

3.19 RUBELLA

Virology

Rubella is an enveloped togavirus, genus *Rubivirus*. The virus has an RNA genome and is closely related to group A arboviruses, but does not require a vector for transmission. It is relatively unstable, and is inactivated by lipid solvents, trypsin, formalin, extremes of heat and pH, amantadine and UV light.¹

Clinical features

Rubella is generally a mild and self-limiting infectious disease.² It causes a transient, generalised, erythematous, maculopapular rash, lymphadenopathy involving the post-auricular and sub-occipital glands, and, occasionally, arthritis and arthralgia. Other complications, such as neurological disorders and thrombocytopenia, may occur but are rare. Clinical diagnosis is unreliable since the symptoms are often fleeting and can be caused by other viruses; in particular, the rash is not unique to rubella and may be absent.^{1,2} Up to 50% of rubella virus infections are subclinical or asymptomatic.¹ A history of rubella should, therefore, not be accepted without serological evidence of previous infection.¹ The incubation period is 14 to 21 days, and the period of infectivity is from 1 week before until 4 days after the onset of the rash.² Rubella infection in pregnancy can result in fetal infection resulting in congenital rubella syndrome (CRS) in a high proportion of cases (see 'Rubella infection in pregnancy' below).

Epidemiology

Rubella occurs worldwide and is spread from person to person by droplet contact and possibly air-borne transmission of infectious respiratory secretions.¹ In temperate climates, the incidence is highest in late winter and early spring.³ The incidence of rubella has fallen rapidly since vaccine licensure, and there has been a shift in the age distribution of cases, with comparatively more cases being seen in older age groups, particularly the 20–24 year age group.⁴ In the early 1990s, rubella epidemics were reported in those States where rubella was notifiable.⁵ Over 3000 cases per year were reported between 1992 and 1995.⁵ In 2004–2005, rubella notifications were the lowest yet recorded with 31 confirmed cases being reported in each year (0.15 per 100 000 per year).⁴ This low notification rate most likely reflects the high vaccine coverage achieved and sustained with the National Measles Control Campaign in late 1998.^{3,6,7}

The number of cases of congenital rubella syndrome has also fallen rapidly since rubella vaccine licensure in Australia. Successful vaccination campaigns and high vaccination coverage resulted in no cases of congenital rubella syndrome occurring in infants of Australian-born mothers between 1998 and 2002. However, 5 cases resulting from infection acquired outside of Australia

were reported during this time.^{8,9} Between 2003 and 2005, an additional 5 cases were reported from infection that occurred in Australia⁹⁻¹¹ which reinforces the need for high vaccination coverage of women of child-bearing age (see 'Rubella infection in pregnancy' below).

The rubella virus was isolated in cell culture in 1962, and vaccines prepared from strains of attenuated virus have been approved for use in Australia since 1970. Mass vaccination of schoolgirls commenced in 1971.^{1,12} Non-pregnant, seronegative adult women were also vaccinated. These programs were successful and there was a significant reduction in the incidence of congenital rubella syndrome from 1977.¹³⁻¹⁵ There has also been a significant increase in the percentage of pregnant women immune to rubella (in NSW from 82% in 1971 to 96% in 1983). Based on a recent study in Melbourne, it was estimated that, in 2000, only 2.5% of all women in Australia of child-bearing age were seronegative. However, susceptibility was higher among overseas-born women, and has been reported as higher among some Indigenous women.^{16,17}

Many adolescent and young adult males are not immune to rubella because they did not receive an MMR vaccine.¹⁸ The MMR vaccination program for all adolescents replaced the rubella program for girls in 1993/94.¹² A serosurvey conducted in 1999 showed that only 84% of males aged 14–18 years (compared to 95% of females) and 89% of males aged 19–49 years (compared to 98% of females) were immune to rubella.¹⁸ For this reason, adolescent and young adult males, as well as females, who do not have a documented history of receipt of 2 doses of MMR, should receive MMR vaccine (see 'Recommendations' below). This is both for their own protection and to prevent transmission of the infection in the community (see 'The public health management of rubella' below).

Rubella infection in pregnancy

Maternal rubella infection in the first 8 to 10 weeks of pregnancy results in fetal damage in up to 90% of affected pregnancies, and multiple defects are common.¹⁹⁻²¹ The risk of damage declines to 10 to 20% by 16 weeks' gestation. After this stage of pregnancy, fetal damage is rare but has been reported up to 20 weeks' gestation.¹⁹ The characteristics of congenital rubella syndrome include intellectual disabilities, cataracts, deafness, cardiac abnormalities, intrauterine growth retardation and inflammatory lesions of the brain, liver, lungs and bone marrow.¹⁹ Any combination of these defects may occur, but defects which commonly occur alone following infection after the first 8 weeks of pregnancy are perceptive deafness and pigmentary retinopathy. Some infected infants may appear normal at birth, but defects, especially sensorineural deafness, may be detected later.²²

Rubella reinfection can occur in individuals who have both natural and vaccine-induced antibody.¹⁹ Occasional cases of congenital rubella syndrome after reinfection in pregnancy have been reported. However, fetal damage is very rare in cases of infection in women in whom antibody has previously been detected.^{20,23-25}

All pregnant women with suspected rubella or exposure to rubella should be serologically tested, irrespective of a history of previous vaccination, clinical rubella or a previous positive rubella antibody result (see 'Serological testing for rubella' below). This is because the rash of rubella is not diagnostic, asymptomatic infection can occur, and acute rubella can be confirmed only by laboratory tests.^{19,23,24} Pregnant women should be counselled to restrict contact with individuals with confirmed, probable or suspected rubella for 6 weeks (2 incubation periods).²⁶ Counselling of pregnant women with confirmed rubella regarding the risk to the fetus should be given in conjunction with the woman's obstetric service.

Serological testing for rubella

A number of commercial assays for testing immunity to rubella are available. These vary according to the method used to determine the positive cut-off value (the WHO cut-off is 10 IU/mL but, at present, there is no recommended Australian minimal level). Available data support the presumption that an antibody level found by use of a licensed assay to be above the standard positive cut-off for that assay can be considered evidence of past exposure to rubella virus.²³ Antibody levels below the cut-off are likely not to be protective, particularly if the antibodies have been generated by vaccination rather than by natural infection, and MMR vaccine (or MMRV if protection against varicella is required in children 12 months to 12 years of age) should be administered according to the 'Recommendations' below. Expert consultation and referral of sera to a reference laboratory are recommended if there is a difficulty interpreting results.

Acute rubella infection is indicated by presence of rubella IgM or 4-fold or greater increase in rubella IgG. Rubella IgM may not appear until a week after clinical symptoms. Sera for IgG testing should be taken 7 to 10 days after onset of illness and repeated 2 to 3 weeks later. The most recent date of potential exposure should be obtained, if possible, to calculate the potential incubation period. As some patients may have more than 1 exposure to a person with a rubella-like illness, and because exposure may occur over a prolonged period, it is important to ascertain the dates of the first and last exposures.²⁶

Seronegative women of child-bearing age should be vaccinated (see 'Recommendations' below) and tested for seroconversion 8 weeks after vaccination. All women should be informed in writing of the result of their antibody test. Women should be screened for rubella antibodies shortly before every pregnancy, or early in the pregnancy, or if pregnancy is contemplated, irrespective of a previous positive rubella antibody result.^{15,19} Very occasionally, errors may result in patients who are seronegative being reported as seropositive. Where possible, specimens from pregnant women should be stored until the completion of the pregnancy.

Serological testing of pregnant women exposed to rubella should always be performed (see 'Rubella infection in pregnancy' above). A blood sample

should be taken and sent to the laboratory with the date of the last menstrual period and the date of presumed exposure (or date of onset of symptoms).²⁶ If the woman has an antibody titre below the protective level, or a low level of antibodies and remains asymptomatic, a second blood specimen should be collected 28 days after the exposure (or onset of symptoms) and tested in parallel with the first. If the woman develops symptoms, the specimen should be collected and tested as soon as possible. A third blood specimen may be required in some circumstances.²⁴

Vaccines

Rubella vaccine is available as either MMR vaccine or as a monovalent rubella vaccine. It is anticipated that combination measles-mumps-rubella-varicella (MMRV) vaccines will become available in the near future. A single dose of rubella vaccine produces an antibody response in more than 95% of vaccinees, but antibody levels are lower than after natural infection.^{19,23,24} Vaccine-induced antibodies have been shown to persist for at least 16 years in the absence of endemic disease.^{23,24,27,28} Protection against clinical rubella appears to be long-term in those who seroconvert.¹⁹

Monovalent rubella vaccine

- **Meruvax II** – CSL Biotherapies/Merck & Co Inc (rubella virus vaccine). Each 0.5 mL monodose of the reconstituted, lyophilised vaccine contains not less than 1000 TCID₅₀ (tissue culture infectious dose 50%) of attenuated rubella virus (Wistar RA 27/3 strain); 25 µg neomycin; 3 mg human serum albumin; sorbitol and gelatin as stabilisers.

Combination measles-mumps-rubella vaccine

- **Priorix (MMR)** – GlaxoSmithKline (live attenuated measles virus (Schwarz strain), RIT 4385 strain of mumps virus (derived from the Jeryl Lynn strain) and the Wistar RA 27/3 rubella virus strain). Each 0.5 mL monodose of the reconstituted, lyophilised vaccine contains not less than 10^{3.0} CCID₅₀ (cell culture infectious dose 50%) of the Schwarz measles, not less than 10^{3.7} CCID₅₀ of the RIT 4385 mumps and not less than 10^{3.0} CCID₅₀ of the Wistar RA 27/3 rubella virus strains; lactose; neomycin; amino acids; sorbitol and mannitol as stabilisers.

Transport, storage and handling

Transport both vaccines according to *National Vaccine Storage Guidelines: Strive for 5*.²⁹ Store at +2°C to +8°C. Protect from light. Do not freeze. Reconstituted vaccine should be used immediately, but can be stored at +2°C to +8°C for up to 8 hours before use.

Dosage and administration

For both children and adults, the dose of MMR and monovalent rubella vaccine is 0.5 mL, administered by either SC or IM injection.

MMR and monovalent rubella vaccine can be given at the same time as other vaccines (including DTPa, hepatitis B, MenCCV and varicella), using separate syringes and injection sites. If MMR or monovalent rubella vaccine is not given simultaneously with other live viral parenteral vaccines (eg. varicella vaccine), they should be given at least 4 weeks apart (see 'Precautions' below).

Recommendations

The principal aim of rubella vaccination is to prevent congenital rubella syndrome by stopping the circulation of rubella virus in the community. Susceptible pregnant women will continue to be at risk of rubella infection in pregnancy until the transmission of rubella virus is interrupted by a sufficiently high uptake of rubella-containing vaccine in children and adults of both sexes.

(i) Routine vaccination of children

Two doses of rubella-containing vaccine are recommended for all children. The first dose should be given at 12 months of age and the second dose at 18 months of age (MMR or MMRV when available). The minimum interval between the first and second doses of MMR or MMRV is 4 weeks. A history of rubella is not a contraindication to vaccination. Individuals who are already immune to rubella have no increased risk of side effects from vaccination.^{19,23}

(ii) Vaccination of women of child-bearing age

Every effort should be made to identify non-pregnant seronegative women of child-bearing age. The following women are more likely to be seronegative to rubella: women born overseas (especially in Asia, Pacific islands, sub-Saharan Africa and South America) who have entered Australia after the age of routine vaccination; non-English speaking women; women over the age of 35; and Muslim women.^{5,13,14,16,30} Seronegative women should be given MMR vaccine and advised not to become pregnant for 28 days after vaccination. Monovalent rubella vaccine can be used where there is a contraindication to the measles or mumps components of MMR. Vaccinated women should be tested for seroconversion 6 to 8 weeks after vaccination (see 'Serological testing for rubella' above). Women who have negative or very low antibody levels after vaccination should be revaccinated. If their antibody levels remain low after a second vaccination, it is unlikely that further vaccinations will improve this.¹⁹ Although 2 doses of MMR vaccine are routinely recommended, if rubella immunity is demonstrated after receipt of 1 dose of a rubella-containing vaccine, no further dose is required, unless indicated by subsequent serological testing (see 'Serological testing for rubella' above).

(iii) Vaccination of adolescent and adult males

All males born during or after 1966 require 2 doses of MMR at least 4 weeks apart if they have no record of receiving the vaccine, as they are especially likely to be non-immune to rubella (see 'Epidemiology' above).

(iv) Vaccination post-partum

Women found to be seronegative on antenatal rubella immunity testing should be vaccinated after delivery and before discharge from the maternity unit. MMR vaccine is recommended, although monovalent rubella vaccine can also be used for this purpose. These women should be tested for rubella immunity 6 to 8 weeks after vaccination (see 'Vaccination of women of child-bearing age' above). Anti-D immunoglobulin does not interfere with the antibody response to vaccine.^{1,19} If anti-D immunoglobulin is also required, the two may be given at the same time in different sites with separate syringes, or at any time in relation to each other²⁴ (see 'Contraindications' below).

(v) Vaccination of healthcare workers and people working with children

All healthcare staff and people working with children, born during or since 1966, including medical, nursing, and other health professional students, either without vaccination records or seronegative upon screening, should receive 2 doses of MMR vaccine, both for their own protection and to avoid the risk of transmitting rubella to pregnant patients and/or colleagues³¹ (see Table 2.3.6 *Recommended vaccinations for those at risk of occupationally acquired vaccine-preventable diseases*). Preferably, MMR should be used. Where necessary, those vaccinated can be tested for seroconversion 8 weeks after vaccination and revaccinated if seronegative (see 'Vaccination of women of child-bearing age' above).

For further recommendations related to MMR vaccination, see Chapter 3.11, *Measles*.

Contraindications

Vaccination is contraindicated in the following circumstances:

(i) Allergy to vaccine components

- anaphylaxis following a previous dose of rubella, MMR or MMRV, or
- anaphylaxis following any vaccine component.

(ii) People with impaired immunity

Rubella-containing vaccine should not be administered to patients with congenital or acquired impaired immunity (see Section 2.3.3, *Vaccination of individuals with impaired immunity due to disease or treatment*). This includes those receiving high-dose corticosteroid or immunosuppressive treatment, general radiation, malignant conditions of the reticuloendothelial system (such as lymphoma, leukaemia, Hodgkin's disease), or in cases where the normal

immunological mechanism may be impaired, as in hypogammaglobulinaemia.^{1,23} Rubella vaccine or MMR may be given to HIV-positive individuals unless they have severely impaired immunity.²³ (For further information on MMR and MMRV vaccines, see Chapter 3.11, *Measles* and Chapter 3.24, *Varicella*).

(iii) Recent administration of antibody-containing blood product

Rubella-containing vaccine should not be given within at least 3 months after an injection of immunoglobulin, other antibody-containing blood product, or whole-blood transfusion, because the expected immune response may be impaired.^{19,24} The recommended intervals for receipt of rubella-containing vaccines after receipt of blood products are given in Table 2.3.5 *Recommended intervals between either immunoglobulins or blood products and MMR, MMRV or varicella vaccination*. Rubella-containing vaccines may be administered concomitantly with, or at any time in relation to, anti-D immunoglobulin, but at a separate injection site. However, women who have received anti-D immunoglobulin should be serologically tested 8 weeks after vaccination to ensure that seroconversion has occurred.^{1,23}

(iv) Pregnant women

MMR and monovalent rubella vaccines should not be given to a woman known to be pregnant, and pregnancy should be avoided for 28 days after vaccination (see 'Use in pregnancy' below).^{1,32} Data on the use of MMRV vaccines in individuals >12 years of age are not available.

Precautions

- If MMR or monovalent rubella vaccine is not given simultaneously with other live viral parenteral vaccines (eg. varicella vaccine), they should be given at least 4 weeks apart.
- Breastfeeding is not a contraindication to rubella vaccination. The rubella vaccine virus may be secreted in human breast milk, and there have been rare cases of transmission of vaccine virus through breast milk reported. However, these infections have been mild.¹
- There is no risk to pregnant women from contact with recently vaccinated individuals. The vaccine virus is not transmitted from vaccinees to susceptible contacts.¹

For precautions related to MMR and MMRV vaccines, see Chapter 3.11, *Measles* and Chapter 3.24, *Varicella*.

Adverse events

Mild adverse events such as fever, sore throat, lymphadenopathy, rash, arthralgia and arthritis may occur after vaccination.^{1,23} Symptoms most often begin 1 to 3 weeks after vaccination and are usually transient. Joint symptoms are more common in adults, especially women (10 to 25%, very common) than in children (0.3%, uncommon).^{1,23} Thrombocytopenia, that is usually self limiting, has been

reported rarely after rubella vaccine.²³ Very rarely, neurological symptoms have been reported, but a causal relationship has not been established.²³

For adverse events related to MMR and MMRV vaccines, see Chapter 3.11, *Measles* and Chapter 3.24, *Varicella*.

The public health management of rubella

All cases of suspected rubella infection should be laboratory tested and false positive results excluded. Infected individuals should be excluded from school/work/institution and should avoid contact with women of child-bearing age for at least 4 days after the onset of the rash.²⁶

All contacts should be identified, especially those who are pregnant. If a contact is pregnant, see 'Rubella infection in pregnancy' above. All contacts >12 months of age without adequate proof of immunity should receive 1 dose of MMR (or MMRV, when available, in those 12 months to 12 years of age). This will not prevent rubella disease if already exposed. If vaccination is refused, the contact should avoid further contact with cases until at least 4 days after onset of the rash in the case.

Exposed healthcare workers without adequate proof of immunity should be excluded from work for 21 days from exposure or for at least 4 days after the onset of a rash.²⁶

Use in pregnancy

Vaccination should be avoided in early pregnancy.¹ However, active surveillance in the USA, UK and Germany indicates that no case of vaccine-induced congenital rubella syndrome occurred among more than 500 women inadvertently vaccinated with rubella vaccine during pregnancy, whose pregnancies continued.³³ In a recent Iranian study performed after mass vaccination with a measles-rubella vaccine, 117 susceptible women were inadvertently vaccinated while pregnant or became pregnant ≤3 months after vaccination. There were no CRS-related abnormalities among the infants born to these women.³⁴ Based on this evidence, the vaccine cannot be considered to be teratogenic, and termination of pregnancy following inadvertent vaccination is not indicated^{1,24} (see Section 2.3.2, *Vaccination of women planning pregnancy, pregnant or breastfeeding women, and preterm infants*).

Use of normal human immunoglobulin (NHIG) to prevent rubella

Post-exposure prophylaxis with NHIG does not prevent infection in non-immune contacts and is, therefore, of little value for protection of pregnant women exposed to rubella.²³ It may, however, prolong the incubation period, which may marginally reduce the risk to the fetus. It may also reduce the likelihood of clinical symptoms in the mother. NHIG should only be used if termination

for confirmed rubella would be unacceptable under any circumstances. In such cases, IM administration of 20 mL of NHIG within 72 hours of rubella exposure might reduce – but will not eliminate – the risk for rubella.²³ Serological follow-up of recipients is essential, and should continue for up to 2 months.

There is some evidence to suggest that, in outbreak situations, pre-exposure NHIG may be effective in preventing infection in women who are likely to be pregnant, and its use may be indicated for such women with low antibody titres in high-risk occupations.³⁵

Variations from product information

The product information recommends that women of child-bearing age should be advised not to become pregnant for 3 months after vaccination with rubella, MMR or MMRV vaccines, whereas NHMRC recommends 28 days.³²

The product information for Meruvax II recommends the vaccine be given by SC injection, but NHMRC recommends administration by either SC or IM injection.

The product information for Meruvax II states that there is no reason to revaccinate individuals who were vaccinated originally when 12 months of age or older. However, NHMRC recommends routine administration of a second dose of rubella vaccine when given as MMR or MMRV to children.

References

Full reference list available on the electronic *Handbook* or website <http://immunise.health.gov.au>.