2012 Antigen Review for the New Zealand National Immunisation Schedule: Measles, mumps and rubella

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Prepared by a scientific team incorporating the Immunisation Advisory Centre, The University of Auckland Institute of Environmental Science and Research Ltd.

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Executive summary

Measles is one of the two most infectious diseases affecting humans along with pertussis and has a basic reproduction number of around 12 - 18. Person to person transmission occurs through large respiratory droplets and it is also spread as aerosolised droplet nuclei.

Vaccines against measles are highly efficacious and immunisation programmes have controlled measles to the point of elimination in many populations. However, outbreaks and epidemics continue to occur where low immunisation rates and/or sufficient numbers of susceptible members of communities are present.

Mumps is often considered a benign disease. However, it has historically been the cause of significant morbidity and mortality, particularly in the military, and continues to occur regularly in military settings. Since vaccination programmes have significantly reduced mumps, the age of infection has shifted into an older age group. Countries that have been using measles, mumps and rubella (MMR) vaccine as a two dose schedule have reduced mumps incidence from around 300 per 100,000 to below 1 per 100,000 population.

Rubella is a relatively mild childhood disease, however, rubella virus is a teratogen and infection during pregnancy is devastating to the developing fetus. The clinical findings in congenital rubella syndrome are extensive. Successful control and possible elimination of rubella depends on immunisation programmes that target the whole population. Rubella has been eliminated in some countries, including the region of the Americas. Rubella vaccine is highly effective with estimates over 95% (85% - 99%).

In New Zealand (NZ) coverage of the MMR vaccine is now over 90% for infants of all ethnicities by their second birthday and 80% receive their first dose of MMR vaccine on time.

Measles still occurs in NZ, although there has not been a large epidemic since 1997. In 2011, there was an epidemic with 597 cases notified. Cases were largely the result of importations on seven separate occasions, two of which resulted in over 100 secondary cases. Most cases occurred in unvaccinated people including those too young for vaccination.

Mumps has remained steady since 1994. There were 51 cases reported in 2011 and two hospitalisations. Of the cases reported, 20% had been fully immunised.

Rubella has declined steadily since 1995. In 2010, there were only four cases notified and 23 cases in 2011, possibly as a result of increased awareness of rashes due to the measles epidemic. One case occurred in a fully vaccinated person.

There have been no new safety issues raised for MMR vaccines during the past four years. A Cochrane review of MMR vaccines published in 2012 supports the safety profile of these vaccines. Conditions known to have an increased risk associated with MMR vaccines are aseptic meningitis within three to five weeks of weeks of Urabe-containing and Leningrad-Zagreb MMR vaccines, febrile seizures within two weeks of MMR vaccines and idiopathic thrombocytopenic purpura (ITP) within six weeks. Measles mumps rubella and varicella (MMRV) vaccines have been found to have a small, but significant, increased risk of febrile events after a first dose when given before four years of age. There is no increased risk for children aged four to six years. MMR vaccines continue to have an excellent safety profile worldwide.

Many countries who have implemented MMR vaccine, achieved high coverage and maintained it have eradicated measles and rubella. The duration and avidity of measles and rubella antibodies over time are superior to mumps antibodies and it is likely that the lower immunogenicity of mumps virus that has resulted in vaccine failure in highly immunised populations rather than escape virus variants. Rubella antibodies endure the longest and have the highest avidity.

The immunogenicity of MMR vaccine in people with DiGeorge syndrome, children treated for acute lymphoblastic leukaemia (ALL), and children treated with chemotherapy, children on highly active antiretroviral therapy (HAART) and children who have undergone haematopoietic stem cell transplantation (HSCT) respond well to revaccination with MMR. Treatment with either methotrexate (MTX) or etanercept does not appear to interfere with the immune response to MMR vaccine.
Data supports the immunogenicity of MMR vaccine given at 12 months. Maternal interference is unlikely at this age for any of the vaccine components.

MMRV vaccine can be given as early as nine months of age providing the second dose is given promptly with a minimum of three month interval. The ProQuad® MMRV vaccine appears more immunogenic than Priorix-Tetra™ for the varicella antigen, but there is no difference for the measles, mumps and rubella antigens.

The 2012 Cochrane review found a single dose of MMR vaccine to be at least 95% effective in preventing clinical measles and 69% - 81% effective in preventing clinical mumps. There were no studies identified for rubella, but as noted above, rubella appears to be the most immunogenic component of the MMR vaccine, with the highest avidity antibodies and eradication has been achieved in some countries. Although, mumps vaccine is less effective than measles and rubella vaccines, cases that have been vaccinated are significantly less likely to experience complications from disease such as orchitis, meningitis and hospitalisation.

Given the number of cases children less than 15 months of age, coupled with the good immunogenicity of the vaccine in children observed at 12 months of age, the first dose of MMR vaccine could be given earlier that currently recommended in NZ. In addition, awareness around possible mumps outbreaks may be prudent due to the shorter duration and lower avidity of mumps antibodies. Current evidence supports the timing of MMR vaccine to occur earlier than currently scheduled. The use of MMRV vaccine in place of MMR is an option, although use as a second dose rather than a first dose would avoid the issues of febrile reactions associated with MMRV as a first dose in children of this age. If varicella vaccine is to be added to the NZ schedule, it may be preferable to give it concurrently with MMR as MMR+V.

Changing the current placement of MMR on the NZ schedule will need to consider mechanisms for maintaining and even improving timeliness. Centring the immunisation event at the time of a Well Child visit may be an effective strategy. Consideration needs to be given to the period that unvaccinated or under-vaccinated children spend susceptible to disease. The use of MMRV in place of MMR vaccine will require careful communication with parents about the increased risk of febrile events should it be used as a first dose in children under four years of age.

MMR vaccines, either individually or as combinations, have been in use around the world for many decades. Global eradication of measles and rubella is currently possible and goals are being set for each region. Factors identified, that consistently enable success in controlling or eliminating measles, are the maintenance of high vaccine coverage, good disease surveillance, political and financial support, good social marketing and the addressing of anti-immunisation activities. NZ now has all of these factors in place.

This report summarises some key literature around the use of MMR vaccines published from 2009 - 2012.
2012 Antigen Review for the New Zealand National Immunisation Schedule: Measles, mumps and rubella

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This review is one of a series of 18 antigen reviews presented in 15 individual reports.
February 2013 (edited December 2014)
## Antigen Review–2012: Measles, mumps and rubella

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<tr>
<td>AEFI</td>
<td>Adverse Event Following Immunisation</td>
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<tr>
<td>ALL</td>
<td>Acute lymphoblastic leukaemia</td>
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<tr>
<td>CRS</td>
<td>Congenital Rubella Syndrome</td>
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<tr>
<td>DHB</td>
<td>District Health Board</td>
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<tr>
<td>ESR</td>
<td>Environmental Science and Research</td>
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<tr>
<td>GBS</td>
<td>Guillain-Barré Syndrome</td>
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<td>GMT</td>
<td>Geometric Mean Titres</td>
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<td>HAART</td>
<td>Highly Active Antiretroviral Therapy</td>
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<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<td>HLA</td>
<td>Human Leukocyte Antigen</td>
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<tr>
<td>HSCT</td>
<td>Haematopoietic Stem Cell Transplantation</td>
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<td>IgG</td>
<td>Immunoglobulin G</td>
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<tr>
<td>IRR</td>
<td>Incidence Risk Ratio</td>
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<tr>
<td>ITP</td>
<td>Idiopathic Thrombocytopenic Purpura</td>
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<td>JIA</td>
<td>Juvenile Idiopathic Arthritis</td>
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<td>MenACWY-CRM</td>
<td>Quadrivalent conjugate meningococcal vaccine</td>
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<td>MMR</td>
<td>Measles Mumps And Rubella Vaccine</td>
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<td>MMRV</td>
<td>Measles Mumps Rubella And Varicella Vaccine</td>
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<td>MTX</td>
<td>Methotrexate</td>
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<td>NP</td>
<td>Nasopharyngeal</td>
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<td>NZ</td>
<td>New Zealand</td>
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<td>OR</td>
<td>Odds Ratio</td>
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<td>rHA</td>
<td>Recombinant human albumin</td>
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<td>TNF-α</td>
<td>Tumour Necrosis Factor-Alpha</td>
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<td>UK</td>
<td>United Kingdom</td>
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<td>US</td>
<td>United States</td>
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<td>World Health Organization</td>
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### Acknowledgements

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1. Background – measles, mumps and rubella diseases and vaccination

1.1 Measles

In the absence of immunisation programmes measles infection is ubiquitous, infecting nearly everybody in a population by adolescence. It is one of the two most infectious diseases affecting humans, along with pertussis, and has a reproduction number of between 12 and 18. Person to person transmission occurs through large respiratory droplets and it is also spread as aerosolised droplet nuclei. The crude herd immunity threshold for measles is estimated to be 92.94% (1).

Measles infection can follow a range of clinical courses which can be modified by the presence of antibody, such as residual maternally derived immunoglobulin G (IgG) or post exposure immunoglobulin. Usually, infection will result in immunity, although a second infection can occur if initial immunity was incomplete. Measles in the immunocompromised host can be particularly severe and prolonged. Severity is likely to be related primarily to impaired cell-mediated immunity. The case fatality in human immunodeficiency virus (HIV) infected individuals can be 50%. Infection with measles virus causes the simultaneous activation of CD8+ cells and suppression of CD4+ cells, the suppression lasts for approximately one month.

Measles vaccines are highly efficacious and immunisation programmes have controlled measles to the point of elimination in many populations (2). Outbreaks and epidemics continue to occur where low immunisation rates and/or sufficient numbers of susceptible members of communities are present.

1.2 Mumps

Mumps is generally viewed as a relatively benign disease. However, historically, it has been the cause of significant morbidity and mortality, particularly in the military and continues to occur regularly in military settings (3). Like measles, mumps follows a varied clinical course which is dependent on age, gender, vaccination status and case definition. Inapparent infections are more likely in young children and older adults. There are a wide range of complications from mumps infection, which occur more frequently in adults and males are three times as likely to have neurological manifestations. Orchitis can be a complication in up to one third of cases in post pubertal men. Mastitis can occur in up to one third of cases in females over the age of 15 years. Maternal mumps has been associated with spontaneous abortion and intrauterine fetal death but not congenital malformations. Transient high frequency deafness occurs in around 2% of mumps cases, permanent deafness occurs in less than one per 20,000 cases.

Since vaccination programmes have significantly reduced mumps, the age of infection has shifted into an older age group. The average annual incidence in most countries has been around 300 per 100,000 population (passively reported so likely much higher). Countries that have been using measles, mumps and rubella (MMR) as a two dose schedule have reduced mumps incidence to below 1 per 100,000 population (3). The basic reproduction number for mumps is considerably lower than for measles at 4 - 7 with an implied crude herd immunity threshold estimated to be 75.86% (1).

1.3 Rubella

Rubella is a relatively mild childhood disease, however rubella virus is a teratogen and infection during pregnancy is devastating to the developing fetus. The clinical findings in congenital rubella syndrome (CRS) are extensive. A pandemic of rubella throughout Europe and the United States (US) in the early 1960s resulted in a wake of medically induced abortions and abnormal infants. Figures from the US 1964-5 epidemic show 12.5 million rubella cases, 2000 cases of encephalitis, more than 30,000 pregnancies affected of which 5000 were electively aborted, 6250 lost to spontaneous abortions, 2100 still births and CRS in 20,000 infants who survived pregnancy. Of these 11,600 were deaf, 3580 blind and 1800 mentally-disabled. The total cost of the epidemic was estimated to be US$1.5 billion in 1965, around US$109 billion in today’s terms (4).
Successful control and possible elimination of rubella depends on immunisation programmes that target the whole population. Poland have the highest rates of rubella in the European Region and this is attributable to their vaccination programme, which only targeted adolescent girls with rubella vaccine until 2005 when MMR was introduced (5). The reproduction number of rubella is estimated to be around 6 - 7 in developed countries and up to 12 in crowded developing countries. The crude immunity threshold is 83-85% (1). Rubella has been eliminated in some countries including the region of the Americas. Rubella vaccine is highly effective with estimates over 95% (85% - 99%) (4).

1.4 MMR vaccine

Most countries who vaccinate against rubella use MMR vaccine. The use of MMR vaccine is extensive and has resulted in elimination and near elimination of these diseases where vaccine coverage has been sustained at a high level. Recently, attenuated varicella virus has been combined with MMR vaccine to give measles, mumps, rubella and varicella (MMRV) vaccines. Immunogenicity for MMR and MMRV vaccine is similar, but an increased risk for febrile convulsions after a first dose of MMRV means its use as a second dose rather than a first dose may be preferred. Vaccine protection against measles and rubella is very high and after two doses over 95% of vaccinees are protected. The mumps component of the vaccine is less effective, likely to be due to the poorer immunity mumps virus induces in general.

It is feasible that vaccination against measles and rubella will lead to global eradication of these diseases (6, 7).

This report summarises some key literature around the use of MMR vaccines published from 2009 – 2012. During an edit of this review in 2014, reference updates were inserted where the data referenced had been published since 2013. A full review of data and vaccination schedules was not conducted.
2. Methodology for review

2.1 Objectives

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

- General specifications
  - Safety
  - Effectiveness
  - Implementation issues (practicality and possible impact on uptake)
  - The differences that need to be considered for each age group such as the variable severity of diseases and issues for vaccination
  - Different options of placement on the schedule, based on international findings and best practice
  - Different vaccine options and comparisons between the options

2.2 New Zealand epidemiology

The NZ epidemiology has been sourced entirely from the 2011 and 2012 Disease Surveillance Reports prepared by ESR (8). At the time of this report, the 2012 annual data was not available. Where it has been reported, information for cases for the first quarter 2012 has been included.

2.3 Literature search strategy

The points below have formed the focus of the literature search

1. Safety
2. Effectiveness in disease control
   a. Children
   b. Adults
   c. Indirect effects/herd immunity
   d. Duration of protection
3. Implementation issues (practicality of and possible impact on uptake)
4. Differences that need to be considered for each age group, for example the variable severity of disease and immunisation concerns that differ with age
   a. High risk groups – definition of which groups most likely to benefit and which vaccine/s
   b. Contacts of high risk groups
5. Different options for placement on the schedule, based on international findings and best practice
6. Different vaccine options for each disease and comparison between the options
7. Current international research and evidence around use of vaccines
   a. Consider this point covered in 1-6
Medline search terms and strategy
MeSH term: Measles, mumps and rubella vaccine (focus)
1959
Limit to Humans, English, 2009 – current
351
NOT Costs NOT attitude NOT survey
328 (keep and view)

Cochrane Library search terms and strategy
Search term measles mumps rubella Vaccin*
Limit to Cochrane Reviews, Other Reviews, trials 2009-present
23 results (keep and view)

Scopus search terms and strategy
Measles mumps rubella Vaccin* Published 2011 – present
1656
Limit to: Medicine, humans, English
Exclude Letter, short survey, editorial and erratum
458 (keep and view)
Reject social science articles. Delete duplicates
Final Endnote Library 326 Articles

2.3.1 Grey literature
One report was accessed and one book.

2.3.2 Additional searches
Where questions arose additional searches were undertaken to ensure there was no further available data. One additional report was accessed.

2.3.3 Final library
The final library includes 329 references. Where systematic reviews and/or meta-analysis were available the preceding literature has been excluded from the review.

2.4 Participants/populations
Study participants included in the studies accessed are healthy individuals over the age of six months of age and persons with conditions that place them at high risk of complications from measles mumps and rubella; risk for poor response to the vaccines and risk for adverse events following vaccination from live vaccines, in particular immunosuppressive conditions.

2.5 Interventions
The interventions included are:
• Measles, mumps and rubella combination vaccines.
• Measles, mumps, rubella and varicella combination vaccines.

The controls are alternative measles, mumps and/or rubella containing vaccines.

2.5.1 Measles, mumps and rubella vaccines (MMR)

2.5.1.1 M-M-R®II
M-M-R® II (Merck Sharp and Dohme) is a live attenuated virus vaccine against measles, mumps and rubella. M-M-R® II is a sterile lyophilised preparation of:
• Attenuvax® (Measles Virus Vaccine Live, MSD), a more attenuated line of measles virus, derived from Enders’ attenuated Edmonston strain and propagated in chick embryo cell culture;
• Mumpsvax® (Mumps Virus Vaccine Live, MSD), the Jeryl Lynn (B level) strain of mumps virus propagated in chick embryo cell culture; and
• Meruvax® II (Rubella Virus Vaccine Live, MSD), the Wistar RA 27/3 strain of live attenuated rubella virus propagated in WI-38 human diploid lung fibroblasts
Each 0.5mL dose contains not less than 1,000 CCID
(50% cell culture infectious dose) of measles virus;
12,500 CCID of mumps virus; and 1,000 CCID of
rubella virus. Each dose of the vaccine is calculated to
contain sorbitol (14.5mg), sodium phosphate, sucrose
(1.9mg), sodium chloride, hydrolysed gelatin (14.5mg),
recombinant human albumin (≤0.3mg), fetal bovine
serum (<1 ppm), other buffer and media ingredients
and approximately 25µg of neomycin.

Measles and mumps virus are grown in Medium
199 (a buffered salt solution containing vitamins
and amino acids and supplemented with fetal
bovine serum) containing SPGA (sucrose, phosphate,
glutamate, and recombinant human albumin) as
stabiliser and neomycin. Rubella virus is grown
in Minimum Essential Medium (a buffered salt
solution containing vitamins and amino acids and
supplemented with fetal bovine serum) containing
recombinant human albumin and neomycin. Sorbitol
and hydrolysed gelatin stabiliser are added to the
individual virus harvests (NZ Datasheet).

2.5.1.2 Priorix®
Priorix® (GlaxoSmithKline) is a lyophilised mixed
preparation of:
• Attenuated Schwarz measles,
• RIT 4385 mumps (derived from Jeryl Lynn strain)
and
• Wistar RA 27/3 rubella

The viruses are separately obtained by propagation
either in chick embryo tissue cultures (mumps and
measles) or MRC5 human diploid cells (rubella). Each
0.5 mL dose of the reconstituted vaccine contains not
less than $10^{3.0}$ CCID of the Schwarz measles, not less
than $10^{3.7}$ CCID of the RIT 4385 mumps, and not less
than $10^{3.0}$ CCID50 of the Wistar RA 27/3 rubella virus
strains. PRIORIX meets the World Health Organisation
(WHO) requirements for manufacture of biological
substances and for MMR vaccines and combined
vaccines (live) (NZ Datasheet).

2.5.1.3 Trimovax®
Trimovax® Merieux (Pasteur-Merieux Serums and
Vaccines) is a live attenuated virus vaccine against
measles, mumps and rubella. It is a lyophilised
preparation of:
• Measles (Schwarz Strain)
• Mumps (Urabe AM-9 strain) and
• Rubella (Wistar RA 27/3M strain)

Each dose of vaccine contains measles virus (Schwarz
strain) cultivated on primary culture of chicken embryo
cells at least 1000 CCID50, mumps virus (Urabe AM-9
strain) cultivated in embryonated hen eggs at least
5000 CCID50, Rubella virus (Wistar RA 27/3M strain)
cultivated on human diploid cells at least 1000 CCID50
(FDA product sheet).

2.5.1.4 Tresivac® (Serum Institute of India)
Tresivac® (Serum Institute of India) is freeze-dried and
prepared from live attenuated strains of:
• Edmonston-Zagreb measles virus propagated on
human diploid cell culture,
• L-Zagreb Mumps virus propagated on chick embryo
fibroblast cells and
• Wistar RA 27/3 Rubella virus propagated on human
diploid cell culture.

Each 0.5mL dose of vaccine contains not less than
1000 CCID of measles virus, 5000 CCID of mumps
virus and 1000 CCID of Rubella virus. The diluent
is sterile water for injection. The vaccine meets the
requirements of WHO expert committee on Biological
Standardisation standards for quality and testing

2.5.1.5 Triviraten™ Berna
Triviraten™ Berna (Swiss Serum Institute) is a live virus
vaccine containing 1000 TCID50 of Edmonston-Zagreb
(EZ 19) measles strain, 5000 TCID50 of Rubini mumps
strain and 1000 TCID50 of Wistar RA 27/3 rubella
strain propagated on human diploid cells. The product
contains 14mg lactose, 8.8mg human albumin, 0.3mg
sodium bicarbonate, 5.7mg medium 199 and distilled
water as solvent.

2.5.1.6 Morupar (Withdrawn 2005)
Morupar™ by Chiron is a live virus vaccine. It contains
a sterile lyophilised preparation of 1000 TCID50 of
Schwarz measles strain propagated in chick embryo
cell culture; 1000 TCID50 Wistar RA 27/3 rubella strain
propagated on human diploid lung fibroblasts; and
5000 TCID50 Urabe AM 9 mumps propagated in chick
embryo cell culture, with neomycin as stabiliser. It was
withdrawn in 2005 due to reactogenicity.
2.5.2 Measles, mumps, rubella and varicella vaccines (MMRV)

2.5.2.1 ProQuad®
ProQuad® (rHA) is a combined attenuated live virus vaccine containing measles, mumps, rubella, and varicella viruses. This vaccine uses recombinant human albumin in place of human serum albumin as viral growth media and is marketed as M-M-RVaxpro® in Europe. ProQuad® is a sterile lyophilised preparation of: 1) the components of M-M-R® II (Measles, Mumps and Rubella Virus Vaccine Live): Measles Virus Vaccine Live, 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 varicella-zoster virus propagated in MRC-5 cells (hereafter referred to as Varivax®)(9).

2.5.2.2 Priorix-Tetra™
Priorix Tetra™ (GlaxoSmithKine) is a live attenuated measles, mumps, rubella and varicella vaccine. Each 0.5mL dose of the reconstituted vaccine contains not less than 103.0 CCID50 of the Schwarz measles, not less than 104.4 CCID50 of the RIT 4385 mumps, not less than 103.0 CCID50 of the Wistar RA 27/3 rubella and not less than 103.3 PFU of the varicella virus strains (10).

2.6 Study designs
The studies included in this update are meta-analysis, systematic reviews, reviews, randomised controlled trials, and observational studies using database matching.
3. Recent New Zealand epidemiology

3.1 Summary of New Zealand epidemiology

3.1.1 Measles

Measles immunisation was introduced in 1969 and measles has been a notifiable disease since June 1996. The largest epidemics recorded in the past 20 years were in 1997, where 2169 cases were notified, and 1991 with the number of cases was estimated to be in the tens of thousands (although the hospitalisation data does not support this figure). In 2011, 597 cases of measles were notified (13.6 per 100,000 population), of which 462 (77.4%) were laboratory confirmed. This was a significant increase from 2010 when 48 cases were notified (1.1 per 100,000) and 15 (31.3%) were laboratory-confirmed. The number of notifications in 2011 was the highest since the peak of 1984 cases notified in 1997.

Measles notifications experienced peaks over the past four years, one in 2009-10 and another 2011-12 (Figure 2).

Auckland experienced seven separate importations of measles from overseas in the first half of 2011. Two of these cases resulted in outbreaks involving over 100 secondary cases occurring in the Hawkes Bay (24 cases), Wellington (2 cases) and Canterbury (1 case). In the first outbreak in Auckland, of the 21 cases eligible for immunisation, one child had received one dose of MMR but had been eligible for two, one adult was of unknown status and the remaining 19 cases were unimmunised, mainly by choice. A second outbreak in Auckland involved a school where 13% of the children were unimmunised, all were excluded from school. A further 17 cases occurred over the next two weeks, 14 related to the initial cases at the school. Of the 48 cases recorded, at the time of the report only one case was immunised appropriately (12).
3.1.1 Vaccination status of measles cases notified in 2011

The vaccination status of measles cases notified in 2011 was known for 79.1% of cases. Of the 472 cases for whom vaccination status was known, 361 were not vaccinated including 80 cases aged under 15 months and therefore not eligible for vaccination. Of the 597 cases, 22 had received the recommended two doses of vaccine (Table 1).

Table 1. Age group and vaccination status of measles notification for 2011 (8)

<table>
<thead>
<tr>
<th>Age group</th>
<th>Total cases</th>
<th>One dose</th>
<th>Two doses</th>
<th>Vaccinated (no dose info)</th>
<th>Not vaccinated</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15 months</td>
<td>90</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>80</td>
<td>2</td>
</tr>
<tr>
<td>15 months-3 years</td>
<td>75</td>
<td>28</td>
<td>0</td>
<td>1</td>
<td>44</td>
<td>2</td>
</tr>
<tr>
<td>4-9 years</td>
<td>95</td>
<td>12</td>
<td>4</td>
<td>0</td>
<td>74</td>
<td>5</td>
</tr>
<tr>
<td>10-19 years</td>
<td>161</td>
<td>15</td>
<td>9</td>
<td>2</td>
<td>115</td>
<td>20</td>
</tr>
<tr>
<td>20+ years</td>
<td>176</td>
<td>21</td>
<td>9</td>
<td>2</td>
<td>48</td>
<td>96</td>
</tr>
<tr>
<td>Total</td>
<td>597</td>
<td>84</td>
<td>22</td>
<td>5</td>
<td>361</td>
<td>125</td>
</tr>
</tbody>
</table>

3.1.2 Mumps

Immunisation against mumps was introduced in 1990 as part of the MMR vaccine. Mumps became notifiable in June 1996. The last epidemic occurred in 1994 and there were 188 hospitalisations. In 2011, 51 cases of mumps were notified (24 were laboratory-confirmed). In comparison, 41 cases of mumps were notified in 2010 (16 were laboratory-confirmed). The 2011 mumps notification rate was 1.2 per 100,000 population, a small increase compared with the rate for 2010 (0.9 per 100,000).

Figure 3. Mumps notifications and laboratory confirmed cases by year, 1997-2011 (8)

The highest notification rates were for Nelson Marlborough (7.1 per 100,000 population, 10 cases) and Auckland (2.2 per 100,000, 10 cases) District Health Boards. Age and sex were recorded for all cases. The highest age-specific rates were in the 5–9 years (5.2 per 100,000 population, 15 cases) and 1–4 years (4.0 per 100,000, 10 cases) age groups. Ethnicity was recorded for 50 (98.0%) cases. The highest rate was in the Asian ethnic group (3.0 per 100,000 population, 12 cases), followed by the Pacific Peoples (1.9 per 100,000, 5 cases) and Māori (1.4 per 100,000, 9 cases) ethnic groups. Hospitalisation status was recorded for 45 (88.2%) cases. Of these, two cases were hospitalised. In 2011, 37 (72.5%) of cases had a known vaccination status (Table 2).
Table 2. Age group of mumps notifications and vaccination status for 2011 (8)

<table>
<thead>
<tr>
<th>Age group</th>
<th>Total cases</th>
<th>One dose</th>
<th>Two doses</th>
<th>Vaccinated (no dose info)</th>
<th>Not vaccinated</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15 months</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>15 months to 3 years</td>
<td>8</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>4–9 years</td>
<td>17</td>
<td>2</td>
<td>10</td>
<td>1</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>10–19 years</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>20+ years</td>
<td>19</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>51</strong></td>
<td><strong>9</strong></td>
<td><strong>10</strong></td>
<td><strong>4</strong></td>
<td><strong>14</strong></td>
<td><strong>14</strong></td>
</tr>
</tbody>
</table>

3.1.3 Rubella

Rubella immunisation was introduced in 1970 and it has been a notifiable disease since June 1996. Twenty-three cases of rubella were notified in 2011 (compared with 4 cases in 2010), of which 16 cases were laboratory-confirmed. Since the last national outbreak in 1995 of 306 cases, there has been a steady decrease in the number of rubella cases notified each year. The increase in 2011 may reflect increased awareness of rash due to the measles outbreak. The highest number of rubella cases in 2011 was in Auckland DHB (8 cases), followed by Canterbury (4 cases) and Waitemata (3 cases) DHBs.

![Figure 4. Rubella notifications and laboratory confirmed cases by year, 1997–2011 (8)](image)

Age and sex were recorded for all cases. The highest numbers of cases were in the 20–29 years (eight cases), less than one year (four cases) and one–four years (three cases) age groups. Rubella notification rates among males (0.7 per 100,000 population, 16 cases) were higher than females (0.3 per 100,000, seven cases). Ethnicity was recorded for 22 (95.7%) cases. Cases were distributed by ethnic group as follows: European or Other (12 cases), Asian (six cases), Māori (three cases) and Pacific Peoples (one case). No hospitalisations due to rubella were reported in 2011. Of the 10 cases for which vaccination status was recorded, six were not vaccinated, including three cases aged less than 15 months. Three cases had received one dose of vaccine and one case reported having completed the MMR vaccination schedule (Table 3).

Table 3. Age group of rubella notifications and vaccination received, 2011 (8)

<table>
<thead>
<tr>
<th>Age group</th>
<th>Total cases</th>
<th>One dose</th>
<th>Two doses</th>
<th>Vaccinated (no dose info)</th>
<th>Not vaccinated</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15 months</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>15 months–3 years</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>4–9 years</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10–19 years</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>20+ years</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>23</strong></td>
<td><strong>3</strong></td>
<td><strong>1</strong></td>
<td><strong>0</strong></td>
<td><strong>6</strong></td>
<td><strong>13</strong></td>
</tr>
</tbody>
</table>
3.1.4 Uptake of MMR vaccine in the NZ population

Vaccine coverage has improved dramatically over the past four years and the proportion of children fully immunised by two years of age is now well over 90% for all ethnic groups. However, only 80% of children received their 15 month immunisation by 18 months of age (on time).

![NZ Immunisation Coverage 1991-2012 by Ethnicity](image)

**Figure 5.** NZ Immunisation coverage, fully immunised with all routinely scheduled vaccines by two years of age (13)


3.2 Summary of New Zealand epidemiology

Measles still occurs in NZ, although there has not been a large epidemic since 1997. In 2011, there was an epidemic with 597 cases notified. Cases were largely the result of importations on seven separate occasions, two of which resulted in over 100 secondary cases. Most cases occurred in unvaccinated people, including those too young for vaccination. Of the 597 notified cases in 2011, 22 (3.6%) had been fully immunised, 15% were under 15 months of age and not eligible for MMR vaccine.

Mumps has remained steady since 1994. In 2011 51 cases were reported. There were two hospitalisations and 46% of the cases had received at least one dose of vaccine. Of the cases, 20% had been fully immunised.

Rubella has declined steadily since 1995. In 2010, there were only four cases notified and 23 cases in 2011, possibly as a result of increased awareness of rashes due to the measles epidemic. One case occurred in a fully vaccinated person.

Coverage of the MMR vaccine is now over 90% for infants of all ethnicities by their second birthday. At total of 80% of NZ infants receive their first dose of MMR vaccine on time (by 18 months of age).
4. Safety

4.1 Objective

The objective for this section is to summarise the safety data of MMR and MMRV vaccines for the past four years. Only adverse events following immunisation (AEFI) are considered here and not reactogenicity which has been described previously. The use of MMR +V compared with MMRV vaccines is a focus and any new issues arising.

4.2 Review

4.2.1 2012 Cochrane review of MMR vaccines

A Cochrane review published in 2012 assessed the adverse effects associated with MMR vaccine in children up the age of 15 years. The authors included randomised controlled trials, a controlled clinical trial, cohort studies, case-control studies, time-series trials, case cross-over trial, ecological studies, and self-controlled case series studies involving approximately 14,700,000 children. Exposure to MMR was found unlikely to be associated with autism, asthma, leukaemia, hay fever, type 1 diabetes, gait disturbance, Crohn’s disease, demyelinating diseases, bacterial or viral infections (14). Conditions found to have an increased risk associated with MMR vaccine are summarised in Table 4. The vaccines included in the review were:

- Triviraten™ Berna
- M-M-R® II
- Morupar
- Priorix®
- Trimovax®

Table 4. Conditions associated with an increased risk following administration with MMR vaccines (14)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Vaccine/component</th>
<th>Risk ratio (RR) (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aseptic meningitis within three weeks of immunisation</td>
<td>Urabe-containing MMR</td>
<td>14.28 (7.93 to 25.71)</td>
</tr>
<tr>
<td>Aseptic meningitis within three weeks of immunisation</td>
<td>Leningrad-Zagreb MMR</td>
<td>22.5 (11.8 to 42.9)</td>
</tr>
<tr>
<td>Aseptic meningitis within five weeks of immunisation</td>
<td>Leningrad-Zagreb MMR</td>
<td>15.6 (10.3 to 24.2)</td>
</tr>
<tr>
<td>Febrile seizures within two weeks</td>
<td>MMR</td>
<td>1.10 (1.05 to 1.15)</td>
</tr>
<tr>
<td>Febrile seizures within six to 11 days in children aged 12-23 months</td>
<td>MMR</td>
<td>RI 4.09 (3.1 to 5.33)</td>
</tr>
<tr>
<td>Febrile seizures within six to 11 days in children aged 12-35 months</td>
<td>MMR</td>
<td>5.68 (2.31 to 13.97)</td>
</tr>
<tr>
<td>Thrombocytopenia purpura within six weeks in children aged 12 to 23 months</td>
<td>MMR</td>
<td>6.3 (1.3 to 30.1) and IRR 5.38 (2.72 to 10.62)</td>
</tr>
<tr>
<td>Thrombocytopenia purpura within six weeks in children aged one month to 18 years</td>
<td>MMR</td>
<td>OR 2.4 (1.2 to 4.7)</td>
</tr>
</tbody>
</table>

4.2.2 Safety studies published since 2012 Cochrane review

In addition to the studies included in the Cochrane review, a review of data from five managed Care Organisations (Kaiser Permanente) in the US. This data included a cohort of 1.8 million children aged six weeks to 17 years of age. Incidence rate ratios (IRR) for immune thrombocytopenic purpura (ITP) were established for the window of 1-42 days after vaccination and control periods. There were 197 chart-confirmed cases of ITP out of the 1.8 million children. There was no elevated risk for ITP following any early childhood vaccine except MMR for which an IRR of 5.45 (1.61-18.64) was found, consistent with that found in other studies (see Table 4) (15).
4.2.3 Background rates of disease to assess vaccine safety

A nationwide population based study in Denmark was carried out to predict the number of outcomes temporally associated, but not causally associated, with vaccination. The participants included all live born infants delivered after 1st January 1980 and the population was followed until hospital admission for a selected outcome diagnosis, death, first emigration, age 18 years or 31 December 2009. Denmark had 82 - 93% vaccine coverage during this period. The study included 2,300,227 live born infants and the median follow-up was 16.8 person years. A range of outcomes temporally associated with vaccine dose per 1,000,000 vaccinated subjects are presented for each age group (16).

4.2.4 Recurrent Guillain-Barré syndrome and MMR

Data from the Kaiser Permanente Northern California database from 1995 – 2006, identified 550 cases of Guillain-Barré syndrome (GBS) over 33 million person years. Following a diagnosis of GBS, 279 individuals received 989 vaccines. There were no cases of recurrent GBS within six weeks of receipt of any vaccine (17).

4.2.5 Type 1 diabetes and measles, mumps and rubella infections

Type 1 diabetes mellitus has been associated with both genetic and environmental factors. While human leukocyte antigen (HLA) genes seem to be the major contributor to the onset of type 1 diabetes, environmental triggers also appear to play a role. Infections have been associated with type 1 diabetes and congenital rubella, rotavirus, Coxsackie B and cytomegalovirus have all been implicated. An Italian study assessed whether there was an association between incidence trends of type 1 diabetes and the notifications of measles, mumps and rubella infections from 1996 - 2001. With the exception of one territory (Sardinia), significant results were obtained for mumps ($\rho = 0.466, 0.043–0.747, \ p = 0.034$) and rubella ($\rho = 0.535, 0.134–0.785, \ p = 0.014$), while no significant results were observed for measles ($\rho = 0.252, 0.202–0.617, \ p = 0.269$). The authors concluded that mumps and rubella viral infections were associated with the onset of type 1 diabetes. The significant difference observed, after excluding the Sardinian data, suggested other environmental factors operating in populations with different genetic susceptibility (18).

4.2.6 Safety of three doses of MMR

As a result of recent mumps outbreaks in highly vaccinated populations in the US, a third dose intervention was implemented in these populations in an attempt to control the outbreak. The safety of this third dose of vaccine was documented and found to be consistent with the second dose safety data for MMR. No serious events were reported (19).

4.2.7 Safety of MMR vaccine in patients with DiGeorge Syndrome

The T-cell lymphocytopenia in patients with DiGeorge Syndrome may preclude the use of MMR vaccine and little is known about the safety of this vaccine in these patients. During the outbreaks in the US recently, physicians were prompted to consider using MMR vaccine in people with immunosuppression including HIV patients. The safety of MMR was studied in 82 patients with 22q11.2 microdeletion (subset of DiGeorge Syndrome) who had near or greater than 500 circulating CD4+ cells/mm$^3$. Events were monitored for 60 days after immunisation and immunological assessments were undertaken. MMR vaccination was found to be safe in these patients (20).

4.2.7.1 Safety of MMR vaccine in children with juvenile idiopathic arthritis

There is very little data on the safety and immunogenicity of live vaccines for patients with juvenile idiopathic arthritis (JIA) who are receiving methotrexate (MTX) or the tumour necrosis factor-alpha (TNF-\(\alpha\)) receptor agonist etanercept. Safety was assessed following MMR revaccination in children with JIA treated with either low-dose MTX therapy alone or in combination with etanercept. No increase in arthritis disease activity or medication use was seen within six months after MMR revaccination, including JIA patients using etanercept. No overt measles, mumps, rubella or secondary severe infections related to vaccination were noted (21).

4.2.7.2 Further studies assessing MMR vaccines and autism

The unfounded association between MMR vaccines and autism and other developmental disorders has been addressed in many countries, using a range of epidemiological methods, and the evidence supporting the safety of these vaccines is overwhelming. However, studies continue to be carried out in populations not included in the earlier investigations. A Japanese case control study assessed the relationship between potential risk factors, including multiple

\(\rho\) Spearman’s Rho (Spearman’s rank correlation)
vaccines, MMR and autistic spectrum disorder. For MMR vaccination, the overall risk (OR) for autistic spectrum disorder was 1.04 (95% CI 0.65–1.68), and no significant differences were found for the other vaccines. For all of the prenatal, perinatal and neonatal factors, there were no significant differences between cases and controls. No significant differences were found in the risk of MMR vaccination and the number of vaccine injections in the conditional multiple regression model (OR 1.10 [95% CI 0.64–1.90]; OR 1.10 [95% CI 0.95–1.26], respectively). There was no evidence found for an association between MMR vaccines, or any evidence for an increasing numbers of vaccines, to be associated with a risk for autistic spectrum disorder in a genetically homogeneous population (22).

### 4.2.8 Safety of MMRV

MMRV (ProQuad®) has also been manufactured using recombinant human albumin (rHA) in place of human serum albumin. The safety profile was not altered as a result of this change and the vaccine is marketed in Europe as M-M-RVAXPRO™ with over 40 million doses distributed. Post-marketing surveillance support the safety of this vaccine. To assess the safety of the rHA-manufactured vaccines in a two-dose regime a European multi-centre clinical trial was carried out in 3388 children at 12 - 22 months of age. Dose two was administered between 28 - 42 days after dose one. The results confirmed that the rHA-manufactured vaccine had a safety profile consistent with the vaccine manufactured with human serum albumin in a two dose schedule. There were no serious allergic reactions (23).

#### 4.2.8.1 Febrile seizures following MMRV

Febrile seizure risk seven - 10 days after MMRV is double that following administration of separate MMR and varicella vaccines among one-year-olds. Whether MMRV or MMR +V affect febrile seizure risk among four to six-year-olds was assessed using the US Vaccine Safety Datalink. From 2006 to 2008, 86,750 children received MMRV; from 2000 to 2008, 67,438 received same-day MMR + V. Seizures were rare throughout days 0 to 42 without peaking during days seven to 10. There was one febrile seizure, seven to 10 days after MMRV and no seizures after MMR + V. Febrile seizure risk was one per 86,750 MMRV doses (95% CI 1 per 3,426 441, 1 per 15,570) and nil per 67,438 MMR + V doses (1 per 18,282). This provides support that MMRV and MMR+V are not associated with an increased risk of febrile seizures among four to six year old children (24).

#### 4.2.8.2 Concomitant administration with MenACWY-CRM

The safety of MenACWY-CRM (quadrivalent conjugate meningococcal vaccine) was assessed in seven to nine month old infants receiving two doses of the meningococcal vaccine. They were randomised to receive MenACWY-CRM with or without MMRV at 12 months of age. No increased reactogenicity was observed with MenACWY-CRM + MMRV compared with MMRV alone, and there were no study-related serious adverse events (25).

### 4.3 Summary vaccine safety

A Cochrane review of MMR vaccines published in 2012 supports the safety profile of these vaccines with no new issues raised. Conditions known to have an increased risk associated with MMR vaccines are aseptic meningitis within three - five weeks of Urabe-containing and Leningrad-Zagreb MMR vaccines, febrile seizures within two weeks of MMR vaccines and ITP within six weeks. More recently Kaiser Permanente data for 1.8 million children found 197 cases of ITP with an increased risk following MMR vaccine (but no other vaccines) and data for 33 million person years found no recurrence of GBS within receipt of any vaccine. A large Italian study found that a history of infection with mumps or rubella was associated with an increased risk for onset of type 1 diabetes. Several studies in high risk groups demonstrated safety in patients with DiGeorge Syndrome and JIA. The most recent study of MMR and autism in a genetically homogenous population found no evidence for an increased risk.

MMRV vaccines have been found to have a small but significant increased risk of febrile events after a first dose when given before four years of age. There is no increased risk for children aged four - six years.

MMR vaccines continue to have an excellent safety profile worldwide.
5. Immunogenicity, efficacy, effectiveness and vaccine impact

5.1 Objective
The objective for this section is to consider the most recent literature on the immunogenicity and effectiveness of MMR and MMRV vaccines.

5.2 Outcomes
Key outcomes are measures of immunogenicity and notifications of measles, mumps and rubella cases in relation to the use of MMR and MMRV vaccines. The vaccine performance in special groups is reviewed.

5.3 Review

5.3.1 Immunogenicity of MMR vaccines
The avidity of antibodies matures after immunisation or infection, and over a period of around six months, more specific higher affinity antibodies are produced. Lower affinity antibodies have been associated with reinfection and disease progression. In Finland, a cohort was recruited at the initiation of the MMR vaccination programme, which commenced in 1982, to study the persistence of vaccine-induced antibodies. By the mid-1990s, Finland had eliminated measles, mumps and rubella and there was little opportunity for natural boosting to occur. The 25-year follow up of this cohort has shown that MMR induced antibodies wane over time. The most recent study of this cohort aimed to investigate the change and correlation of antibody concentration and avidity over time after vaccination, and also to determine if there was a difference in antibody avidity between vaccine-induced and infection-induced antibody (26).

The groups in the study were as follows:

- Two groups from an MMR vaccination cohort studied since 1982.
- Group one (n = 71) consisted of individuals recruited in 1982. All were seronegative for measles, mumps and rubella before receiving two MMR vaccinations at 14–18 months and six years of age. Samples were taken at six months (1987) and 20 years (2007) after the second MMR vaccination. Persistence of MMR antibodies in this group during the last 20 years has been previously described.
- Group two (n = 48) included older individuals from the cohort recruited in 1982. This group had received a monoclonal measles vaccine (Rimevax containing the Schwarz strain) at around 12 months of age, and all were seronegative for mumps and rubella before being vaccinated with MMR vaccine at six and 11–13 years of age. Samples were taken 18–20 years (2007) after the second MMR vaccination.

- Group 3 (n = 50) included children aged 10–11 years born after the elimination of MMR diseases from Finland. The samples were taken from residual sera collected four–five years after age for the second dose of MMR in 2005 at the Helsinki and Uusimaa hospital district laboratory. The vaccination status was not verified; however, vaccination coverage was >95% during their lifetime and all individuals were positive for rubella immunoglobulin G (IgG), indicating vaccination.

- Group 4 (n = 50), also collected from the same set of residual sera, were presumably naturally infected 50–59-year olds not covered by the MMR vaccination program. The men in this group (n = 24) most likely received one dose of inactivated mumps vaccine (Enders strain) at the age of about 20 years as army recruits during compulsory army service.

There were no measurable measles IgG antibodies for 15.5%, 10.4%, 4%, and 0% of individuals from groups 1, 2, 3, and 4, respectively. There were no measurable mumps IgG antibodies for 23%, 10%, 26%, and 8% of individuals from groups 1, 2, 3, and 4, respectively. All individuals in all study groups had measurable antibodies against rubella. The geometric mean titres (GMT) and avidity indexes for all groups are presented in Table 5. The antibody avidity indexes were high for measles and rubella but low for mumps. Twenty years after a second MMR vaccination, antibody levels for all three viruses waned. Also, the mean avidity index decreased by 8% for measles, 24% for mumps, and remained unchanged for rubella. Antibody avidity correlated with antibody concentration for measles.

\^Avidity index is the dissolution of bound antibody-antigen complex with a reagent divided by dissolution without a reagent
There was partial correlation for rubella and no correlation for mumps. The authors concluded that measles and rubella induced high-avidity antibodies and mumps induced low-avidity antibodies after both vaccination and natural infection. Waning of both the concentration as well as the avidity of antibodies might contribute to measles and mumps infections individuals who have received two doses of MMR (26).

Table 5. Geometric Mean Antibody Concentrations and Mean Avidity Indexes for Groups 1, 2, 3, and 4 for measles, mumps, and rubella and the number and percentage of Low-, Intermediate-, and High-Avidity Samples (26)

<table>
<thead>
<tr>
<th>Measles</th>
<th>Mumps</th>
<th>Rubella</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No.</strong></td>
<td><strong>No.</strong></td>
<td><strong>No.</strong></td>
</tr>
<tr>
<td><strong>Group 1 6 mo</strong></td>
<td>66</td>
<td>62</td>
</tr>
<tr>
<td><strong>Group 1 20 y</strong></td>
<td>66</td>
<td>62</td>
</tr>
<tr>
<td><strong>Group 2</strong></td>
<td>45</td>
<td>46</td>
</tr>
<tr>
<td><strong>Group 3</strong></td>
<td>49</td>
<td>44</td>
</tr>
<tr>
<td><strong>Group 4</strong></td>
<td>50</td>
<td>45</td>
</tr>
</tbody>
</table>

5.3.1.1 Immunogenicity of MMR vaccine in patients with DiGeorge Syndrome

The T-cell lymphocytopenia in patients with DiGeorge Syndrome may preclude the use of MMR vaccine and little is known about the immunogenicity of this vaccine in these patients. During the outbreaks in the US recently, physicians were prompted to consider using MMR vaccine in people with immunosuppression including HIV patients. The safety and immunogenicity of MMR in 82 patients with 22q11.2 microdeletion (subgroup of DiGeorge Syndrome) who had near or greater than 500 circulating CD4+ cells/mm3 was studied. The vaccine was immunogenic but the ability to sustain long term protection was lower than for age-matched controls. The authors recommend that persons with 22q11.2 microdeletion should be periodically assessed for antibody levels and re-immunised accordingly (20). Safety in these patients is summarised in 4.3.2.

5.3.1.2 Immunogenicity of MMR vaccine in children with juvenile idiopathic arthritis

There is very little data on the safety and immunogenicity of live vaccines for patients with JIA who are receiving methotrexate (MTX) or the TNF-α receptor agonist, etanercept. To assess the cell-mediated immune response to MMR vaccine, IFN-γ production by T-cells specific for the three components of MMR vaccine and seroprevalence of virus-specific IgG antibodies were investigated following MMR revaccination in children with JIA treated with either low-dose MTX therapy alone or in combination with etanercept. Low-dose MTX therapy following MMR vaccination did not affect T-cell mediated immunity in vitro. Neither low-dose MTX nor etanercept treatment, given simultaneously with revaccination, significantly interfered with the generation of long-lived virus-restricted T-cells or protective levels of virus-specific IgG antibodies (21).
A Dutch study analysed the persistence of MMR vaccine-specific antibody concentrations in 400 children with JIA and 2176 age-matched controls. When corrected for age and the number of vaccinations, lower vaccine-specific geometric mean antibody concentrations were found in patients with JIA against mumps and rubella. Measles-specific geometric mean antibody concentrations were higher compared with healthy controls (p < 0.001). The prevalence of protective antibody concentrations was significantly lower in patients for mumps (OR 0.4; 95% CI 0.3 to 0.6) and rubella (OR 0.4; 95% CI 0.3 to 0.7). The seroprotection rates against measles did not differ between patients and healthy controls (OR 1.4; 95% CI 0.8 to 2.5). The MTX and glucocorticosteroid use did not affect pathogen-specific geometric mean antibody concentrations or seroprotection rates (27).

5.3.3.3 Immunogenicity of MMR in children following chemotherapy for acute lymphoblastic leukaemia

Immune competence in people with acute lymphoblastic leukaemia (ALL) results from both the chemotherapy-induced neutropenia and also the reduction of pre-existing serum antibodies. Current recommendations around vaccination of children who have received chemotherapy are debated.

A Brazilian study evaluated antibody levels against hepatitis B, rubella, measles and mumps vaccine antigens in 33 children after completing chemotherapy (before and after vaccine booster doses) and the results were compared to the data of 33 healthy children matched for gender, age and social class. After chemotherapy, 75.9%, 67.9%, 59.3% and 51.7% of the patients showed low antibody titres that would be unlikely to protect against exposure to measles, rubella, hepatitis B and mumps, respectively. After receiving a vaccine booster dose, the patients developed high antibody levels consistent with protective levels against measles, mumps and hepatitis B, but not against rubella. The authors recommended additional doses of MMR (and hepatitis B) vaccine in patients following haematological recovery. They suggest viral vaccine antibodies be assessed to verify the individuals protective status (28).

5.3.1.4 Immunogenicity of the measles component of MMR in children following haematopoietic stem cell transplantation

Following allogeneic haematopoietic stem cell transplantation (HSCT), pre-transplant levels of antibodies decline and patients require re-vaccination. Responses to vaccination are influenced by the time passed since transplant, vaccine doses received and graft-versus-host disease. To measure immunity to vaccine preventable diseases in paediatric allogeneic haematopoietic stem cell transplant patients, a Finnish study assessed the responses to scheduled vaccines in 23 paediatric patients. Prior to revaccination 9/23 (39%) of patients had protective levels of measles antibodies. After revaccination 15/18 (83%) achieved levels considered protective (29).

St Jude Children’s Research Hospital (Memphis, US) conducted a longitudinal study of the antibody responses to vaccination in 210 survivors of all-HSCT and analysed the factors that were associated with negative antibody titres. Of 130 patients tested for measles antibodies before immunisation, 39 (30%) were positive. After immunisation, positive antibody responses were seen in approximately two thirds of patients at the first-year follow-up and stabilised thereafter [66.7% (16/24) at more than five years]. Lower CD3 counts were significantly associated with negative titres (p = 0.026). Of the 138 patients tested for mumps titres before vaccination, 41 (29.7%) were positive. Positive antibody responses increased over time, but only 61.5% of patients had responses after the second year (16/26 at more than five years). Negative titres before immunisation and lower serum IgG concentrations were associated with negative titres after immunisation (p = 0.033, p = 0.052, respectively). Of the 133 patients tested for rubella antibodies before immunisation, 59 (44.4%) were positive. Contrary to the pattern observed for measles and mumps, the percentage of patients positive for rubella antibodies more than doubled [93.3% (83/89)] within a year of vaccination, and more than 90% of patients continued to have positive antibodies [92.3% (24/26) at more than five years]. The authors recommend long term follow-up of these patients, and if necessary, re-vaccinated those at risk (30).
5.3.1.5 Measles – duration of maternal antibodies

Maternally acquired immunity poses challenges for immunisation programmes, in that, maternal antibodies both protect from measles infection during early life, but also interfere with effective responses to measles vaccination. Timing of vaccination needs to occur as soon as possible after maternally derived antibodies have waned and before disease can occur. Spain introduced vaccination against measles with MMR vaccine in 1981 and added a second dose from 1988. Measles transmission ceased in Catalonia in 2000, with only sporadic imported cases occurring until an outbreak in 2006. The cohort most susceptible during this outbreak were children under 15 months of age and interventions during outbreak control included administering a dose of MMR vaccine to infants aged nine months of age. A study was conducted in 58 mothers and their 61 children to determine the level of measles antibodies in children vaccinated at nine months (and their mothers) at the time of vaccination and the response to vaccination measured by antibody titres after vaccination. Seroconversion was defined as the presence of antibodies after vaccination in subjects without antibodies before vaccination. Fewer than approximately 38% of the children had pre-existing maternal antibodies. Interference by maternal antibodies occurred in 30% of the children (95% CI 11.9% - 54.3%). The response to vaccination in the nine month old infants was 74%. Advancing the first dose of measles vaccine in Catalonia from 15 months to 12 months was considered an appropriate strategy (31).

5.3.1.6 Measles - immunogenicity in children with HIV receiving high active antiretroviral therapy

The response to measles vaccine is reduced in children with HIV who are not receiving highly active antiretroviral therapy (HAART). A study, which included 193 HIV-infected children aged two - 19 years with HIV loads <30,000 copies/antibody concentrations, before and at three points post vaccination, determined the measles antibody concentrations following MMR vaccination. At entry, 52% of 193 subjects were seroprotected (PRN ≥120 mIU/mL). Seroprotection increased to 89% eight weeks post-vaccination, and remained at 80% by 80 weeks post-vaccination. Of 65 subjects revaccinated 4 - 5 years later, 85% demonstrated an anamnestic response based on seroprotection before or seven days after vaccination. Lower HIV load (≤400 copies/mL) at initial study vaccination was associated with higher seroprotection rates, greater antibody concentrations and memory. The authors concluded that measles revaccination induced high rates of seroprotection in children receiving HAART (32).

5.3.1.7 Mumps

5.3.1.7.1 Immunity against escape virus strains

The recent mumps outbreaks in vaccinated populations have raised concern that there may be mumps virus strains that are escaping vaccine-induced immunity. To investigate this possibility, sera from 96 children aged four - six years receiving MMR vaccine (containing the Jeryl Lynn strain) were obtained six weeks after vaccination and the ability to neutralise a diverse selection of mumps virus strains was assessed. There was a range of neutralising antibody geometric mean titres against some virus strains, but all viruses were readily neutralised by the sera suggesting that immune escape is unlikely (33).

5.3.1.7.2 Maternally acquired immunity to mumps

Maternally derived antibodies to mumps offers primary protection to the neonate. The duration of the presence of maternal mumps antibodies was assessed in a prospective cohort study in Belgium. Mumps IgG was assessed from samples from 213 mother–child pairs at seven time points between pregnancy and 12 months of age. Non-linear mixed models were used to model maternal antibody decay in infants. The model-based median time to loss of antibodies was 3.6 months. The median time to loss of antibodies in children of naturally immune women (3.8 months) and children of vaccinated women (2.4 months) differed significantly (p = 0.025). The duration of maternal antibodies in the infants was correlated with the antibody level of the mother and the birth weight of the infant (p < 0.0001). The authors concluded that the children of vaccinated mothers lose maternal mumps antibodies earlier than children born to mothers with naturally acquired immunity and that vaccination with mumps-containing vaccine earlier than 12 months of age is not expected to be affected by maternal antibody (34).
5.3.2 Immunogenicity of MMRV vaccine

The WHO recommends a first dose of measles vaccination at nine months of age with a second dose given between 12 - 18 months of age. In countries where there is a relatively low level of measles transmission, the WHO recommends measles vaccination at 12 months to optimise the improved immunogenicity to the vaccine that occurs at an older age. In countries where measles immunisation programmes have been in place for many years, over 99% infants born to vaccinated women (95% to naturally immune) are observed to lose maternally acquired antibody by six months of age. The immunogenicity of MMRV (ProQuad®), given from nine months of age in a two dose schedule given three months apart, was evaluated. The outcome was the non-inferiority of the response rates compared with administration of the vaccine at 11 and 12 months of age. The non-inferiority of the response after dose two was reached when dose one was administered at 11 months (98%) compared with 12 months (99%) but was not reached when dose one was administered at nine months (95%). The response rate to measles following dose one increased with age, from 73% to 88% and 90% at nine, 11 and 12 months, respectively. For mumps, rubella and varicella, response rates were no different after dose one (>95%) or dose two (>99%) regardless of whether dose one was administered at nine, 11 or 12 months of age. MMRV can be given as early as nine months providing a second dose is given promptly with a minimum of a three months interval (35).

The persistence of immunity to three years, induced by MMRV (Priorix-Tetra™) or MMR (Priorix®) and V (Varilrix®), was assessed in 494 German and Austrian children aged 12-18 months of age at first dose. The children received either two doses of MMRV 42 - 56 days apart or one dose of MMR and V administered at the same time followed by a second dose of MMR 42 - 56 days later. Three years post-vaccination, seropositivity rates in subjects seronegative prior to vaccination were: MMRV-measles, 98.5% (GMT=3,599.6); mumps, 97.4% (GMT=1,754.5); rubella, 100% (GMT=51.9); varicella, 99.4% (GMT=225.5); MMR + V-measles, 97.0% (GMT=1,818.8); mumps, 93.8% (GMT=1,454.6); rubella, 100% (GMT=53.8); and varicella, 96.8% (GMT=105.8). Of the subjects, 15–20% reported contact with individuals with varicella/zoster each year. After three years, the cumulative varicella breakthrough disease rate was 0.7% (two cases) in the MMRV group and 5.4% (five cases) in the MMR + V group. There were no physician confirmed breakthrough cases of measles, mumps or rubella (36).

5.3.2.1 Concomitant administration with MenACWY-CRM

The immunogenicity of MenACWY-CRM was assessed in seven - nine month old infants receiving two doses of the meningococcal vaccine. They were randomised to receive MenACWY-CRM with or without MMRV at 12 months of age. Concomitant administration of MMRV with MenACWY-CRM did not affect the immune response to either vaccine. The two-dose series of MenACWY-CRM induced adequate immune response to all four meningococcal serogroups (25).

5.3.2.2 Concomitant administration of MMRV with hepatitis A and pneumococcal conjugate vaccines

The immunogenicity of Priorix-Tetra™ (refrigerated and frozen version) and ProQuad® were each co-administered as a first dose with hepatitis A vaccine and PCV-7 vaccines to 1783 infants aged 12 to 14 months and noninferiority of the Priorix-Tetra™ was compared with ProQuad®. Noninferiority was demonstrated for measles, mumps and rubella viruses, but not fully demonstrated for varicella virus. Noninferiority to the hepatitis and pneumococcal vaccines was also demonstrated. The clinical significance of the differences in anti-varicella responses is not yet known. The seroresponse rates to varicella (>75 mIU/mL) were 86.7% for the ProQuad® vaccinees and 69.8% for Priorix-Tetra™ stored at -20°C and 57.1% for Priorix-Tetra™ stored at +4°C (37).

5.3.3 2012 Cochrane review of the effectiveness of MMR vaccines

The 2012 Cochrane review that included randomised controlled trials, a controlled clinical trial, cohort studies, case-control studies, time-series trials, case cross-over trial, ecological studies, self-controlled case series studies involving approximately 14,700,000 children also assessed the effectiveness of MMR vaccine (14).

5.3.3.1 Measles

Based on the available evidence, a single dose of MMR vaccine dose is at least 95% effective in preventing clinical measles and 92% effective in preventing secondary cases among household contacts (14).
5.3.3.2 Mumps

Effectiveness of at least one dose of MMR in preventing clinical mumps in children was estimated to be between 69 - 81% for the vaccine prepared with Jeryl Lynn mumps strain and between 70 - 75% for the vaccine containing the Urabe strain. Vaccination with MMR containing the Urabe strain has demonstrated to be 73% effective in preventing secondary mumps cases. Effectiveness of Jeryl Lynn containing MMR in preventing laboratory-confirmed mumps cases in children and adolescents was estimated to be between 64 - 66% for one dose and 83 - 88% for two vaccine doses (14).

5.3.3.3 Rubella

The Cochrane review did not identify any studies assessing the effectiveness of MMR in preventing clinical or laboratory-confirmed rubella (14).

5.3.4 Effectiveness of MMR vaccine during mumps outbreaks

Implementation of vaccination against mumps has been highly successful in controlling the disease. In the US, mumps incidence declined rapidly following introduction of a single dose of mumps vaccine from around 50 to 251 reported cases per 100,000 prior to 1967 to 2 per 100,000 by the 1980s. In 1989, the US introduced two doses of MMR vaccine to improve measles control; this strategy resulted in a further decline in mumps incidence to 0.1 cases per 100,000 and less than 300 cases per year. However, in 2006 and 2009-10, there were mumps outbreaks in populations with high two-dose coverage rates. A study evaluating the impact of a third dose of MMR vaccine in one of these populations demonstrated that the immune responses were anamnestic in the previously vaccinated and that the intervention rapidly controlled the outbreaks. The authors concluded that the administration of a third dose of MMR vaccine during an outbreak in highly vaccinated populations may be an effective (and safe, see section 4) method of controlling mumps (19).

A mumps outbreak in the Netherlands in an unimmunised community spread to a highly vaccinated population where secondary vaccine failures occurred. The causes of failure appeared to be the waning of vaccine-induced immunity, a relative mismatch between vaccine and outbreak strain and intense social contact in the affected group (see section 5.3.1 for studies on immunity generated by mumps). Orchitis was a frequently reported complication. Among the cases, the previous receipt of MMR vaccine was associated with a reduction in complications (see Table 6) (38).

Table 6. Mumps complications by MMR vaccination status, the Netherlands, December 1, 2009 to June 14, 2011 (38)

<table>
<thead>
<tr>
<th>Complication</th>
<th>MMR doses received</th>
<th>No. mumps cases</th>
<th>No. cases with complications (%)</th>
<th>OR</th>
<th>aOR†</th>
<th>p value</th>
<th>Adjusted VE‡ % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orchitis§</td>
<td>0</td>
<td>86</td>
<td>20 (23)</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>48</td>
<td>5 (10)</td>
<td>0.38</td>
<td>0.34</td>
<td>0.05</td>
<td>66 (1 to 88)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>338</td>
<td>31 (9)</td>
<td>0.32</td>
<td>0.26</td>
<td>&lt;0.01</td>
<td>74 (49 to 87)</td>
</tr>
<tr>
<td>Other complications¶</td>
<td>0</td>
<td>117</td>
<td>1 (1)</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>85</td>
<td>1 (1)</td>
<td>1.38</td>
<td>0.88</td>
<td>0.93</td>
<td>12 (–14 to 95)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>571</td>
<td>6 (1)</td>
<td>1.23</td>
<td>0.75</td>
<td>0.8</td>
<td>25 (–5 to 91)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>0</td>
<td>130</td>
<td>4 (3)</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>83</td>
<td>2 (2)</td>
<td>0.8</td>
<td>0.7</td>
<td>0.69</td>
<td>30 (–312 to 88)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>535</td>
<td>6 (1)</td>
<td>0.4</td>
<td>0.43</td>
<td>0.25</td>
<td>57 (–84 to 90)</td>
</tr>
</tbody>
</table>

* Only those for whom complication and vaccination status were known are included; therefore, totals may differ. MMR, mumps, measles, rubella; OR, odds ratio; aOR, adjusted odds ratio; VE, vaccine effectiveness; ref, reference categories.
† OR and VE adjusted for age group (<18, 18–25, >25 y) and sex, except for orchitis, where the OR and VE were adjusted only for age group. ‡ VE = 1 – OR where the OR is an approximation of the relative risk.
§ Only men ≥12 years of age are included.
¶ Includes the following reported complications: pancreatitis (n = 2), meningitis (3), thyroiditis (1), bronchitis (1), high fever and shortness of breath (1).
The complications of mumps in relation to vaccination status were studied in England and Wales based on data from hospital admissions and enhanced mumps surveillance for outbreak and non-outbreak periods from 2002 - 2006. Risk was reduced for hospitalisation (OR 0.54, 0.43–0.68), mumps orchitis (OR 0.72, 0.56–0.93) and mumps meningitis (OR 0.28, 0.14–0.56) when patients had received one dose of MMR vaccine. It was concluded that the protective effect of vaccination on disease severity is a critical factor for consideration when assessing the total effects of current and future mumps control strategies. The association between vaccination and mumps complications is summarised in Table 7 (39).

Table 7. Association between receipt of vaccination and mumps complications, adjusted for age and sex, England and Wales, April 1, 2002 - March 31, 2006 (39)

<table>
<thead>
<tr>
<th>Complication</th>
<th>Vaccine dose</th>
<th>Total mumps cases</th>
<th>No. cases (%)</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization</td>
<td>0</td>
<td>8298</td>
<td>317 (3.8)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>6312</td>
<td>122 (1.9)</td>
<td>0.50 (0.40-0.61)</td>
<td>0.54 (0.43-0.68)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>914</td>
<td>13 (1.4)</td>
<td>0.36 (0.21-0.64)</td>
<td>0.45 (0.25-0.80)</td>
</tr>
<tr>
<td>Orchitis†</td>
<td>0</td>
<td>4574</td>
<td>356 (7.8)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>3241</td>
<td>123 (3.8)</td>
<td>0.44 (0.36-0.55)</td>
<td>0.72 (0.56-0.93)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>475</td>
<td>7 (1.5)</td>
<td>0.17 (0.08-0.37)</td>
<td>0.64 (0.28-1.44)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>0</td>
<td>8298</td>
<td>42 (0.5)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>6312</td>
<td>10 (0.2)</td>
<td>0.31 (0.16-0.62)</td>
<td>0.28 (0.14-0.56)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>914</td>
<td>1 (0.1)</td>
<td>0.22 (0.03-1.57)</td>
<td>0.17 (0.02-1.26)</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>0</td>
<td>8298</td>
<td>26 (0.3)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>6312</td>
<td>12 (0.2)</td>
<td>0.61 (0.31-1.20)</td>
<td>0.95 (0.41-2.190)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>914</td>
<td>0 (0.0)</td>
<td>0. (0.0-1.34)‡</td>
<td>-</td>
</tr>
</tbody>
</table>

OR - odds ratio; CI - confidence interval; ‡ not estimable
† Adjusted for age only; ‡ exact CI
5.4 Summary of effectiveness

Many countries who have implemented MMR vaccine, achieved high coverage and maintained it, have eradicated measles and rubella. The duration of protection offered by MMR vaccine is uncertain as the vaccine has only been in use since the early 1980s. Data from Finland, where there is no circulation of wild disease to boost population immunity, shows that MMR-induced antibodies wane over time. The duration and avidity of measles and rubella antibodies over time are superior to mumps antibodies, and it is likely the lower immunogenicity of mumps virus that has resulted in vaccine failure in highly immunised populations, rather than escape virus variants. Rubella antibodies endure the longest and have the highest avidity.

The immunogenicity of MMR vaccine in people with DiGeorge syndrome is of shorter duration than in matched controls, and monitoring of immunity is recommended in these patients. Children treated for ALL were at risk of losing protective levels of antibody against measles and mumps, but not rubella. Booster doses were highly effective at raising antibody levels to levels consistent with protection. As with children treated with chemotherapy, children who have undergone HSCT have little protective immunity, however, respond well to revaccination. Treatment with MTX or etanercept does not appear to interfere with the immune response to MMR vaccine. Vaccination of children receiving HAART response well to vaccination, particularly when they have an HIV load of fewer than 400 copies/mL.

Data supports the immunogenicity of MMR vaccine given at 12 months. Maternal interference is unlikely at this age for any of the vaccine components.

MMRV vaccine can be given as early as nine months of age providing the second dose is given promptly with a minimum of three month interval. The ProQuad® MMRV vaccine appears more immunogenic than Priorix-Tetra™ for the varicella antigen, but there is no difference for the measles, mumps and rubella antigens. The temperature the Priorix-Tetra™ is stored at appears to make a difference to the varicella immunogenicity with freezing the better method.

The 2012 Cochrane review found a single dose of MMR vaccine to be at least 95% effective in preventing clinical measles and 69% - 81% effective in preventing clinical mumps. There were no studies identified for rubella, but as noted above, rubella appears to be the most immunogenic component of the MMR vaccine inducing the highest avidity antibodies, and eradication has been achieved in some countries. A third dose of MMR vaccine has been used safely and effectively during mumps outbreaks in highly immunised populations. Although the mumps vaccine is less effective than measles and rubella vaccines, cases that have been vaccinated are significantly less likely to experience complications from disease such as orchitis, meningitis and hospitalisation.
6. Age-specific issues

6.1 Objective

The objective for this section is to identify age-specific issues that may impact on the age when MMR vaccine is given.

6.2 Review

MMR vaccines have been generally demonstrated to be highly immunogenic in all ages over 12 months. Based on recent literature, there appear to be two key areas where age is a consideration for placement of vaccination.

- Vulnerable cohort from six - 15 months when most infants have lost maternally derived antibody to measles and not reached eligibility for vaccination
- Waning of mumps antibody and associated lower avidity resulting in secondary vaccine failure, most notable in adolescents and young adults

6.2.1 Protection of children over six months of age

During measles outbreaks, vaccination is recommended for infants as young as six months of age and, for infants vaccinated prior to 12 months, revaccination should occur as soon as possible after 12 months of age (40).

6.2.2 Waning immunity to mumps

Mumps cases have remained relatively stable in NZ over the past few years. Most cases of mumps notified in 2011 occurred in persons who had received at least one dose of MMR vaccine. International experience suggests a pattern of mumps outbreaks in countries where mumps vaccine has been used for many years. Such outbreaks have a tendency to be concentrated among young adults – cohorts born too early to have received mumps vaccine and too late to have been exposed naturally as children (1). Mumps vaccination in NZ commenced in 1990 and the last epidemic was in 1994. The crude herd immunity threshold for mumps is estimated to be 75-86%, the vaccine is estimated to be around 78% effective (75-82%), which is lower than the efficacy, and NZ has had poor coverage of MMR vaccine until relatively recently (1, 3).

Given international experience, NZ epidemiology and vaccine coverage history, it is possible that mumps outbreaks could occur in NZ, particularly among young adults.

6.3 Summary of age-specific issues

The primary age-related issue for MMR vaccine is around age at first dose. Given the epidemiology in children less than 15 months of age and the good immunogenicity of the vaccine in children at observed 12 months of age the first dose of MMR vaccine could be given earlier than currently recommend in NZ. In addition, awareness around possible mumps outbreaks may be prudent, due to the shorter duration and lower avidity of mumps antibodies.
7.0 Vaccines and options for scheduling

7.1 Objective
The objective of this section is to consider the different vaccines available and the options for routine scheduling. Recent data for special groups is also summarised.

7.2 Review
There are two key areas for consideration for reviewing the use of MMR and MMRV vaccines and their placement on the schedule.

1. Age of target population for each dose
2. Use of MMRV vaccine

7.2.1 Age of target population
Despite significant improvements in immunisation coverage in NZ, there are both older cohorts from years where vaccine coverage has been low and children who are younger than 15 months or delayed for their immunisation who remain susceptible to measles, mumps and rubella.

As a significant proportion of cases of measles (15% in 2011) have occurred in children too young to be targeted by the current vaccination programme, moving the timing of the first dose of MMR vaccine forward to 12 months and focusing on timeliness is likely to improve the protection in this age group and reduce opportunity for transmission.

In contrast to measles, there are few mumps cases in the under 15 month age group. Based on recent literature, the challenge with mumps appears to lie in the reduced immunogenicity conferred by both natural infection and vaccine resulting in secondary vaccine failure during adolescence. Overseas experience supports a third dose of MMR vaccine during mumps outbreaks.

The optimal age for receiving MMR vaccine has to be balanced between the age that most vaccinees will respond to the measles component of the vaccine and the window of susceptibility to disease.

Routine scheduling of dose one of MMR vaccine could occur at either 12 or 15 months of age. Given the numbers of cases of disease occurring in children under 15 months of age, moving dose one to 12 months of age may be prudent. The choice of vaccine for dose one of MMR vaccine is either MMR or MMRV. The increased risk for febrile events following dose one of MMRV may make MMR, with or without concomitant V, the preferred choice.

The options for the second dose of MMR are as above, but without the significant risk of febrile events should MMRV be the choice. Timing of the second dose may be decided based on other vaccines given in the second year of life; concomitant administration has been demonstrated to be safe and immunogenic with a variety of other vaccines.

For children older than 48 months requiring MMR vaccine, even as a first dose, the MMRV vaccine can be used without the increased risk of febrile events.

7.2.2 Special groups

7.2.2.1 Use of MMR vaccine in children with HIV
There are approximately 55 cases of HIV notified in children in NZ (41). Recently, new guidelines have been published on vaccinating HIV-positive children across Europe. The guidelines are detailed; the recommended schedule for primary immunisation and booster doses for children infected with HIV is presented below in Table 8 and is based on vaccines currently available in the United Kingdom (UK). The schedule can be modified according to local schedules and availability (42).
Table 8. Recommended schedule of primary immunisation and booster doses for HIV-infected children from the European guidelines 2012 (42).

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

Consistent with the above recommendations, the US also recommend a first dose of MMR vaccine at 12 months and a second at least one month later for HIV infected persons (40).

7.3 Summary of options for scheduling of MMR vaccine

Current evidence supports the timing of MMR vaccine to occur earlier than currently scheduled. The use of MMRV vaccine in place of MMR is an option, although, use as a second dose rather than a first dose would avoid the issues of febrile reactions associated with MMRV as a first dose in children of this age. If varicella vaccine is to be added to the NZ schedule it may be preferable to give it concurrently with MMR as MMR+V.
8. Implementation issues

8.1 Objective

The section considers the potential issues around implementation of a different MMR vaccine to the NZ schedule.

8.2 Review

8.2.1 Issues around moving MMR vaccination to 12 months of age

Currently, there are no vaccines scheduled for 12 months of age in NZ. If the timing of the MMR vaccine were to be brought forward to 12 months of age, currently, it would be as a standalone visit to the practice unless it coincided with the 9-12 month Well Child Visit. The MMR vaccine may be given concurrently with pneumococcal conjugate vaccines, should NZ move to a 2+1 schedule for pneumococcal vaccine with the booster at 12-13 months of age and also move the *Haemophilus influenzae* type B (Hib) booster to this age.

One of the key challenges in controlling measles is achieving and maintaining high vaccination coverage. Available vaccines are highly efficacious, but to prevent transmission over 95% of the population need to be immune. Interruption of endemic transmission has been achieved in countries where very high coverage has been achieved, such as Finland and some South American countries. Timing of vaccination is also important. Health insurance data for a cohort of over 40,000 children, born in Switzerland during 2006 – 2008, were used to describe the patterns of measles vaccination. In the study cohort, 62.6% of 13-month-old children were up-to-date for the 12 month measles immunisation. Approximately 59% of 25-month-old children were up-to-date for second dose, which is recommended at 15–24 months of age. Most doses were delivered during months in a child’s life when Well Child visits are recommended (e.g. 12 months of age). For the second measles vaccine dose, accelerations in vaccine delivery occurred at time points for Well Child visits during the months 19 and 25 of age, but with lower final uptake than for the first measles vaccine dose. Until their second birthday, children in this cohort spent on average 177 days and 89 days susceptible to measles, due to policy recommendations and additional delays, respectively. In a group of children aged six months to two years, reflecting the cohort age distribution, effective vaccine coverage was only 48.6% (43).

In improving measles immunisation coverage, the proposed timing and relation of recommended vaccination to Well Child visits could be considered when implementing strategies to enhancing measles coverage.

8.2.2 Issues around the use of MMRV and MMR+V

When vaccinators are considering administering MMRV in children less than four years of age, they should discuss the benefits and risks of both vaccination options with the parents or caregivers. Parents need to be made fully aware of the slight increase in risk of febrile seizures with the combination MMRV compared with separate MMR and varicella injections, where there are problems around clearly communicating these benefits and risks, for any reason, the MMR and varicella vaccines should be administered separately.

8.3 Summary for implementation issues

Changing the current placement of MMR on the NZ schedule will need to consider the mechanisms for maintaining and even improving timeliness. Centring the immunisation event on a Well Child visit may be an effective strategy. Consideration needs to be given to the period that unvaccinated or under-vaccinated children spend susceptible to disease. The use of MMRV in place of MMR vaccine will require careful communication with parents about the increased risk of febrile events should it be used as a first dose in children under four years of age.
9. International policy and practice

9.1 Objective

The objective of this section is to briefly summarise some of the strategies and policies for MMR vaccination in place in other countries. As eradication of measles and rubella is now being planned, there is a summary of recent discussions and current status in different regions of the world.

9.2 Review

9.2.1 Towards measles and rubella eradication

The ad hoc Measles Advisory Group has concluded that measles can and should be eradicated. Objectives established by the World Health Assembly in 2010 included:

- First-dose measles vaccination coverage of at least 90% at the national level and 80% in all districts.
- Reported measles incidence of fewer than five cases per million population.
- At least 95% measles mortality reduction compared with 2000.

While some regions, such as the Americas, achieved measles elimination in 2002, Europe and Eastern Mediterranean Regions had target dates of 2010 and the Western Pacific Region had a target elimination date of 2012. The World Health Assembly concluded that a target date for measles eradication should be set once the South East Asian Region had established an elimination target. It was thought 2020 would be feasible. It was also considered that, currently, there is a window of opportunity to eradicate measles due to the large proportion of the population with natural immunity. As mothers with vaccine-induced immunity transfer less antibody onto their infants, their infants become susceptible at an earlier age, and to date, there is no certainty about the duration of vaccine-induced immunity. With respect to eradication, it appears that faster may be better (44).

9.2.1.1 Regional progress

The Pan American Health Organization reported that the elimination of rubella in that region has served as a catalyst to strengthen and sustain measles elimination. Contributing to the success are targeted campaigns of adolescents and good surveillance. Achieving high vaccine coverage in people up the age of 39 years has also played an important role. The challenges to maintain the status are reported to be the maintenance of homogenous routine vaccine coverage, sustaining the disease surveillance and obtaining the political and financial support required (44).

In Europe, the enabling factors toward measles elimination are reported to be strong health care systems, adequate human resources and good surveillance. Europe has experienced challenges from the anti-vaccination movement in some countries and calls for more efforts to counter anti-vaccine rumours. A program has been established at the Imperial College, London to track rumours and it is thought that increasing vaccine demand will require improved social marketing and further research. The region is considering 2020 as a new target from elimination of measles (44).

In Southeast Asia, measles incidence decreased by nearly 50% during 2000 - 2009. This progress is much higher in countries that have implemented measles control strategies. Factors that have contributed to the success are political and financial support, community acceptance of vaccination and good laboratory infrastructure (44).

The Western Pacific Region has experienced a 92% reduction in measles incidence between 2000 – 2009, with most countries at or near elimination with the exception of China. Political commitment and high vaccine coverage are largely responsible for this achievement. Challenges to closing the remaining gaps include gaps in immunisation coverage, delayed follow-up campaigns, cases occurring in young infants too young for immunisation and importations (44).

As most countries in the Western Pacific Region use rubella vaccine routinely, the Regional Technical Advisory Group recommends that countries in the region aim to reduce CRS to less than one case per 100,000 live births by 2015. NZ has not had a case of CRS since 1998, according to the NZ Paediatric Surveillance Unit 2011 Annual Report.

Maintaining high routine coverage has hindered disease control in the African region, and although significant reduction in measles has occurred, outbreaks are common. Disruptions to health services due to insecurity, data issues and personnel shortages hinder progress in the Eastern Mediterranean Region.
9.2.2 International use of MMR and MMRV vaccines

The recommended ages for vaccination against measles, mumps and rubella (and varicella) are 12 - 15 months for dose one and four – six years for dose two. The American Academy of Pediatrics recommends, if the first dose at ages 12 - 47 months that either MMR and varicella vaccines administered separately, or MMRV can be used. Use of separate MMR and varicella vaccines averts the slight increase in risk of fever and febrile seizures after MMRV administration, but at the cost of the pain associated with an extra injection and the risk of an infant falling behind schedule if all vaccines indicated at that visit are not given (45).

Table 9 summarises the schedules for MMR vaccine in a number of countries (3)

Table 9. Schedule of MMR vaccine use in select countries, reproduced with permission Plotkin et al. (3)

<table>
<thead>
<tr>
<th>Country</th>
<th>Year of MMR introduction into national immunization plan</th>
<th>Current recommended schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>One-dose program</td>
<td>Two-dose program</td>
</tr>
<tr>
<td>Australia</td>
<td>1981</td>
<td>1994</td>
</tr>
<tr>
<td>Austria</td>
<td>1974</td>
<td>1994</td>
</tr>
<tr>
<td>Canada</td>
<td>1975</td>
<td>1996</td>
</tr>
<tr>
<td>Croatia</td>
<td>1976</td>
<td>1994</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>1987</td>
<td>1987</td>
</tr>
<tr>
<td>Denmark</td>
<td>1987</td>
<td>1987</td>
</tr>
<tr>
<td>France</td>
<td>1986</td>
<td>1986</td>
</tr>
<tr>
<td>Finland</td>
<td>1982</td>
<td>1982</td>
</tr>
<tr>
<td>Germany</td>
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<td>1991</td>
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<tr>
<td>Ireland</td>
<td>1988</td>
<td>1992</td>
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<td>Israel</td>
<td>1984</td>
<td>1994</td>
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<tr>
<td>Italy</td>
<td>1982</td>
<td>1999</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>1986</td>
<td>1994</td>
</tr>
<tr>
<td>Macedonia, Rep of</td>
<td>1983</td>
<td>1997</td>
</tr>
<tr>
<td>Moldova, Rep of</td>
<td>1983</td>
<td>2002</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>1987</td>
<td>1987</td>
</tr>
<tr>
<td>Portugal</td>
<td>1987</td>
<td>1990</td>
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<tr>
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<td>1982</td>
<td>1996</td>
</tr>
<tr>
<td>United Kingdom</td>
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<td>1994</td>
</tr>
<tr>
<td>United States</td>
<td>1971</td>
<td>1989</td>
</tr>
</tbody>
</table>

9.3 Summary of international policy and practice

MMR vaccines, either individually or as combinations, have been in use around the world for many decades. Global eradication of measles and rubella are currently possible and goals are being set for each region. Factors identified that consistently enable success in controlling or eliminating measles are the maintenance of high vaccine coverage, good disease surveillance, political and financial support, good social marketing and the addressing of anti-immunisation activities. NZ now has all of these factors in place.

There are a range of practices internationally in terms of the timing of MMR doses ranging from 12 months of age to two years with a second dose ranging from four weeks after the first dose to around 10 years after the first dose.
References


