a second dose to 92% (95% CI 88-95%). These estimates were primarily within the first decade post vaccination and two-thirds of the studies included were conducted during outbreak investigations which may result in underestimation of the performance of the vaccine. The studies used in the meta-analyses originated from the US, China, Germany, Israel, Italy, Spain, Taiwan, Australia, Turkey and Uruguay. It was noted that most studies were conducted in high-income countries and none in low-income countries.[44]

The effectiveness of varicella vaccination was assessed in Puglia, Italy during 2006-2012. Universal varicella vaccination was begun in 2006 in this region; MMRV replaced MMR + V in 2009 given at 13 months of age and a second dose of MMRV or MMR+V was given at 5-6 or 11-12 years of age. Coverage of one dose of varicella vaccine by the age of 24 months increased from 49% in 2006 birth cohort (given at age 15 months) to 91% in the 2010 cohort (given as MMRV at age 13 months). Two-dose coverage was 64.8% in the 2005 birth cohort. The study found that the VE of one dose of varicella vaccine against all varicella disease was 98.8% and against severe hospitalised disease was 99%. The number of reported varicella cases decreased from 7330 in 2004 to 234 in 2012, and varicella hospitalisations fell from 216 in 2004 to 22 in 2012. This decrease was most significant in the 1 – 4 year-old age group.[45]

A matched case-control study found that one dose of varicella vaccine was 83.4% (95% CI 71.4-90.3) effective in elementary schools and daycare centres in China. Breakthrough varicella was significantly associated with receipt of the vaccine more than five years prior to the outbreak, but not with age of vaccination (VE 47% at ≥5 years after vaccination). Vaccination coverage varied widely across the schools (mean 41%; range 0 - 93.8%).[46]

Vaccine effectiveness of one dose against hospitalised varicella was assessed in children aged 19 months to 10 years in Australia during August 2007 to December 2014. Using the Paediatric Active Enhanced Surveillance (PAEDS) network data, 121 hospitalised cases of varicella were identified. Based on these, VE was estimated to be 75.7% (95% CI 61.1-84.8%), and 82.6% (95% CI 66.8-90.8%) when restricted to immunocompetent children only.[47]

5.4.4   Effectiveness of one dose of vaccine in adolescents and adults

From 2008-2011 in Beijing, a total of 3195 varicella cases were reported in one district; 221 (6.9%) of cases were adolescents aged 15-19 years and 252 (7.9%) were adults over 20 years of age. One dose varicella of vaccine had been received by 40 (8.5%) cases and 433 (91.5%) were unvaccinated. The mean time for disease onset following vaccination was 5.7 ± 4.4 years (range 6 months to 12 years, excluding one case that developed varicella less than 42 days after vaccination). Of the 39 breakthrough cases, 18 had received a single dose of vaccine over the age of 15 years of age (mean 18.3 ± 3 years) as a catch-up. The incidence of moderate-severe cases was 19.2% lower in the breakthrough case group than the unvaccinated cases. VE for one dose was calculated to be 55.4% against moderate-severe disease in adults and adolescents.[48]

5.4.5   Breakthrough varicella infection following single dose of vaccine

A study in Turkey investigated hospitalisations due to breakthrough cases of varicella in previously immunised children from 2008-2013, prior to introduction of routine varicella vaccinations. Out of 1939 children who were hospitalised due to varicella infection, 36 had received a single dose of varicella vaccine approximately 5 years previously. Underlying immune compromising disease was present in 14 of these children (10 were healthy when they received the vaccine). During the time period of this study, fewer than 10% of children in Turkey had been vaccinated against varicella. A follow-up study is being conducted since the introduction of the varicella vaccine at 12 months of age to the immunisation schedule in 2013.[49]

In a preschool in Beijing, China, the index case of an outbreak of varicella was identified as a child who had been vaccinated four years previously. A total of 12 cases occurred, ten of which had breakthrough varicella. Out of 150 children at the preschool, 135 (93.7%) had been vaccinated with one dose of varicella vaccine and none had prior history of varicella disease. The authors concluded that breakthrough infections may be as infectious as varicella infections in unvaccinated persons, and suggested that a second dose of vaccine may help to control an outbreak.[50]

A US case report described life-threatening breakthrough wild-type varicella in two children (aged 3 and 15 years) with cancer. Both children had been vaccinated with a single dose of vaccine prior to the onset of cancer. The authors suggested that the same varicella prophylaxis as used for unvaccinated immunocompromised children should be applied to high-risk immunocompromised children who have received one dose of varicella vaccine.[51]

A retrospective case-control study examined breakthrough varicella infection in children aged 1-15 years at least 42 days after one dose of varicella vaccine in Italy. The study included 45 breakthrough cases and 135 vaccinated matched controls in the same school or kindergarten class without symptoms. No differences were seen in the proportion of cases or controls reporting allergies, asthma or hospital admissions, however, the proportion of those with chronic illness was higher among the varicella cases than the controls (p=0.002). In this study, breakthrough disease was significantly associated with the time in months from vaccination to VZV exposure (OR 1.02, 95% CI 1.001-1.04, p=0.04), not potential risk factors.[45]

5.4.6   Effectiveness of one dose of varicella vaccine during an outbreak in adult detainees

The use of varicella vaccination during an outbreak of varicella in two Israeli detention centres for 2500 illegal immigrants from Eritrea and Sudan was described. Over a seven month period, June – December 2012, 109 men aged 18-40 years were diagnosed with varicella and placed into quarantine until resolution of disease. Vaccination of all susceptible detainees was initiated in late December (no staff were susceptible). Within two weeks of completion of the first dose of vaccine, despite 15.6% of detainees declining immunisation, there was only one additional case reported of a detainee vaccinated 13 days prior to diagnosis. These results demonstrate the effectiveness of varicella vaccine in controlling an outbreak in susceptible adults by reducing disease circulation. The authors recommended early immunisation during an outbreak or cluster of connected varicella cases in a closed-residential setting.[52]

5.4.7   Effectiveness of two doses varicella vaccine in children

A case-controlled study conducted in Navarre, Spain, found VE of one dose of varicella vaccine to be 87% (95% CI 60-97%; n=5 cases, 112 controls) in children aged 15 months

to 10 years and 97% (95% CI 64-94%; n=1 case, 63 controls) following two doses. Universal varicella vaccination (one dose at 13 months of age) was introduced in Navarre in 2007 and a second dose was added at 3 years of age in 2009. During 2009-2011, vaccination coverage was 95% for dose 1 and over 89% for dose 2. Over the study period 2010-2012, 70 clinical cases of varicella were reported and 54 were confirmed as VZV by PCR (89% unvaccinated, 38% of vaccinate cases). Each of these confirmed cases were matched with eight controls; none of whom required hospitalisation or treatment for varicella complications. A decline in VE was observed after 36 months following one dose, however, the number of cases was very small (VE 61%; n=3 cases, 35 controls). [53]

Universal two-dose varicella vaccination has been recommended in the US since 2006. A case-control study was conducted in schools in West Virginia, US, from January 2010 to May 2011. The VE of two doses of varicella vaccine and rash severity was assessed in varicella outbreaks in school settings. During this period, 266 varicella cases were reported across 30 schools; 133 cases out of 163 who were contactable were included in the study together with 365 matched controls with an average age of 11 years. Significantly more cases were unvaccinated and more controls had received two doses of vaccine. VE against all varicella disease was 83.2% (95% CI 69.2-90.8%) for dose 1 and 93.9% (95% CI 86.9-97.1%) for dose 2. One dose was 88.2% effective in preventing moderate-severe varicella and two doses were 97.5% effective. VE following one dose declined with time to 81.8% after more than 10 years (p<0.001 for trend). No difference was observed between one dose and two doses for rash severity, although no severe rash cases were observed following two-dose vaccination compared with two (3.6%) one-dose cases and five (8.8%) of unvaccinated cases. Of the unvaccinated cases, 33% had moderate-severe rash, compared with just 5.5% of one-dose recipients and 5% of two-dose recipients. The authors concluded that both one and two-dose varicella vaccinations were highly effective in preventing varicella; two doses provided greater protection than one dose. [54]

A population-based observational study in Germany compared the vaccine effectiveness (VE) of one or two doses of varicella vaccine. From 2004, one dose of varicella vaccine was recommended for all children aged 11-14 months, then from 2009, two doses were recommended for children aged 15-23 months with at least 4 weeks between doses. Individual catch-up of missed doses was recommended before the 18th birthday. By 2013, 82.7% of children aged 4-7 years had received one dose and 76.8% of children had received 2 doses. The study found that the overall estimated VE for one dose was 86.6% (95% CI 85.2-87.9) and the overall estimated VE for two doses was 97.3% (95% CI 97.0-97.6). The incremental increase in effectiveness of a two-dose schedule was calculated to be 84.6% compared with a single dose. The authors conclude that a schedule whereby a second dose given early in life is as effective as a second dose given 3-5 years after the first. [55]

5.4.8   Effectiveness in liver transplant patients

A Japanese study investigated the effectiveness of varicella vaccines in 39 paediatric living-donor liver transplant recipients (median age of transplant 17 months, range 3 - 202 months) when given at least a year post-transplant (median 18 months) to children who were not severely immunosuppressed. In this study, the children received live-attenuated measles-rubella, mumps and varicella vaccines, and inactivated hepatitis B, DTaP-IPV and Japanese encephalitis vaccines. Overall, seroprotection rate following post-transplant immunisation with live vaccines was 47% (9/19) for varicella vaccine, 54% (14/26), 100% (27/27), 64% (16/25) for measles, rubella and mumps, respectively; seroconversion for each of the inactivated vaccines was over 80%. Following a first dose of varicella vaccine, seroprotection criteria was met in 32% (6/19) patients. A second vaccination was given when antibody titres did not reach seroconversion cut-off, following which seroprotection

was achieved in half of the second dose recipients (5/10); seroprotection was achieved in just 25% (1/4) of those who received a third vaccine dose. The seroprotection rates following live vaccines were lower than previously reported in other studies of transplant patients, which may have been as a result of higher seroconversion cut-off rates than in other studies. However, the authors conclude verification of seroprotection should be measured routinely when live vaccines are given in these groups. [29]

5.5   Summary of immunogenicity and effectiveness

Seroconversion rates in immunocompetent children are at least 95 – 100% following two doses of either MMR+V or MMRV. There is no evidence of a significant difference in immunogenicity against varicella between the first doses of MMR+V or MMRV. When given as a second dose, MMRV may be more immunogenic than MMR+V. MMRV has comparable immunogenicity to MMR or MMR+V in healthy children against measles, mumps and rubella.

There does not appear to be a difference between concomitant MMR+V, varicella vaccine alone or combined MMRV in the protection against varicella. A large clinical trial found the efficacy of two doses of MMRV was shown to be 94.9% against all varicella and 99.5% against moderate-severe disease.

Varicella vaccines are highly effective in preventing moderate-severe varicella (95-99%). One dose schedules provide less prolonged protection than two-dose schedules and are less effective against all cases of varicella (around 80%) than against severe disease. However, when breakthrough cases do occur, particularly for those recipients whose immunity is not sufficiently primed by the first dose, they are usually mild and do not worsen with time post-vaccination. Two-dose schedules provide longer lived protection against varicella and severe disease (around 93% for all varicella cases). There is not sufficient data to gauge the duration of protection following two doses of a varicella vaccine, but one study demonstrated no breakthrough cases after 14 years when administered to children.

There is insufficient data on the effectiveness of varicella vaccines given to immunodeficient individuals. The immune response following one or even two doses may not be adequate to fully prime the immune system in immunocompromised patients and breakthrough disease may occur. However, there is evidence that disease severity is reduced by the vaccine and that in most mildly immunosuppressed patients seroconversion is possible. Careful consideration should be given as to who is suitable to receive these live vaccines.

Varicella vaccination of children undergoing cancer chemotherapy was shown to induce VZV-specific T cell immunity, however, seroconversion rates varied. Vaccination of oncology patients requires individual close monitoring and antiviral treatment may be required if vaccine-virus rashes occurs. Consideration also needs to be given of their close contacts, particularly in a hospital environment, since the vaccine-rash is infectious through direct contact.

6 Impact and effect of varicella vaccination programmes

6.1 Objectives

The objective of this section is to review the most recent data investigating the impact of varicella vaccine programmes for currently licenced vaccines. The focus will be on how vaccination programmes have been implemented and the effect these programmes have had nationally on disease incidence. Consideration is given to relevant studies that contribute to the current understanding of the impact that universal varicella vaccination has had on varicella disease.

6.2 Outcomes

The impact of the introduction of varicella vaccination programmes on disease incidence and national prevalence of varicella are summarised.

6.3 Review

Most long term studies of the impact of varicella vaccine programmes encompass both one dose and two-dose schedules. Many countries, including the US and Canada, that have introduced the vaccine to their schedule began with one-dose schedule in the late 1990s and expanded it a decade later to a two-dose schedule, frequently, concomitantly with MMR. Catch-up programmes and two-dose schedules for susceptible individuals also varied between countries and regions within the same country. Despite this, varicella vaccination appears to have a positive impact on the varicella incidence and rate of varicella-associated hospitalisations.

As well as national and regional variations in delivery of universal varicella vaccination, there is also variability in surveillance systems and whether varicella is notifiable. For example, in the UK varicella is not notifiable in England and Wales, but is in Scotland and Northern Ireland. Varicella is not currently notifiable in NZ. Even where there is mandatory reporting, mild cases often go unreported since these cases may not been seen, or only present in primary care. Therefore, assessing the full impact of vaccination is difficult. Overall, regions that have introduced varicella vaccine programmes have seen significant reductions in the severity of disease, hospitalisations and circulation of VZV.

6.4 Impact of two-dose schedules, including MMRV or MMR+V

6.4.1 Impact in North America

6.4.1.1 United States

A US-based study investigated the incidence of varicella since the introduction of varicella vaccination in 1995 in Kaiser Permanente of North Carolina healthcare system (membership of 3.1 million in 2009). The study found that varicella vaccine coverage has gradually increased since 2000; coverage as of 2014 was more than 90% among children aged 19-35 months. In 2006, a second dose was recommend for 4-6 year old (no details of types of vaccines given). The study found that the incidence of varicella in 5-19 year-olds decreased by 90-95% from 25.8 to 1.3 per 1000 person-years from 1995-2009. There was no evidence

of a shift in burden of varicella to older age groups. A ten-fold decrease was observed in the overall age-adjusted varicella hospitalisation rates, from 2.13 to 0.25 per 100,000 in 1994 and 2009, respectively.[56]

Another US-based study found that during the first five years since introduction of the two-dose varicella vaccination programme, from 2006-2010, the incidence of varicella had declined in all age groups, including infants too young to be immunised. Of the reported varicella cases with vaccination status information (n=1302) in three surveillance areas, 61.7% had received one dose and 7.5% had received two doses of varicella vaccine.[57]

A review of varicella-associated deaths reported to the CDC in the US found that, following the introduction of routine two-dose varicella vaccination in 2007, an additional 70% decline in varicella mortality among children and adolescents occurred compared with 2005-2007 (p<0.01). Compared to pre-vaccination era 1990-1994, the deaths due to varicella in those aged under 20 years declined by 99% during 2008-2011. On average, during 2005-2007 and 2008-2001, there were 1.7 and 0.5 deaths per year, respectively, in this age group. During 1996-2013, 24 deaths (29%) were immunocompromised individuals; five had received 1 dose of varicella vaccine at least 42 days prior to breakthrough disease. The authors note that there are further opportunities to prevent varicella and its associated morbidity through routine varicella vaccination, catch-up vaccination and ensuring that household contacts of immunocompromised patients have evidence of immunity.[58]

6.4.1.2 Impact in Canada

A study conducted in Canada, which investigated 10,762 varicella-related hospitalisations across seven age categories, found that hospitalisations declined significantly across all age groups and provinces (ranging from 34 to 83%) from 1990 to 2010. The greatest declines were seen in the younger age groups. The risk ratio (RR) for hospitalisation of children aged 1-4 years was 0.17 (95% CI 0.16-0.20); for infants aged under-1 year RR=0.26 (0.23-0.30) – demonstrating benefit to this age group through a reduction in varicella circulation. Varicella immunisation was introduced between 2000 and 2007, whereby children received the first varicella dose at 12-15 months of age with catch-up doses for susceptible children available at preschool and preadolescent ages.[59]

6.4.1.3 Impact on varicella-related hospitalisations in Native American peoples.

The average annual varicella-related hospitalisation rate in American Indian and Alaskan Native (AI/AN) people was 0.66/10,000 persons (200 hospitalisations) pre-varicella vaccination during 1995-1998. Following varicella vaccination during 2007-2010, this rate decreased by 95% to 11 hospitalisation (0.03/10,000), which was lower than the varicella hospitalisation rate for the general US population (0.06/10,000) across all age groups apart from under-1-year-olds. The hospitalisation rate declined significantly for all paediatric (p<0.01), but not adult, age groups. Vaccine coverage data was not available for all children; however, coverage of at least one dose of varicella vaccine increased from 42.9% in 2001 in AI/AN children aged 16-18 months to 75.5% in 2010. As of 2010, 88-91% of AI/AN children aged 19-35 months had documented receipt of at least one dose of varicella vaccine.[60]

6.4.2   Impact in Saudi Arabia

Varicella vaccination was introduced in 1998 in Saudi Arabia. A mandatory two-dose schedule was introduced in 2008 for children aged 12 months to 12 years with a catch-up second dose given to children aged up to 12 years of age (no description of which vaccines are given). From 1998 to 2007 the vaccine was available voluntarily. The incidence of varicella from 1994-2011 within the Saudi Aramco Medical Services Organization (SAMSO),

which represents medical care of 370,000 employees and dependents, was investigated. The study found that during the pre-vaccination period 1994-1997, the total number of varicella cases was 10,070. The overall number of cases decreased significantly by 84% following the implementation of mandatory vaccination during 2008-2011 with just 1577 cases reported. The mean incidence rate was 2850.5 ± 474.1 per 100,000 in 1994-1997 pre-vaccination and 394.8 ± 382.8 per 100,000 during 2008-2011 mandatory vaccination period.[61]

6.4.3   Impact of varicella vaccination in the European Union (EU)

6.4.3.1 Germany

Germany has the most experience of universal varicella vaccination in the EU. Universal vaccination was introduced in 2004 as one dose for children >11 months of age and expanded to two doses in 2007, with the second dose given preferably between 15-23 months at least 4-6 weeks after the first dose. Catch-up doses were offered to non-immune adolescents. Following the introduction of routine vaccination in Germany, an up to 75% decline in varicella morbidity was confirmed from sentinel and regional surveillance. This included a reduction in varicella associated complications and hospitalisation. Herd protection was also observed in infants <1 year of age. Studies report that there is growing acceptance of varicella vaccination by doctors and parents, which may be attributed to the availability of MMRV.[62]

The Bavarian Varicella Surveillance Project (BaVariPro) was conducted during 2006-2011 to investigate the effects of routine varicella vaccination on varicella epidemiology in the Munich area, Germany. Data on varicella vaccination, cases and complications were collected in three parts covering around 238,000 paediatric inhabitants: through annual parent cross-sectional surveys (for children aged 18 – 36 months), monthly paediatric practice surveillance and paediatric hospital databases. From these data annual varicella incidence and hospitalisations were estimated. One dose of monovalent varicella vaccine was introduced in 2004 at 11-14 months of age. In 2006, two-dose MMRV was licenced. From 2009, when a two-dose schedule was introduced with a second dose at 15-23 months, MMRV was reimbursed and preferred. As a single dose, varicella vaccine coverage was around 51% in 2007 when reimbursement was for the monovalent varicella vaccine. As of September 2011 more than 85% of all first doses were as a combined vaccine and more than 90% of children were reported to have received MMRV in the November 2011 parent survey. The study found a strong impact of the varicella vaccination programme together with increasing acceptance. Two pronounced increases in coverage were followed by decreases in paediatric varicella cases - an overall decrease of 67% of all paediatric cases and 43% of paediatric varicella hospitalisations was observed during the five-year period. The greatest decrease (75%) was observed in children under 5 years of age.[63, 64]

6.4.3.2 Spain

Based on varicella-related hospital discharge data in Spain from 2005 to 2010, decreases in severe varicella incidence were significantly greater in the regions with universal varicella immunisation at 15-18 months of age (42.7 cases per 100,000 in 2005 [95% CI 35.8-49.6] to 7.0 [4.5-9.1] in 2010) than those regions that only vaccinated susceptible adolescents aged 10-14 years (46.4 [43.3-49.6] per 100,000 in 2005 to 29.8 [27.5-32.2] in 2010). More than 50% of hospitalisations were of children aged under five years. In this age group, across Spain, the hospitalisation rate decreased significantly from 46.8 per 100,000 (95% CI 43.8-49.7) to 26.6 per 100,000 (95% CI 24.5-28.6; p=0.02). The overall annual hospitalisation rate related to varicella was 4.14 cases per 100,000 over the six year study period; this decreased significantly from 4.53 per 100,000 in 2005 to 2.95 per 100,000 in 2010 (p=0.036).[65]

One region in Spain that introduced universal varicella vaccination with two doses of Varivax® was Navarre in 2007 (population of 644,566 in 2012). Two doses of varicella vaccine, given at 15 months and 3 years of age, were introduced in 2007. Prior to 2006, the vaccine was administered to susceptible adolescents. In 2012, vaccination coverage was around 95% for first varicella dose (Varivax® concomitant with MMR) and more than 89% for the second varicella dose. From 2006-2012, there was a significant 98.5% reduction in annual varicella incidence in children aged 1-8 years (p<0.0001).[66]

6.4.3.3 Italy

Universal varicella immunisation has been gradually introduced to eight regions in Italy since 2003. A two-dose schedule at 13-15 months and 5-6 years has been implemented by all eight regions with differing schedules of MMRV or MMR+V. In 2012, first dose immunisation coverage at 24 months of age was between 84-95% across these regions. Prior to the introduction of universal varicella vaccination nationally, the impact of vaccination on varicella incidence and hospitalization due to varicella complications was evaluated from 2003 to 2012. An almost linear decrease in varicella incidence was observed in the first regions to introduce varicella immunisation. A measurable, positive effect was seen after only two years in the regions that had more recently introduced the varicella immunisation programme. However, a decline in incidence rates was not as clear for the regions that had introduced the programme for less than two years. The authors noted that the number of under-reported milder varicella cases is likely to be high despite mandatory notification.
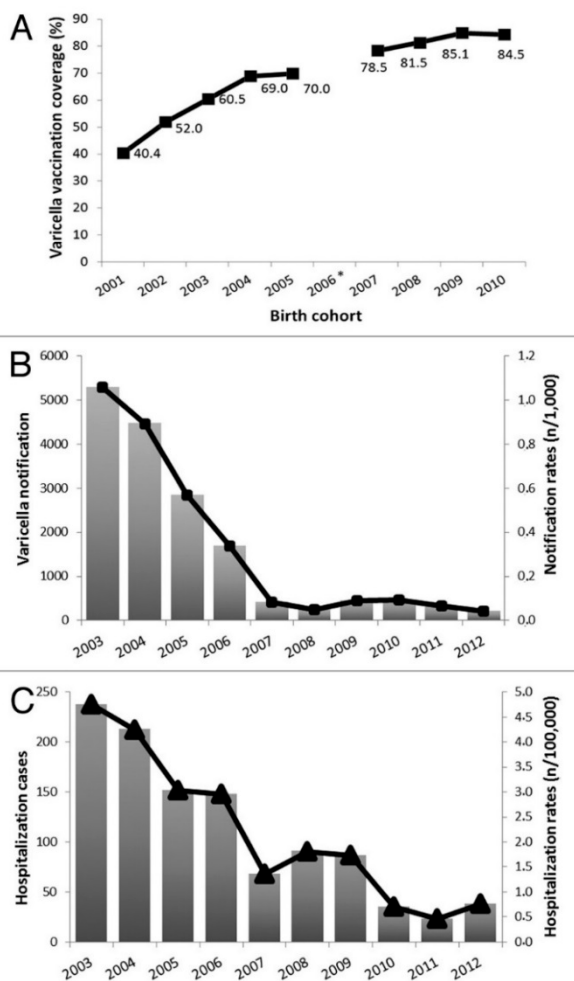

Figure 3: (A) Varicella vaccination coverage by birth cohort in Sicily (*birth cohort data lacking); (B) Notifications for varicella in Sicily, 2003-2012; (C) Hospitalisations with varicella diagnosis in Sicily 2003-2012. Reproduced with permission (Amodio et al).

Varicella-associated hospitalisation rates were reduced by almost 75% from 2004 to 2012. [67]

Sicily was the first Italian region to introduce universal varicella immunisation. A study analysing Sicilian administrative and clinical data on varicella case notifications and hospitalisations found that from 2003-2012, 15,433 varicella cases were notified. As shown in Figure 3, there was a decrease in notifications from 1.1 per 100,000 population in 2003 to 0.1 per 100,000 in 2012 (p<0.001). The risk of hospitalisation decreased 6-fold over the same period (4.8 to 0.8 per 100,000 population, p<0.0001). An increase in varicella vaccine coverage was inversely correlated to varicella notification and hospitalisation rates (p<0.001). For the 2010 birth cohort, immunisation coverage was 84.5%.[68]

6.5 Impact of single dose varicella vaccination in Australia

The implementation of a varicella immunisation programme since 2005 was evaluated in Australia where a monovalent varicella vaccination was being given to children at 18 months of age and as a catch-up dose to adolescents aged 10-13 years as part of school-based immunisations. Children with parental-reported prior varicella infection were excluded. Vaccination uptake was good, considering the prior infection exclusion criterion, with 83% of 18 month olds and 33% of adolescents receiving the vaccine. Compared with prevaccination era, varicella hospitalisation rates decreased significantly for those up to 40 years of age. Four and half years after the programme commenced, varicella hospitalisations of children age 1-4 years declined 34.1 per 100,000 (95% CI 8.5-10.3) to 9.4 per 100,000 (8.5-10.3). No significant change was observed over the same time period in the hospitalisation rates for 12-13 years old adolescents (3.3 vs 2.6 per 100,000). The authors suggested that a one-off catch-up given to all children and adolescents up to the age of 14 years as well as the 18 month dose may have helped to reduce this upwards shift in age distribution of the disease. In July 2013, varicella vaccination was replaced with MMRV, providing the second dose of MMR at 18 months rather than 4-6 years of age.[69]

6.6 Evidence of herd immunity

Several studies investigating the effectiveness and impact of varicella vaccination programmes have confirmed that protection against varicella extends beyond those who are vaccinated, providing herd or community immunity.

6.6.1 Herd immunity in North America

In the US, compared to the pre-vaccination era 1990-1994, deaths due to varicella in those aged under 20 years declined by 99% during 2008-2011. During 1990-1994, there were an average of 105 deaths listed per year with varicella as the underlying cause of death (8.4% aged <1 year, 33.0% aged 20-49 years) and 39.6 deaths with varicella as a contributing cause (7.6% aged <1 year, 29.3% aged 20-49 years). During 2008-2011, on average there were 17 deaths caused by varicella (0% aged <1 year, 2.9% aged 20-49 years) and 16.3 deaths in which varicella contributed (0% < 1 year, 12.3% aged 20-49 years). An 87% decline in varicella mortality was observed across all age groups, providing good evidence of herd immunity.[58]

A study conducted in Canada, which investigated 10,762 varicella-related hospitalisations across seven age categories, found that hospitalisations declined significantly across all age groups. A single dose of varicella vaccine was introduced to the infant immunisation schedules of different provinces at 12 months of age between 2000 and 2007, most provinces also included catch-up for susceptible children at preschool or aged ≤12 years. Declines in hospitalisation were statistically significant for children aged 1-4 years ranging

from 65 – 93% across the provinces and children under 1 year with a range from 48-100%. Significant declines were also observed from adults aged 20-39 years (range 55-100%) and aged 40-59 years (range 39-76%). The authors concluded that decreases in varicella circulation appear to contribute significantly to declines in varicella-related hospitalisations for young infants and adults aged 20-39 years.[59]

6.6.2   Herd immunity in Europe

A European report found that there was a wide variation in the herd immunity thresholds for varicella infection. These thresholds indicate the proportion of the population that needs to be immunised in order to prevent endemic transmission of the virus. Thresholds in Europe were estimated to range from 70% in Italy to 94% in the Netherlands (these studies were conducted prior to 2013). Differences in mixing patterns, particularly of younger age groups, were considered to contribute to this variability.[62]

In Germany, herd immunity effects were observed through decreases in varicella incidence and hospitalisation in all paediatric age groups. In the Munich region, herd immunity was observed following the introduction of universal varicella vaccination for children aged 11-14 months, and was increased following improvements in coverage that were associated with the introduction of a two-dose varicella vaccine regimen and the introduction of MMRV at 15-23 months. In infants under one year and older children and adolescents there was a 71% and 63% decrease in varicella, respectively.[63]

Each region in Spain has implemented different varicella vaccination programmes. In some regions universal varicella vaccination is given at 15-18 months of age, whereas other regions have introduced vaccination of susceptible adolescents. In the Navarre region, as mentioned above, significant 98.5% reduction in annual varicella incidence in children aged 1-8 years (p<0.0001) was shown during 2006-2012 following implementation of a childhood varicella vaccination programme in 2007. Herd immunity was also observed with significant reductions in incidence for unvaccinated infants aged under one year (by 90.5%; p<0.0001), unvaccinated 9-year-olds (89.4%; p<0.0001) and people aged 22 years or over (92.4%; p<0.0001). These data demonstrate indirect effects of vaccination by reducing circulating disease and hence herd immunity. [66]

Severe varicella infections in Spain were shown to significantly decrease during 2005-2010. When restricting to a principal diagnosis of varicella, the overall hospitalisations decreased from 3.05 per 100,000 in 2005 to 1.92 per 100,000 in 2010. Hospitalisation rates in regions that implemented varicella vaccination at 15-18 months of age had decreased significantly more than in the regions that vaccinated susceptible adolescents at 10-14 years. From 2006 to 2010, there was a 78% reduction in varicella hospitalisation in Spanish regions vaccinating at 15-18 months of age (from 6.77 [95% CI 6.14-7.40] to 1.46 [1.18-1.74] per 100,000], where as a 37% decrease was seen in regions vaccinating only susceptible adolescents (5.12 [95% CI 4.87-5.35] per 100,000 to 3.22 93.04-3.40] per 100,000). The authors noted that as well as children under 5 years of age directly benefiting from vaccination given at 15-18 months of age, there was a herd immunity effect and reduced circulation of VZV in older children and adolescents.[65]

6.6.3   Herd immunity in Saudi Arabia

Mandatory two-dose varicella vaccination, for those aged 12 months to 12 years, was introduced in 2008 following introduction of the vaccine to Saudi Arabia in 1998. A study found that the overall number of cases decreased significantly by 84% following the implementation of mandatory vaccination during 2008-2011 with just 1577 cases reported within the Saudi Aramco Medical Services Organization. Prior to introduction of the vaccine, 8.3% of varicella cases occurred in children aged under-one year in 1994-1997, and during

the initial voluntary phase of vaccine period 1998-2008, 5.4% of cases were in this age group. There was a significant reduction to 3.4% of cases in under-1 year olds during the mandatory period 2008-2011 (p<0.0001) providing evidence of herd immunity to this age group. However, the peak age for infections increased from under-5 years of age to between 5-9 years following the introduction of the vaccine. The percentages of cases in other older age groups also increased during 2008-2011, with a significant increase in the proportion of cases in adults aged 40 years and older from 2.2% in 1994-1997 to 11.5% in 2008-2011, respectively (p<0.0001). The authors noted that this was not a nationwide study, rather a select population, and the impact on morbidity or mortality was not assessed.[61]

6.7   Summary of impact

In regions where universal varicella vaccination has been implemented, significant declines in varicella cases and hospitalisation have been observed. These programmes are reducing circulating VZV and providing protection through herd immunity for those who are unable to be immunised, such as the under one-year-old infants. Not all countries have implemented universal vaccination nationwide, however as seen in Spain, disease circulation is reducing even in areas without universal vaccination of infants.

It is unclear what impact adolescent catch-up campaigns have had. The greatest impacts have been seen in regions with vaccination for children 12 months to under 5 years of age - the age groups most likely to develop varicella in temperate climates. However there is some suggestion that, while VZV is still in circulation the incidence of varicella may be pushed to older age-groups, in which case vaccination of non-immune adolescents may be warranted.

Most countries with universal immunisation have changed from single dose varicella vaccination to two-dose schedules due to increased incidence in breakthrough disease. The risk of breakthrough disease is highest where VZV is still in circulation, therefore, a two-dose schedule appears to be most important when the programmes are first introduced before circulation is diminished. Improvements in vaccine effectiveness were noted in Germany following the introduction of a two-dose schedule due to improvements in coverage.

8 Vaccines and options for scheduling

8.1 Objectives

The objectives of this section are to summarise the available vaccines and present options of using varicella vaccines on the New Zealand Immunisation Schedule. It will also provide a summary of the information for consideration of the use of MMR+V or MMRV for the first dose in young children and the age of target population of each dose. Options for catch-up doses, and use of post-exposure prophylaxis and protection of vulnerable groups will also be considered.

8.2 Outcomes

The options for scheduling varicella vaccination types and national programmes are summarised.

8.3 Vaccine options

Varicella vaccines are available as monovalent vaccines or combined measles, mumps, rubella and varicella (MMRV) vaccines.

8.4 Routine varicella vaccination

8.4.1 Recommendation for MMR+V as first dose in children younger than 48 months.

The use of concomitant MMR+V, given as two separate injections at the same visit, is generally recommended for children under 23 months of age due to an increase in febrile convulsions following MMRV in the younger age groups. The risk of febrile convulsions is higher in infants aged 16-23 months and therefore, the optimum timing for a first dose is 12-15 months of age. MMRV is the preferred choice for a second dose at any age to reduce the number of injections given.

The Advisory Committee on Immunization Practices (ACIP) stated in 2008 that it does not have a preference over MMR+V or MMRV as a first dose. However, in June 2009, ACIP suggested that MMR+V should be given as the first dose to infants aged 12-47 months, unless caregivers state a preference for MMRV. For children aged 15 months to 12 years receiving a second dose, and for those receiving a first dose over the age of 48 months, combined MMRV is preferred.[70]

However, there are some reports that coverage is better with MMRV rather than MMR+V, which is an important consideration to help to reduce circulating VZV. For example, in Germany, following advice from the US ACIP and German Advisory Committee on Vaccinations, separate MMR+V injections were introduced from 2011 for the first dose in the younger children. Since then, surveillance in Bavaria observed up to 12% decline in coverage, which may not be sufficient for VZV control. MMRV had been used for first dose vaccinations at 11-14 months of age from 2009, and was used for 86% of first dose vaccinations by 2011.[62 64]

In the Puglia region of Italy, coverage increased significantly when MMR+V was replaced with MMRV in 2009 (with a second dose of MMRV or MMR+V at 5-6 years or 11-12 years of age). Coverage of one dose of varicella vaccine by the age of 24 months increased from

49% in the 2006 birth cohort (given at age 15 months) to 91% in the 2010 cohort (given as MMRV at age 13 months).[45]

8.4.2   Single dose strategy

As of July 2013, Australia introduced a single dose of MMRV at 18 months of age, following a dose of MMR at 12 months of age. This replaced the MMR dose previously given at 4 years of age and monovalent varicella at 18 months. One rationale for this is that the risk of febrile convulsion in this age group is lessened by receiving MMRV as the second dose for MMR.[71]

An Australian modelling study to predict trends in varicella and HZ incidence and morbidity between 2015 and 2050 compared four strategies:

1. One-dose infant programme with discontinuation of adolescent catch-up in 2015
2. One-dose infant programme with continued adolescent catch-up until 2050
3. Two-dose universal schedule – 18 months and 12 years
4. Two-dose universal schedule – 12 month and 18 months

Regardless of 18 month coverage, strategy 4 was predicted to produce the lowest incidence of varicella (natural infection and breakthrough), whereas strategy 1 produced the highest incidence. However, the difference between the strategies was reduced when coverage for the first dose was increased from 83% to 95% by 2050. With the higher coverage, an almost linear decline in varicella incidence in infants was predicted and the incremental benefit of two doses fell by 70%.

When modelling the incidence of breakthrough infection, two-dose strategies achieved large reductions in natural infection and contained a rise in breakthrough infections (as shown in Figure 4). A universal adolescent dose (strategy 3) was predicted to be most protective against rises in adult cases, although as infant coverage improves with time, fewer adolescents would require catch-up doses. The authors concluded that considerable reductions in severe varicella morbidity are obtainable using one-dose vaccination if coverage of 95% is achieved, particularly in infancy, making a second dose less efficient and likely to be less cost-effective.[72]
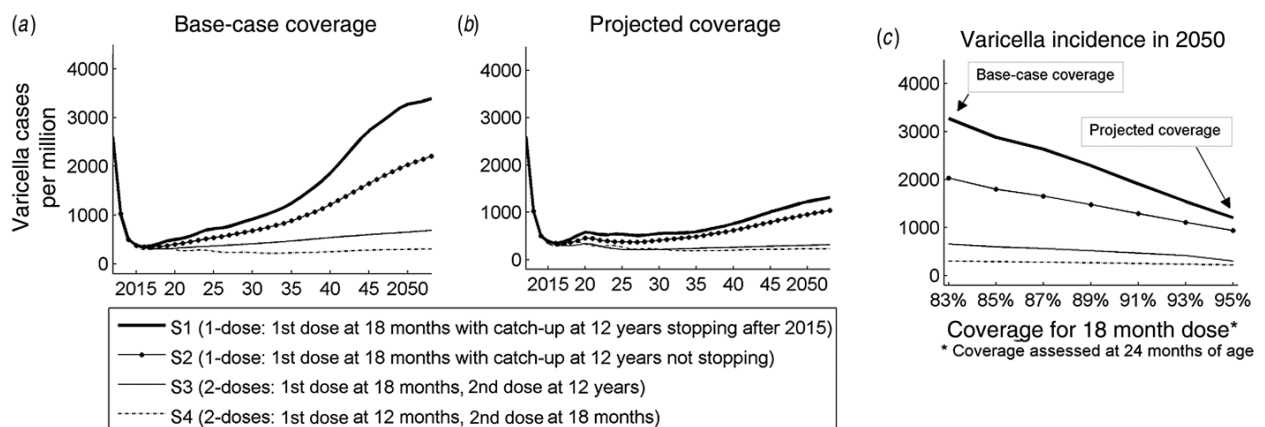

Figure 4: (a, b) Varicella incidence (natural plus breakthrough) for four strategies after 2015; (c) Estimated varicella incidence in 2015 by coverage for 18 month dose from base-case coverage (83%) to projected coverage (95%). Reproduced with permission (Gao et al).

As was noted in Germany, infant coverage of varicella vaccination was improved by the introduction of MMRV to the childhood schedule and it was found that when the first dose of varicella vaccine recommendations was changed to as MMR+V instead of MMRV, a 12% decline in varicella vaccine uptake, but not MMR uptake, was observed.[63, 64]

8.4.3   Timing between two doses

A review of literature from 1995 to 2012 on varicella vaccine failure concluded that a short interval between two doses might be preferable to reduce the risk of breakthrough varicella after the first dose, particularly in those who did not mount an adequate immune response following the first dose and in countries with predominant circulation of wild-type virus. Literature findings suggested that the first dose may not sufficiently prime the immune response.

Unlike the response seen for other live vaccines, the second dose of varicella vaccine often induces a large booster effect, in which anti-varicella antibody GMTs increase by about 10-fold (range 5-39 fold), even when the interval between doses is short. In this situation, it is suggested that the second dose completes the full immune response rather than acting as a boost for waning immunity. On this basis, it is suggested that a second dose should be given soon after the first i.e. after a minimum of four weeks, to protect those in whom there is a primary vaccine failure. By changing the timing of a second dose from 4-6 years of age to the second year of life, assuming no waning immunity and 1-3% rate for breakthrough varicella, around 2-fold cumulative breakthrough varicella cases could be prevented. The authors conclude that a high primary vaccine failure rate could allow continued circulation of the virus and that timing of the two doses would be particularly important to consider in countries that have still have high levels of circulating VZV. It was noted however that the existing schedule should be taken into consideration when making decisions to introduce a shortened interval between doses since a reduction vaccine coverage increases circulating disease.[73]

8.4.4   Prophylaxis post exposure

The WHO position statement on varicella vaccines states that a single dose of varicella vaccine is highly effective for prevention of moderate to severe varicella disease (79-100%) when administered within 3-5 days of exposure. However, for the prevention of any severity of disease the estimates are varied (9-93%).[2]

A Cochrane review investigated the use of varicella vaccines as post-exposure prophylaxis (PEP) for varicella infection. The results from three trials involving 110 healthy children suggested that varicella vaccine administered within three days of exposure to sibling varicella cases reduced the rate of infection and severity of cases. Out of 56 vaccine recipients, 13 (18%) developed varicella compared with 42/54 controls (placebo or no vaccine recipients; 78%). Most of the vaccine recipients developed mild disease (fewer than 50 lesions). One vaccine recipient developed moderate-severe disease compared with 21 controls. There was not sufficient data to evaluate vaccine given more than three days after exposure nor use in adolescents or adults, in whom one dose may be insufficient to generate a primary immune response.[20, 74]

A quantitative assessment was conducted to model the impact of varicella vaccine as PEP in adults with uncertain varicella history. The mean number of varicella exposures during the lifetime in adults was estimated to be 6 (95% CI 2-13). Working from sentinel data in France, the risk of infection after exposure in adults was 32% (95% CI 16-43%) with 1 in 6 exposures being a close relative. Through Bayesian modelling, the study showed that varicella vaccine given as PEP could reduce 26% of adult varicella cases and 31% of

hospitalisations in a country without universal varicella immunisation (assuming 70% acceptance of PEP vaccination).[75]

8.5   Special groups

For immunocompromised individuals, a balance is needed between the risks of complications from wild-type varicella infection compared with the risks of vaccinating with a live attenuated virus. There have been several case reports of disseminated varicella infections caused by vaccine virus in undiagnosed cases of immunosuppression, particularly in children. The Infectious Disease Society of America (IDSA) has identified gaps in knowledge around the vaccination of immunocompromised patients, for varicella vaccines in particular these included:

- o   A registry to record the safety outcomes of giving live vaccines to immunocompromised patients.
- o   Optimal timing between live vaccination and transplantation, and the optimal timing of post transplantation vaccinations.
- o   Efficacy and safety of varicella vaccination in patients with chronic inflammatory disease being treated with mildly immunosuppressant therapies.[76]

8.5.1   Vaccination of individuals with HIV infection

Guidelines in the US recommend varicella vaccination of non-immune household contacts of HIV-infected persons to prevent transmission. Vaccination (two doses, three months apart) may be considered in VZV seronegative, HIV seropositive individuals over the age of 8 years with CD4+ lymphocyte counts of at least 200 cells/µL. Aciclovir treatment is recommended in the rare event that vaccine type-varicella infection occurs.[77]

A study conducted in Spain found that a third of HIV-infected immigrants were susceptible to at least one of measles, mumps, rubella or varicella disease. Of 289 patients, 14 were negative for VZV-IgG (4.8%) and in potential need of VZV vaccination. Eight patients were from sub-Saharan Africa and susceptible due to low VZV transmission in these countries. None of the four patients who developed varicella during follow-up had CD4+ cell counts high enough to have been vaccinated. VZV-negative serology is rare in HIV-infected adults and therefore routine serological screening of all HIV-positive immigrants may not be of value.[78]

8.5.2   Solid organ transplant recipients

Recommendations in the US suggest that for seronegative organ transplant candidates, two doses of varicella vaccine should be given at least two weeks, preferably at least four weeks, prior to transplantation with a minimum interval of 4-6 weeks between doses. Serology is recommended after immunisation since seroconversion may have been reduced in patients with end-stage kidney and liver disease and a further dose may be required. It is not generally recommended to give adults varicella vaccine post-transplantation. Seronegative children on low levels of immunosuppression have safely received varicella vaccination post-transplantation. It is more important to ensure that household contacts and health professionals are immune, either through prior disease or vaccination to reduce the risk of exposure to the transplant recipient.[79]

8.5.3   Inflammatory bowel disease

Immunomodulatory therapies are being used increasingly in patients with inflammatory bowel diseases (IBD). Vaccination and screening is now standard of care for patients with IBD. An observational study to investigate the use of a proforma to assist gastroenterologist

in this screening was conducted in 7 Australian and 1 UK hospital. The study found that of the total IBD population who had varicella serology tested (n=439), 11% were not immune. Immunity was confirmed in 94% of patients who recalled having varicella or previous varicella immunisation. Vaccine uptake was less than 40% in those for whom it was deemed appropriate.[80]

8.5.4   Haematopoietic Stem Cell Transplant (HSCT) recipients

Following a review of scientific evidence, the 2013 IDSA clinical practice guidelines recommend that non-immune HSCT candidates aged ≥ 12 months be vaccinated at least four weeks prior to immunosuppression, and if time, with two doses. Vaccination of donors can improve post-transplant immunity of recipients, however, ethically this can only be done for the benefit of the donor not the recipient, and should be appropriate to the donor's varicella immunity status and age. It is also unknown whether vaccination within four weeks of stem cell harvest with MMRV or varicella is safe for the HSCT recipient. These guidelines recommend that two doses of varicella vaccine should be given 24 months after HSCT in varicella-seronegative patients who do not have graft-versus-host disease, ongoing immunosuppression, or within 8-11 months of intravenous IgG. In one reviewed study, a CD4 lymphocyte count of >200 cells/μl and documented response to at least one other vaccine was required prior to varicella administration post transplantation.[76]

8.6   Varicella immunisation of adolescents

Many countries have funded catch-up doses for adolescents. In the US, a two-dose catch-up campaign for adolescents was begun in 2006 when the two-dose routine schedule was introduced for all children. Logistic regressions analyses were performed to investigate factors associated with the receipt of two doses of varicella vaccine among 10,542 adolescents with no history of varicella aged between 13-17 years. In 2010, 90.5% of adolescents received at least one dose; however, coverage for two doses was 58.1%, ranging from 19.7% to 85.3% between states. Coverage was significantly higher among adolescents who had also received meningococcal vaccine and Tdap compared with those who had received one or neither (76.0% versus 34.6%). Younger teens (13-14 years) had higher coverage rates that older adolescents (16-17 years). The authors note that this older age-group would have been offered two doses in 2006 when it was first recommended and may have missed that significant opportunity to receive a second dose.[81]

Australia added a single dose varicella vaccine catch-up for adolescents aged 11-13 years to existing school-based immunisation programmes in 2006 together with a single dose given at 18 months of age. Findings from an evaluation of the Australian varicella vaccination programme showed that the adolescent catch-up dose coverage had increased marginally from 30 to 33% from 2006 to 2009. Adolescents were not vaccinated if they met parent-reported natural infection exclusion criteria or had been vaccinated previously. A 1996-1999 serosurvey found that 83% of 10-14 year-olds were seropositive for VZV. There was no significant change shown in this age group by a 2007 serosurvey (p=0.32). These results were not unexpected since the proportion of vaccine-induced immunity was low in 2007 and were consistent with the low reported uptake of the catch-up dose. The evaluation found that the concurrent introduction of routine childhood immunisation with adolescent catch-up programmes, particularly when part of school-based programmes, was a seen as a strength, although there was a challenge in the validity of parental-reported natural infections.[69] This Australian adolescent catch-up programme was discontinued in 2015.

A study in Beijing, China, found evidence that varicella vaccination was associated with attenuated disease severity in adolescents and adult varicella case, even when a catch-up

dose was given to those aged over 15 years. However, breakthrough cases represented only 8% of the total cases. At the time of the study, varicella vaccination was recommended, but not funded, for adolescents over the age of 12 years who are susceptible to VZV, and as of 2013, a two-dose schedule is also recommended for preschool children in Beijing.[48]

8.7 Summary

One of the considerations for a varicella vaccination programme includes the use of a one-dose or two-dose regimen and the concomitant use with MMR schedules. To reduce the number of injections children received, the combination MMRV vaccine is recommended. However, there is an increased risk of febrile seizures in children younger than 23 months, so most schedules recommend the first dose as an MMR+V. Furthermore to reduce the incidence of febrile reactions, in particular febrile convulsions the first dose is recommended to be delivered in the 12-15 month age group rather than the 15 months plus. Also, the timing between doses suggests that a shorter time period is more effective than a long one in generating adequately long-lived immunity thereby preventing breakthrough disease in a schedule with a longer gap from the first to the second dose.

There are variable approaches to the use of catch-up campaigns alongside the introduction of a universal vaccination programme. The greatest gain appears to be in enabling the reduction in circulating disease, thus obtaining less breakthrough disease and some herd immunity. Programmes that have started with a two-dose regimen, and/or included a catch up programme appear to have greater gains.

The risk of breakthrough varicella should be taken into consideration when timing the second dose of a varicella vaccine. Some studies suggest that a second dose should be given a minimum of four weeks, as opposed to two years after the first, since in some individuals immunity is not sufficiently primed by one dose alone. However, good coverage has a greater effect on preventing breakthrough disease by reducing circulating VZV and thereby the risk of exposure.

There is a lack of evidence for the advantage of adolescent catch-up dose. Coverage in adolescents is likely to be quite low initially in New Zealand, since while VZV is in circulation many adolescents will have been exposed as children. Also, in this age group uptake may also be poor. Some countries have added varicella to school-based vaccination programmes to help to improve coverage for those who are reported not to be immune.

In special groups at high risk of severe disease, a careful balance is required between the risk of the disease and the risk to the individual of receiving a live vaccine. For those with mild-moderate immunosuppression or immunodeficiencies, the vaccine may be administered safely but further doses may be required to develop protective immunity. It is recommended that in these cases seroconversion is monitored. It is important to ensure that household contacts of immunocompromised individuals are immunised if susceptible to reduce the risk of exposure to those most at risk of severe disease.

Post exposure prophylaxis with varicella vaccine is effective at reducing severe disease in children, if administered within 3 days of exposure. Data for a longer delay or in older age groups is not yet available. Mathematical modelling suggests a 26% reduction in adult varicella incidence and 31% of varicella-associated hospitalisations if the vaccine is administered prophylactically.

9 Impact of childhood varicella vaccination on herpes zoster incidence

9.1 Objective

The objective of this section is to assess whether a reduction in circulating varicella-zoster virus as a result of vaccination has an effect on the incidence of herpes zoster. Consideration will be given to relevant studies and systematic literature reviews investigating the incidence of HZ in regions where varicella vaccination programmes have been introduced.

9.2 Outcomes

The effect varicella vaccination programmes and declines in circulating VZV have had on the incidence of HZ is reviewed. The basis of mathematical modelling studies and their predictions are evaluated.

9.3 Review

There is concern that with the introduction of universal varicella vaccination there would be a decrease in exogenous exposure to naturally circulating VZV.

The exogenous boosting hypothesis was first proposed by Hope-Simpson in 1965.[82] Exogenous exposure is postulated to play a role in boosting the VZV immunity to maintain latency of VZV virus and preventing reactivation as HZ. However, researchers are unclear of what significance this may have in terms of varicella vaccination programmes.

There is also evidence of VZV-specific immune responses in adults without recent VZV exposure. This is described as endogenous boosting, whereby, an immune response to subclinical reactivation of latent VZV is thought to help to suppress the virus.[83] Despite these hypotheses, the mechanism of maintaining latency remains undetermined.

The WHO reported that although an increase in HZ incidence has been demonstrated in various developed countries (Australia, Canada, Japan, Spain, UK and US), this increase began years prior to the introduction of varicella vaccine. Indeed, the incidence of HZ has increased in countries with and without varicella vaccination programmes. An analysis conducted in the US did not show any difference in the slope of increasing HZ incidence rates since introduction of universal varicella vaccination.

However, despite a lack of convincing evidence that exogenous boosting is required to minimise VZV reactivation, modelling studies have assumed that the lack of exogenous boosting increases HZ incidence as a result in the decline of circulating VZV. Such studies have predicted that routine varicella vaccination will increase HZ incidence for up to 50 years.[2]

A systematic review of literature concluded that although exogenous boosting exists, it does not occur for everyone nor in all situations. More data is required around VZV immunology, duration of boosting and surveillance to improve assumptions made for mathematical models.[84]

9.3.1 Effect of varicella vaccination programmes on the incidence of HZ

9.3.1.1 HZ incidence in the United States

According to a retrospective study, there was no evidence of a significant increase in HZ incidence after the introduction of the varicella vaccination programme in the US in 1996. The study has examined whether the US varicella vaccination programme had influenced HZ incidence in those over 65 years of age. During 1992 to 2010, a total of 281,317 HZ incidences were claimed through Medicare from 2,848,765 people over 65 years of age. The rate of HZ incidence increased by 39% from 10.0 per 1000 person-years in 1992 to 13.9 per 1000 person-years in 2010; however, the increase was not associated with the introduction of the vaccine.[85]

HZ-case data was collected from 2000 as part of a US-based surveillance project, Antelope Valley Varicella Active Surveillance Project (AV-VASP), conducted in California. Analysis of these data supported the exogenous-boosting hypothesis, since as varicella vaccination coverage increased there was a corresponding decline in varicella cases, and increases in the number of HZ in younger age groups. These data were controversial and in contradiction to the CDC findings at the time.[86]

9.3.1.2 HZ incidence in Australia

No increases in HZ hospitalisations were seen following the introduction of a single varicella vaccine dose in childhood in Australia. During 1 July 1998 to 30 June 2010, age standardised HZ hospitalization rates decline at an average of 0.57% per year (95% CI 0.25-0.91%). Vaccine coverage during the funded vaccination period was more than 80% by 24 months of age in 2008 and by the end of 2012 coverage was 90% by 60 months of age. The age standardised rate of HZ hospitalisations with HZ as the principal diagnosis were 11% (95% CI 10.8-11.2) during the pre-vaccination era, which declined to 10.4% (10.2-10.6) during the funded vaccine period (incidence rate ratio [IRR] 0.95 [0.87-0.9]). For all HZ-related hospitalisations, the age standardised rate was 27.8% (27.4-28.1) pre-vaccination and 24.5% (24.2-24.8) during funded vaccination, IRR = 0.88 (0.87-0.90). The limitation of this study is that it only considered HZ hospitalisations and not milder cases.[87]

A subsequent study, conducted in Victoria, Australia, used sentinel consultation data from deputising practices to assess the impact of childhood varicella vaccination on the incidence risk of HZ. During 1998 – 2002, pre-vaccination, the age standardised HZ incidence risk remained constant (1 per 1000 consultations); it had almost doubled by 2012 (1.8 per 1000 consultations). This increase was significant in the under 70 age group (p<0.01 for under 60 years and p<0.02 for <60-69 year olds), but no increase for people aged > 70 years. The authors conclude that HZ vaccination may be beneficial to help to reduce HZ incidence depending on age of administration.[88]

9.3.1.3 Varicella exposure in paediatricians

The cellular and humoral immune responses of paediatricians highly exposed to various infections found a boosting of CD8+ memory T cells and persistently higher levels of IFN-γ producing-T cell upon stimulation with VZV-specific antigens than normally exposed controls, but no significant difference in VZV antibody titres and humoral immunity. This study did identify specific VZV-antigens that specifically boost cellular immunity which may have potential as HZ vaccine antigens.[89]

9.3.2 Latency of vaccine-type VZV

As with wild-type VZV, the Oka strain of VZV used in the vaccines can remain latent within the body and can lead to vaccine-strain HZ after varicella vaccination. A study conducted in

the US during 2005-2009 investigated the incidence of vaccine-type HZ in 322 children (aged 1 – 17 years). Out of the 309 specimens collected, 214 (84%) were identified as wild-type VZV, 38 (15%) were vaccine-strain and 2 (0.8%) were possible wild-type/vaccine VZV recombinants. A third (88) of these samples were from vaccinated participants, of which 43 (52%) were wild-type HZ, 38 (46%) were vaccine-strain HZ and 2 (2%) had possible recombinant VZV. Those with vaccine-strain HZ were significantly younger at diagnosis than other groups (p<0.0001). Vaccinated children had 79% lower incidence of HZ overall than unvaccinated children (48 vs 230 per 100,000 person-years, respectively, p<0.001). The lowest rates were amongst children aged 3-9 years and 10-17 years; HZ incidence was higher among vaccinated children in the age 1-2 year group (p=0.01). The authors believe that the HZ incidence rate in unvaccinated children would have been higher if those with no history of varicella had been excluded, since many of the unvaccinated children in this study may not have been exposed to VZV due to a decline in circulation in the US and were not at risk of HZ. It was noted that HZ rash among vaccinated children occurred more commonly in the dermatomes corresponding to the site of vaccine injection (cervical and lumbar).[32]

9.3.3 Mathematical modelling of HZ epidemiology after introduction of varicella immunisation

Through three different models of VZM immunity, post vaccination patterns of HZ incidence were predicted to be qualitatively similar, showing increases in natural HZ in the medium term (up to 50 years) and long-term (up to 100 years) emergence of vaccine-related HZ. A progressive model, that postulated that immunity is accumulated upon repeat VZV exposure, predicts a long term increase in vaccine-related HZ reaching levels of HZ higher than seen in the pre-vaccination era. However, the authors note that the models used all assume that the exogenous boosting hypothesis of Hope-Simpson is valid. They state that there is currently a lack of knowledge and uncertainty on exogenous boosting and the impact varicella vaccination has on HZ epidemiology. Further studies are required to investigate immune mechanisms of VZV.[90]

A mathematical modelling study, using within-host VZV cell-mediated immunity (VZV-CMI) data and between-host transmission data, was used to predict the effect childhood varicella vaccination could have on HZ incidence based on the hypothesis that VZV-CMI is boosted through re-exposure to VZV. The model suggested that VZV re-exposure through contact with infected people would only provide about two years extra protection; this is shorter than previous predictions of up to 20 years. There was no significant effect from endogenous boosting. The model also predicted that although the implementation of a childhood varicella vaccination programme could result in 1.75 fold increase in the number of shingles cases peaking 31 years later, this increase would be temporary (for a 100% coverage at one year of age with a 100% effective vaccine). The authors state that the predicted increase in shingles cases in the younger 31-40 years old age group was unexpected; however, this population were less likely to develop lasting HZ complications.[91]

An Australian modelling study to predict trends in varicella and HZ incidence and morbidity between 2015 and 2050 compared four strategies. The study predicted that following an initial rise in HZ incidence, the incidence of HZ would decline to levels lower than in 2015 by 2050, regardless of coverage. Any differences in HZ incidence between vaccination strategies (one dose or two doses, with or without adolescent doses) would be very small compared with the changes in varicella incidence. This study assumed that exogenous boosting was responsible for maintaining V latency.[72]

9.3.4   Evidence for endogenous varicella virus reactivation

An alternative hypothesis to exogenous boosting is that latent VZV reactivates sub-clinically from time to time and the immune system, particularly T cell-mediated immunity, is stimulated endogenously to help to maintain suppression of the infection and to restore latency.

Observations in astronauts during Space Shuttle missions have demonstrated asymptomatic reactivation of latent viruses and altered virus-specific T cell immunity during space flights – a situation where no varicella is circulating. A recent study investigated reactivation of three latent viruses, Epstein-Barr virus (EBV), VZV and cytomegalovirus (CMV) in 17 astronauts, before, during and after short-duration spaceflights in relation to stress hormone levels. It was found that during flight, VZV and EBV DNA copies were elevated in the astronauts saliva compared with pre- and post-flight. Seven astronauts out of 14 who shed EBV also shed VZV in their saliva during flight, and changes in cell-mediated immunity were seen. None of the healthy controls shed VZV, although 2-5% shed EBV. VZV is a neurotropic virus and does not normally appear in saliva of healthy subjects. However, the authors report that in stressful conditions VZV has been previously shown to be shed from saliva following replication in the dorsal root ganglia. This study provides evidence of endogenous re-exposure to VZV.[92]

9.4   Summary

There is insufficient data to determine whether childhood varicella vaccination results in increased incidence of HZ as a result of a decline in circulation of wild-type VZV. Experience to date, in countries that have introduced vaccination programmes, has not definitively shown an increase in HZ, even after more than two decades of vaccine use and achieving very low incidence of circulating varicella. Many countries, even those without varicella vaccination programmes, have observed increases in HZ over recent decades and other hypotheses for these increases include aging populations or use of immunosuppressant therapies. There have been no consistent findings from recent studies. Not enough is known about the control of VZV latency to model the effect of varicella vaccination programmes accurately and there is insufficient HZ surveillance data or laboratory confirmation of HZ in most countries. There are two types of HZ to be considered: latent VZV reactivation in people who were exposed to wild-type VZV prior to the commencement of a vaccination programme and reactivation of vaccine-type VZV in vaccine recipients.

HZ generally occurs more frequently in those over the age of 50 years. However, it has been suggested through mathematic modelling that HZ may be seen in younger age groups who carry wild-type varicella but are not re-exposed to circulating VZV to boost cell-mediated immunity to maintain latency. This scenario assumes that exogenous boosting is responsible for maintaining VZV latency.

While the Gao et al. 2015 paper predicts an initial rise in HZ, this is based on the assumption that exogenous boosting is responsible for minimising HZ. However, the exact role and magnitude of exogenous boosting has not been demonstrated. Therefore these predictions are speculative based on an assumption that has not been well supported by evidence.

There are few studies investigating the role of endogenous boosting or other potential mechanisms for control of VZV latency and HZ.

For countries that have implemented universal varicella vaccination, there is a recommendation to consider introducing HZ vaccine to people who are likely to have latent

wild-type VZV infections. However, the effectiveness, duration of protection and optimum age of administration of the HZ vaccine is undefined. Further surveillance data and better informed modelling is required.

There is insufficient data to determine if there is risk of vaccine-type HZ as vaccine-recipients age, particularly in adults. In older children, the incidence of HZ has been shown to be lower for vaccine recipients than those who are unvaccinated.

10 International policy and practice

10.1 Objective

To provide a review of international vaccine schedules and recommendations for the prevention of VZV.

10.2 Review

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

10.2.1 United States

Varicella vaccine was licensed in the US in 1995 and the US was first country to introduce a universal vaccination programme for varicella. A single dose schedule was replaced in 2006 with a two-dose schedule. The CDC recommends two doses of varicella vaccine for children, adolescents and adults without evidence of varicella immunity.

Routine two-dose varicella schedule

- First dose - 12 to 15 months of age (see below for details of MMRV).
- Second dose - four to six years of age. This dose may be given at a younger age providing there is at least three months between first and second dose.

Second dose catch-up

For those who received dose 1 prior to introduction of two-dose schedule:

- Given at least 3 months after the first dose for children aged up to 13 years.
- Second dose can be given at least four weeks after the first dose for adolescents and adults over 13 years.

Adults and adolescents aged 13 years or older

- Two doses given four to eight weeks apart.
- Healthy adults should be assessed for varicella immunity.
- Adults at increased risk of exposure or transmission should receive special consideration for vaccination. These include:
  - Healthcare professionals
  - Household contacts or carers of immunocompromised individuals
  - Teachers and childcare workers
  - Residents and staff in residential and nursing homes
  - Students and military personnel in communal accommodation
  - Inmates and staff of correctional institutions

- o Women of child bearing age who are not pregnant (pregnancy should be delayed for at least a month after vaccination)
- o Adults and adolescents living with children
- o International travellers

Combine MMRV

- First dose, age 12-47 months – MMR+V is recommended, however, MMRV may be given if preferred by caregiver.
- First dose, aged over 48 months – MMRV.
- Second dose age 15 months – 12 years – MMRV.
- For those with a family history of seizures of any etiology – MMR+V is recommended for both doses.

Special groups

- Children infected with HIV can receive a single antigen varicella vaccine if CD4+ T cells are over 15%.
- Those with impaired humoral immunity may be vaccinated with single antigen varicella vaccine.
- Postpartum vaccination of women without evidence of varicella immunity is recommended, including while breastfeeding.

10.2.2 Canada

All Canadian provinces and territories have included two doses of varicella vaccine to their schedules for children aged 12 months to 12 years, and for susceptible adolescents and adults. Those who previously received one dose of varicella vaccine should be offered a second dose.[93]

Routine two-dose schedule

- Dose 1: 12 months of age, single antigen MMR+V.
- Dose 2: 4-6 years as MMRV.
- Catch-up for susceptible individuals aged ≥13 years – two doses at least 28 days apart.
- Priority groups, if susceptible, include:
  - o Women of childbearing age
  - o Household contacts of immunocompromised people
  - o Healthcare and childcare workers
  - o Immigrants and refugees from tropical regions
  - o People receiving chronic salicylate therapy
  - o People with cystic fibrosis
  - o Persons exposed to a case of varicella

10.2.3 Australia

Children under 14 years

At least one dose of a varicella containing vaccine is recommended for all children from 18 months of age.[94]

Routine schedule

- MMRV at 18 months of age (as second dose of MMR).

Non-immune adolescents and adults (aged 14 years and over)

Two doses of varicella vaccine at least 4 weeks apart.

Priority groups:

- o Women of childbearing age
- o Household contacts of immunocompromised persons
- o Healthcare workers
- o Early childhood education and childcare staff
- o Long-term care facility staff

10.2.4 United Kingdom (UK)

Varicella is notifiable in Scotland and Northern Ireland.[95]

There is no routine schedule for varicella vaccine in the UK. According to the NHS website, children from one year of age and adults are recommended, but not funded, to receive two doses of varicella vaccine 4 to 8 weeks apart. Varicella vaccination is recommended for those in close contact with immunocompromised patients and healthcare workers from the age of 12 months.

10.2.5 European Union

In many European Union (EU) countries, two-dose varicella vaccination is recommended for children, but not always funded. Recommendations also vary for non-immune adolescents and adults.[96] Regional variations are seen within Italy and Spain, whereby some regions have introduced universal varicella vaccination in childhood but others have not. For example, universal vaccination was introduced into Sicily in 2003 and in Navarre, Spain in 2007.[66, 67]

A working group as part of European Centre for Disease Preventions and Control conducted a review of varicella vaccination in 2014 to provide guidance for EU member states in childhood varicella immunisation decisions.[62]

Table 1: Summary of international immunisation recommendations for varicella vaccines, as of May 2016 (adapted from ECDC)

Country	Age of VZV vaccination	Number of doses	Special recommendations
USA	12 – 15 months + 4 – 6 years	Two	Either MMR+V or MMRV then MMRV
	Catch up: in children < 13 years	Two, 2nd at least 3 months after first	MMRV if required
	Adults/adolescents ≥13 years	Two, at least 28 days apart	
Canada	12 – 15 months + >18 months	Two	MMRV, no later than school entry
	Catch-up: ≥7 – 12 years	Two, 3 months apart	MMRV or V
	>12 years	Two, 3 months apart	In susceptible adolescents/adults
Australia	18 months	One	MMRV
	4 years catch-up:		

Country	Age of VZV vaccination	Number of doses	Special recommendations
	10 – <15 years (school based catch-up)		If unvaccinated with no history of varicella.
NZ	12 months – 12 years	Two	Not funded
Austria	9 - 24 months 9–17 years catch-up	Two , at least 4 weeks apart	Not funded No history of vaccination or disease
Belgium	Over 12 years	Two, 4-8 weeks apart	If negative serology and close contacts to immunocompromised patients. Not funded
Cyprus	13-18 months + 4-6 years	Two	Not funded
Czech Republic	15 months + 21 months to 4 years	Two	
Germany	11-15 + 15-24 months 2 – 17 years (catch-up)	Two, 4-6 weeks apart	
Greece	12–15 months + 4-6 years	Two	All ages if susceptible and in contact with those at risk of severe or in specific occupations
Italy†	11-18 years	Two	In adolescents if susceptible
Latvia	12–15 month	One	
Liechtenstein	10-15 years	Two, 4 weeks apart	If no evidence of disease
Luxembourg	12 months + 15-24 months	Two	
Poland	From 9 months (usually 13 months) – 12 years		Specific risk groups only
Spain†	12 years		If no history of disease or vaccination
Switzerland	11–15 months (at risk)	Two, 1 month apart	At risk of complications. No history of varicella.
UK	From 12 months	Two, 4-8 weeks apart	Non-immune HCW and close contacts of immunocompromised patients
† Universal immunisation schedule has been introduced within some regions and provinces			

10.3 Summary

International recommendations are summarised in Table 1.

Most countries that recommend varicella vaccines have implemented a two-dose varicella schedule for young children aged 12-24 months, with catch-up available for adolescents without evidence of VZV immunity. The first dose is generally MMR+V or a choice of MMR+V or MMRV. The second dose is generally MMRV. Australia has introduced MMRV to be given at 18 months of age as a second dose of MMR.

11 Options for New Zealand

11.1 Objective

The objectives for this section are to consider the different vaccine options available to NZ in terms of available vaccines and schedules. The focus will be on the prevention of varicella disease in children, reduction of varicella virus circulation, implications of breakthrough disease and the role of herd immunity in protecting those who are not able to be immunised. Consideration will also be given to the surveillance systems and data collection required to monitor safety and effectiveness of the introduction of varicella vaccination to the childhood immunisation schedule.

11.2 Outcomes

The timing options for varicella vaccination and effect these timings have on coverage and on herd immunity are examined. The role of VZV surveillance prior to and following varicella vaccination programme introduction is reviewed.

11.3 Review

11.3.1 Timing of doses

In New Zealand, VZV is in circulation and therefore a two-dose schedule may be required. The timing between doses would need careful consideration.

Most countries that have already introduced routine varicella vaccination began with a single dose but found incidences of breakthrough disease and subsequently added a second dose to the schedule. There is evidence that the timing between the first and second doses is important in controlling breakthrough varicella. Breakthrough varicella, although frequently milder than varicella in unvaccinated individuals, is contagious and those for whom herd immunity is protecting are at risk of being infected. Until there is sufficient coverage and a significant decline in circulating disease, two doses have been found to be necessary to protect against all cases of varicella.

It appears that a period of 4-8 weeks between doses is optimum at reducing breakthrough disease. However, there is not sufficient data to determine whether there is any waning of immunity when these doses are close together and if the duration of immunity is as good as elicited by wild-type disease.

Changing the existing immunisation schedule may result in declines in coverage of MMR as well as varicella vaccination. High coverage is essential to provide adequate herd immunity to those who are unable to be vaccinated, such as young infants, immunocompromised individuals and pregnant women, and to significantly reduce circulating disease.

11.3.2 Surveillance

Varicella is currently not a notifiable disease in New Zealand. Hospital discharge codes give an indication of hospitalisations due to varicella-associated complications; however, there is no sentinel surveillance of milder cases of varicella. Even in countries with mandatory varicella notification, mild cases do not always seek medical advice. Some cases of varicella have subclinical symptoms but are still able to pass the disease to others through nasal secretions. With the introduction of universal varicella vaccination, there is an increased likelihood of milder breakthrough disease which would make subclinical cases even more difficult to diagnose.

The Vaccine Preventable Disease programme of the European Centre for Disease Prevention and Control (ECDC) developed guidelines to help EU member states make national decisions with regard to childhood varicella vaccination.[62] The conclusions of the ECDC guidelines are:

- When considering the introduction of a vaccination programme, countries should assess their individual epidemiological and socioeconomic situation as well as the capacity to achieve high vaccination coverage.
- Surveillance systems must be established to assess the impact of a potential immunisation programme ideally prior to the start of a programme.
- The key elements to survey should be:
  - Vaccine coverage
  - Vaccine effectiveness
  - Occurrence of adverse events
  - Age-specific disease incidence of varicella and HZ
  - Age-specific incidence of severe disease and hospitalisation
- Sources could be sentinel systems, hospital admission/discharge codes or mandatory notifications.
- Surveillance for HZ is needed to evaluate the impact of varicella vaccination on HZ incidence.
- A potential system for HZ surveillance must be long-term effort as, according to modelling data, the impact of HZ may only be visible after more than 10-15 years.

11.3.2.1 Active versus passive varicella surveillance

A study comparing active and passive varicella surveillance during 2005-2010 was conducted in Philadelphia, US, prior to a transition to national varicella surveillance. It found that passive surveillance provided comparable data to active surveillance for monitoring disease trends in breakthrough and moderate-to-severe varicella. Active surveillance better classified the disease cases as 'confirmed' or 'excluded', whereas most cases identified through passive surveillance were classified as 'probable'. To improve the quality of passive surveillance data, the authors recommended that periodic enhanced surveillance should be considered with laboratory testing and collection of additional varicella-specific variables, such as rash characteristics, to improve the identification of varicella cases and exclusion of non-varicella cases.[97]

11.3.3 Effect of coverage on herd immunity

Varicella immunisation programmes provide herd (community) immunity for those who are unable to receive the vaccine, such as young infants, pregnant women and immunocompromised individuals, whilst VZV is in circulation. For herd immunity to be effective coverage requires to be sufficiently high to prevent disease transmission (around 95%).

A recent modelling study found that when the herd immunity threshold has not quite been reached, the average age at which an infection occurs is older than for the pre-vaccine era and as a result the severity of the disease increases to 2.2 times worse for varicella. For varicella, the average age of first infection pre-vaccination era was calculated to be 9.1 years and when vaccine coverage is at 20% sub-herd immunity threshold, the computed average age of first infection increases to 29.9 years – an age at which pregnancy is likely. The authors conclude that a vaccine-preventable disease does not remain a constant-valued threat as disease circulation declines, hence there is a risk that those who decline vaccination will have more severe disease, particularly in adolescence or adulthood, if exposed when coverage is not sufficiently high.[98] This effect has been observed in NZ through an increased incidence of measles in adolescent age groups during outbreaks.[99]

11.4 Summary

The timing of two doses of varicella vaccination should take into consideration the risk of breakthrough disease if the spacing is too long, compared with a need for further booster doses if immunity wanes later in life, particularly in the absence of circulating disease to provide potential exogenous boosting. Maintaining the current immunisation schedule and the effect schedule changes may have on coverage should also be considered, particularly in relation to MMR vaccinations. Currently in NZ, MMR is scheduled at 15 months and 4 years of age. However, a lack of confidence in the vaccine as a result of breakthrough disease would also result in lower uptake, affecting coverage and protection afforded through herd immunity.

An alternative to a universal two-dose schedule is to administer a second dose only to those most likely to not be sufficiently primed by a single dose and who are greater risk from breakthrough disease, such as children with mild or moderate immunosuppression.

Surveillance systems are recommended to monitor disease breakthrough. Passive surveillance could be adequate if laboratory confirmation and rash characterisation was conducted periodically to identify or exclude possible cases. There is also a potential for vaccine-strain VZV breakthrough disease in those who do not generate adequate immunity after dose one.

As circulation of wild-type disease declines as a result of vaccination, the incidence of varicella is likely move to unvaccinated older children, adolescents and adulthood while varicella immunity (and vaccine coverage) is below the herd immunity threshold. This has implications for the severity of disease and the risk of congenital varicella syndrome if varicella is contracted during pregnancy. A catch-up campaign is recommended for non-immune individuals to help to protect those who are unable to be vaccinated with varicella vaccine from severe disease.

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