Refer to *Schedule*.

PREGNANCY AND BREASTFEEDING

Infants living in households with pregnant women can be vaccinated. The risk of infection and disease from vaccine virus is low because most women of childbearing age have pre-existing immunity to RV through natural exposure and RV infection during pregnancy is not known to pose a risk to the fetus.

The efficacy of RV vaccines is similar among infants who are breastfed and those who are not; therefore, breastfed infants can receive RV vaccine.

Refer to Immunization in Pregnancy and Breastfeeding in Part 3 for additional general information.

IMMUNOCOMPROMISED PERSONS

In general, immunocompromised persons should not receive live vaccines because of the risk of disease caused by the vaccine strains. When considering immunization of an immunocompromised patient, approval from the infant's attending physician should be obtained and referral to a consultant with expertise in immunization and/or immunodeficiency is advised. Severe cases of RV gastroenteritis have been reported after vaccination of infants with Severe Combined Immunodeficiency so RV vaccine is contraindicated in these infants.

Household contacts

Following administration of RV vaccine, viral antigen shedding in the stool may be detected in some vaccinees. Data on the potential for transmission of vaccine virus from vaccinees to household contacts has not been published; however, many experts believe that the benefit of protecting immunocompromised household contacts from naturally occurring RV by immunizing infants outweighs the theoretical risk of transmitting vaccine virus. Thus, infants living in households with persons who have or are suspected to have immunosuppressive conditions or who are receiving immunosuppressive medications can be vaccinated. To minimize the risk of transmission of RV vaccine virus, careful hand washing should be used after contact with the vaccinated infant, especially after handling feces (e.g., after changing a diaper), and before food preparation or direct contact with the immunocompromised person.

Refer to *Contraindications and Precautions*. Refer to Immunization of Immunocompromised Persons in Part 3 for additional general information.

TRAVELLERS

Infants who are travelling (particularly to developing countries) should receive RV vaccine as appropriate for age. Refer to Immunization of Travellers in Part 3 for additional general information.

VACCINE ADMINISTRATION

DOSE, ROUTE OF ADMINISTRATION, AND SCHEDULE

Dose

Each dose of Rot-5 vaccine is 2.0 mL. Each dose of Rot-1 vaccine is 1.5 mL.

Route of administration

RV vaccines are for oral administration only and must not be injected. All doses should be given in a clinic/office setting under the direction of a health care provider.

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Schedule

Healthy infants

Vaccination may be provided with either RV vaccine:

- Rot-5 vaccine is given as 3 separate 2.0 mL oral doses
- Rot-1 vaccine is given as 2 separate 1.5 mL oral doses

The first dose of RV vaccine should be given between 6 weeks and 14 weeks of age. Vaccination should not be initiated in infants aged 15 weeks or older as the safety of providing the first dose of RV vaccine in older infants is not known. The minimum interval between doses of RV vaccine is 4 weeks. All doses of RV vaccine should be administered by age 8 months.

For infants in whom the first dose of RV vaccine is inadvertently administered at age 15 weeks or older, the rest of the RV vaccine vaccination series should be completed with a minimum of 4 weeks between each dose and all doses should be administered by age 8 months plus 0 days.
If an incomplete dose is administered for any reason (e.g., infant spits or regurgitates the vaccine) a replacement dose should NOT be administered.

SEROLOGICAL TESTING

Serologic testing is not recommended before or after receiving RV vaccine.

STORAGE REQUIREMENTS

Store and transport RV vaccine at +2°C to +8°C and do not freeze. Protect from light. Refer to Storage and Handling of Immunizing Agents in Part 1 for additional general information.

SIMULTANEOUS ADMINISTRATION WITH OTHER VACCINES

RV vaccine may be administered concomitantly with routine infant vaccines. The impact of concomitant administration of Rot-1 vaccine with diphtheria/tetanus/acellular pertussis/hepatitis B/inactivated poliomyelitis /*Haemophilus influenzae* type b (DTaP-HB-IPV-Hib), DTaP, DTaP-IPV, Hib, DTP(whole cell)-HB, HB, pneumococcal conjugate, meningococcal serogroup C conjugate, and IPV vaccines have been evaluated and the immune responses and safety profile have been shown to be unaffected by concomitant administration. Concomitant administration of Rot-1 vaccine and oral poliomyelitis vaccine (OPV) may result in reduced immune response to Rot-1 vaccine; therefore, Rot-1 vaccine and OPV should be given at least 2 weeks apart. OPV is not available in Canada.

Live *oral* vaccines, like RV vaccine, may be given concomitantly with, or at any time before or after, live *parenteral* vaccines. This is an exception to the general rule to give live parenteral vaccines either simultaneously or at least four weeks apart. Refer to Timing of Vaccine Administration in Part 1 for additional general information.

VACCINE SAFETY AND ADVERSE EVENTS

Refer to Vaccine Safety Part 2 for additional general information.

COMMON AND LOCAL ADVERSE EVENTS

In large clinical trials, RV vaccines did not exhibit many differences in adverse events compared to placebo. In one large study, infants who received Rot-5 vaccine had a small, but statistically significant

increased rate of diarrhea in the 7-day period after vaccination (10% to 18% versus 6% to 15%). Vaccinees also had a small, but statistically significant, greater rate of vomiting (12% versus 10%).

LESS COMMON AND SERIOUS OR SEVERE ADVERSE EVENTS

Serious adverse events are rare following immunization and, in most cases, data are insufficient to determine a causal association. Serious adverse events were not found to be different between RV vaccine and placebo in clinical trials. Among infants given Rot-5 vaccine or placebo in clinical trials, the incidence of serious adverse events was 2.4% in vaccinees and 2.6% in placebo recipients, which was not significantly different. In a study of Rot-1 vaccine or placebo recipients, at least 1 serious adverse event was reported in 1.7% of vaccinees and 1.9% of placebo recipients.

OTHER REPORTED ADVERSE EVENTS AND CONDITIONS

Intussusception

Intussusception in infancy is rare, peaking in the first year of life and occurring at a background rate of about 34 infants per 100,000 per year. In 1998, a RV vaccine (RotaShield®, Wyeth-Ayerst) was recommended for routine vaccination of US infants. In the first 9 months after introduction of the vaccine into routine programs, more than 600,000 children were immunized and 15 of these children developed intussusceptions in the 2-week period immediately following vaccine administration. Subsequent epidemiologic investigations confirmed the increased incidence following vaccination, especially in infants receiving their first dose at age greater than 3 months. As a result, the vaccine was withdrawn from the US market. When the next generation of RV vaccines was developed, very large safety trials were conducted and administration of the first dose of vaccine was limited to infants less than 90 days of age, before the period when intussusception is most common, to ensure greater safety than with the previous vaccine.

The risk of intussusception was evaluated in large safety and efficacy trials of Rot-1 and Rot-5 vaccines, and no evidence of clustering of cases of intussusception was observed within a 7-day or 14-day window after vaccination for any dose. Of 71,725 infants enrolled in Rot-5 vaccine trials, six cases of intussusception were observed in the Rot-5 vaccine group versus five cases in the placebo group within 42 days of any vaccine dose. Of 63,225 infants enrolled in Rot-1 vaccine trials, six cases of intussusception occurred within 31 days of either dose of vaccine in the Rot-1 vaccine group and 7 cases in the placebo group. Across all clinical trials, the reported frequency of intussusception was 0.047% for Rot-1 vaccine recipients and 0.05% for placebo recipients. None of these differences were statistically significant.

There is new evidence from post-marketing surveillance for intussusception following the introduction of routine infant RV immunization programs in Mexico, Brazil, and Australia suggesting a small increased risk of IS in infants following RV vaccine. This increase appears to occur mainly in the period 1-7 days following the first dose of RV vaccine. In Mexico, receipt of Rot-1 was associated with a small excess risk of IS in the 7 days following dose 1 of approximately 1:51,000 vaccinated infants. A small but less consistent increased risk was observed following dose 2. Surveillance in Brazil, where OPV is used, did not demonstrate an increased risk of IS in the 7 days following the first dose of Rot-1 but did demonstrate a small excess risk of IS in the 7 days following dose 2 of 1:68,000 vaccinated infants. In Australia, post-marketing surveillance has demonstrated a small excess risk of IS following the first dose of either Rot-1 or Rot-5 of 2: 100,000 (or 1:50,000) vaccinated infants. The small excess risk of IS observed in Brazil, Mexico and Australia has not been demonstrated in the US. Analysis conducted by the Vaccine Safety Data Link in the US following administration of over 300,000 first doses and 750,000 total doses of Rot-5 identified 56 cases of IS, 30 in vaccinated infants and 26 in infants who had not received Rot-5. After adjustment for age, no increased risk of IS was demonstrated in either the first 7 or 30 days following dose 1 in the US. The Global Advisory Committee on Vaccine Safety (GACVS) has reviewed the data and indicated that the benefits of rotavirus vaccine outweigh the potential risks.

Parents should be informed of the small risk of IS following RV vaccine observed in some countries.

and counseled regarding the signs and symptoms of IS and the importance of seeking medical care should symptoms develop. Providers should report any observed case of IS.

Hematochezia

In infants, hematochezia (bloody stools) in conjunction with abdominal pain is associated with intussusception. No significant increase in the frequency of bloody stools has been found following use of either RV vaccine.

Kawasaki disease

During a large clinical trial of more than 30,000 children, there were 5 cases of Kawasaki disease in the vaccinated group. The GACVS reviewed all available data from the US (where Rot-5 vaccine is used) and the European Union (where Rot-1 vaccine is used), to determine if there was any association between Kawasaki disease and RV vaccines, and concluded there was no evidence for a causal association between RV vaccines and Kawasaki disease.

Seizures

In a study of 63,225 infants, 16 infants in the group receiving Rot-1 vaccine had adverse events coded as convulsions compared to 6 subjects in the group receiving placebo. Although this difference was statistically significant, no difference between vaccine and placebo recipients was noted when all convulsion-like events were combined. In studies of Rot-5 vaccine there was no difference in the frequency of seizures in vaccine and placebo recipients.

Porcine circovirus (PCV)

Components of porcine circovirus-1 (PCV-1) were found to be present in Rot-1 vaccine when an independent US academic research team applied a new technology for detecting viral genetic material. Subsequently, components of PCV-1 and porcine circovirus-2 (PCV-2) were also found in Rot-5 vaccine. Health Canada is reviewing information regarding the presence of PCV-1 and PCV-2 DNA in both Rot-1 and Rot-5 vaccines. Porcine circovirus does not cause illness in humans. There is no evidence that the presence of PCV-1 or PCV-2 in RV vaccines poses a safety risk to vaccinees, and the WHO and the US Food and Drug Administration have recommended that the vaccines continue to be used.

GUIDANCE ON REPORTING ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)

Vaccine providers are asked to report the following AEFI in particular, through local public health officials:

- Intussusception in the first 7 to 14 days following any dose of RV vaccine
- Any serious or unexpected adverse event felt to be temporally related to vaccination. An unexpected AEFI is an event that is not listed in available product information but may be due to the immunization, or a change in the frequency of a known AEFI.

Refer to Reporting Adverse Events Following Immunization (AEFI) in Canada in Vaccine Safety Part 2 for additional information about AEFI reporting. (http://www.phac-aspc.gc.ca/im/aefi-essi_guide/index-eng.php)

CONTRAINDICATIONS AND PRECAUTIONS

RV vaccines are contraindicated in infants with Severe Combined Immunodeficiency Disease (SCID), a history of anaphylaxis after previous administration of the vaccine and in infants with proven immediate or anaphylactic hypersensitivity to any component of the vaccine or its container. Refer *to Table 1* in Components of Immunizing Agents Available in Canada in Part 1 for lists of all vaccines available for use in Canada and their contents. There is no longer latex in the stopper of Rotarix vaccine.

Previous history of intussusception

Infants with a history of intussusception should not be given RV vaccines; however, there is no evidence that children who have a history of intussusception are at a higher risk of another

intussusception after receiving RV vaccine. The recommendation to not administer RV vaccine to children who have previously had intussusception is based on expert opinion, considering the following evidence: about 4% of infants with intussusception will have another episode in the following year; an earlier generation RV vaccine was associated with increased rates of intussusception and there is an incomplete understanding of the pathogenic mechanisms underlying that increased risk; and there is no data on use of the vaccine in infants who have had intussusception as children with a history of intussusception were excluded from immunogenicity and efficacy trials.

Immunodeficiency

Infants known or suspected to be immunocompromised should not receive RV vaccine without consultation with a physician with expertise in immunization and/or immunodeficiency.

Individuals with Severe Combined Immunodeficiency Disease (SCID) should not receive either RV vaccine. Cases of gastroenteritis associated with RV vaccine virus have been reported in infants with SCID.

Infants with a known or suspected family history of congenital or hereditary immunodeficiency that is a contraindication to vaccination with live vaccine should not receive RV vaccine unless their immune competence has been established.

Refer to Immunization of Immunocompromised Persons in Part 3 for additional general information.

Other medical conditions

RV vaccines can be administered to infants with minor acute illness, with or without fever.

In infants with moderate-to-severe gastroenteritis, RV vaccine should be deferred until the condition improves unless deferral will result in scheduling of the first dose after 14 weeks plus 6 days of age. Infants with mild gastroenteritis can be vaccinated. The immunogenicity and efficacy of the RV vaccines has not been studied in infants with concurrent gastroenteritis; however, immunogenicity and effectiveness of the vaccine may theoretically be reduced.

The safety and efficacy of RV vaccines has not been established in children with pre-existing chronic gastrointestinal conditions. However, infants with chronic gastrointestinal disease who are not considered immunocompromised are likely to benefit from RV vaccine and can be vaccinated.

Infants with uncorrected congenital malformation (such as Meckel's diverticulum) of the gastrointestinal tract that would predispose for intussusception should not receive RV vaccine.

Refer to General Contraindications and Precautions in Part 2 for additional general information.

DRUG INTERACTIONS

There are no restrictions on the infant's consumption of food or liquid, including breast milk, either before or after vaccination with RV vaccine.

No safety or efficacy data are available for the administration of RV vaccines to infants who have recently received immune globulins or other blood products. In theory, such infants might have a reduced immunologic response to a dose of RV vaccine. However, 2 or 3 doses of vaccine (depending on the product) are administered in the full RV vaccine series, and no increased risk for adverse events is expected. Therefore, RV vaccine may be administered at any time before, concurrent with, or after administration of immune globulins or other blood products.

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OTHER CONSIDERATIONS

INTERCHANGEABILITY OF VACCINES

There are no data on safety, immunogenicity, or efficacy when Rot-1 vaccine is administered as the first dose and Rot-5 vaccine is used as the second dose or vice versa. Given that the two vaccines differ in composition and schedule, the vaccine series should be completed with the same product whenever possible. However, in the event that the product used for a previous dose(s) is unknown, the series should be completed with the available product. If any dose in the series was Rot-5 vaccine, a total of 3 doses of vaccine should be administered.

SELECTED REFERENCES

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PART 4

RUBELLA VACCINE

KEY INFORMATION (refer to text for details)

What	• Up to 50% of rubella infections are subclinical; if a woman develops rubella during pregnancy, it can result in Congenital Rubella Syndrome (CRS) in the infant. • Rubella vaccine is available as measles-mumps-rubella (MMR) or measles-mumps-rubella-varicella (MMRV) vaccine. • Over 97% of individuals develop immunity after one dose of rubella vaccine. • Reactions to MMR and MMRV vaccine are generally mild and transient and include pain and redness at the injection site, low-grade fever and rash.

Who	• Rubella-containing vaccine is recommended for routine immunization of healthy children and for immunization of children and adolescents who missed rubella immunization on the routine schedule.
	• Rubella-containing vaccine is recommended for all susceptible adults.
	• Priority groups for rubella immunization include:
	  ○ Non-pregnant women of childbearing age - especially foreign-born, and staff and students in educational settings
	  ○ People who work with children (e.g., child care workers, teachers)
	  ○ Health care workers
	  ○ Travellers to rubella-endemic areas

How	• **Routine childhood immunization:** administer one dose of rubella-containing vaccine at 12 to 15 months of age. MMRV vaccine may be used in healthy children aged 12 months to 12 years. • **Susceptible children, adolescents and adults:** administer one dose of MMR vaccine
Why	• Rubella occurs worldwide and is highly communicable. • Rubella during pregnancy can result in CRS in the infant. • MMR and MMRV vaccines are safe and effective.

Since the publication of the *2006 Canadian Immunization Guide* a new combined multivalent vaccine (measles-mumps-rubella-varicella vaccine [MMRV]) has become available for children aged 12 months to 12 years.

For additional information, refer to the National Advisory Committee on Immunization (NACI) Statements: *Statement on Measles-Mumps-Rubella-Varicella Vaccine* (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/10vol36/acs-9/index-eng.php) and *Updated Recommendations for the use of Varicella and MMR Vaccines in HIV-infected Individuals* (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/10vol36/acs-7/index-eng.php)

EPIDEMIOLOGY

DISEASE DESCRIPTION

Infectious agent

Rubella (German measles) is caused by rubella virus, a ribonucleic acid (RNA) virus of the *Togaviridae* family.

Reservoir

Humans

Transmission

Rubella virus is highly communicable and is transmitted by droplet spread or direct contact with nasopharyngeal secretions of infected people. Transplacental transmission from an infected mother to her fetus during pregnancy may result in Congenital Rubella Syndrome (CRS) in the infant. Infants with CRS may shed the virus in their urine and nasopharyngeal secretions for 1 year or more. The incubation period for rubella is from 14 to 17 days (range, 14 to 21 days). The period of communicability extends from 1 week before to at least 4 days after the onset of rash. People who recover from rubella have lifetime immunity.

Risk factors

People of any age who have not been successfully vaccinated or have not had rubella disease are at risk of being infected. In Canada, routine infant immunization programs have resulted in sustained high rates of immunity in the general population, but the risk of limited transmission resulting from importation still exists.

Seasonal/temporal pattern

Historically, the incidence of rubella peaked in the spring and winter months in temperate zones; rubella is now limited to sporadic cases and outbreaks.

Spectrum of clinical illness

Rubella results in a transient erythematous rash, post-auricular and suboccipital lymphadenopathy, arthralgia and low-grade fever. As symptoms are non-specific, it may be mistaken for infection due to other viruses. Adult infection is frequently accompanied by transient polyarthralgia or polyarthritis. Serious complications are rare, and up to 50% of infections are subclinical.

Rubella infection in pregnancy may give rise to CRS, which can result in miscarriage, stillbirth and fetal malformations, including congenital heart disease, cataracts, deafness and mental retardation. Fetal infection can occur at any stage of pregnancy, but the risk of fetal damage following maternal infection is particularly high in the earliest months after conception (85% in the first trimester) with progressive diminution of risk thereafter, and it is very uncommon after the 20th week of pregnancy. Infected infants who appear normal at birth may later show eye, ear or brain damage.

DISEASE DISTRIBUTION

Incidence/prevalence

Global

Rubella occurs worldwide; however, during the last decade, rubella vaccination programs have greatly reduced incidence rates of rubella in most industrialized countries. By 2008, 66% of World Health Organization (WHO) member countries had included rubella in their childhood immunization schedule. In 2003, the Pan American Health Organization established a goal to eliminate indigenous rubella and CRS from the WHO region of the Americas by 2010. By October 2008, all 38 countries and territories in the Americas, with the exception of Haiti, had introduced MMR vaccine into routine immunization schedules. Beginning in 2009, Haiti planned to introduce measles-rubella (MR) vaccine into its routine immunization program after completion of a one-time MR mass vaccination campaign. In the region of the Americas, the average annual number of cases for the period of 2003 to 2008 dropped 92% compared with the annual number of cases for the period of 1997 to 2002.

National

In Canada, the MMR immunization program for infants was introduced in April 1983 and has resulted in sustained high rates of immunity in the general population. In addition, measles elimination strategies employed since the mid-1990s have indirectly resulted in a reduction in the proportion of the population that is rubella-susceptible because of the use of rubella-containing vaccines for the two dose routine immunization program and measles elimination catch-up campaigns.

The average annual number of rubella cases reported in Canada decreased from approximately 5,300 (1971-1982), to about 1,800 (1983-1997), to less than 30 (1998 -2004). From 2006 to 2010, on average fewer than 5 cases were reported annually.

In 2005, the incidence rate of rubella in Canada increased to about 10 per 1,000,000 with the majority of cases occurring in a large outbreak in southwestern Ontario (refer to Recent outbreaks). The average annual incidence rate of rubella has decreased from 2.1 per 1,000,000 in 1998 to 0.29 per 1,000,000 in 2010.

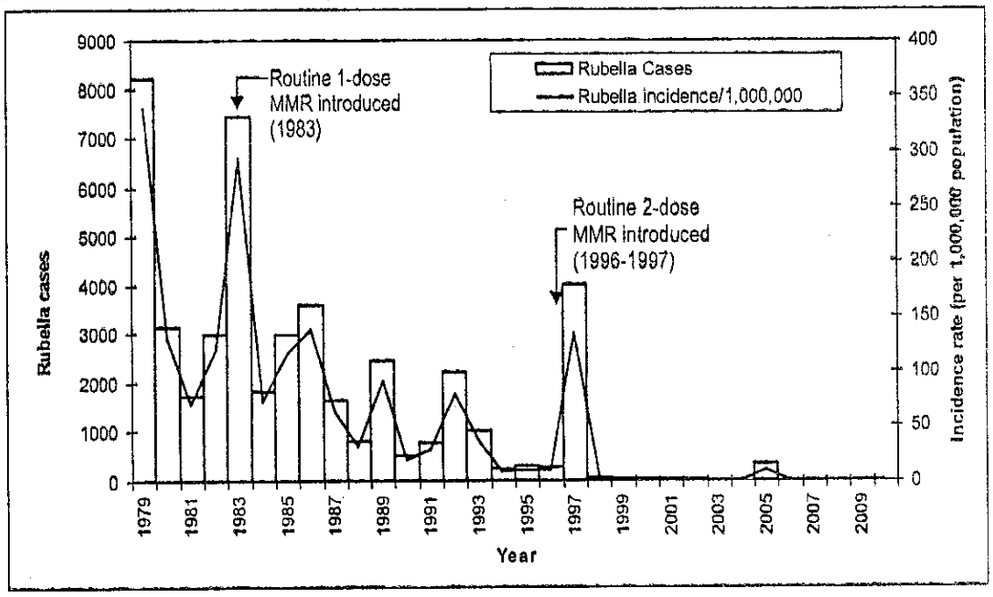
From 1996 to 2010, fewer than 3 cases of CRS were reported each year in Canada and most of these infants were born to foreign-born women. There have been no CRS cases due to exposure to rubella in Canada since 2000. Since that time, the six CRS cases reported were imported from other countries.

RECENT OUTBREAKS

In the two decades following the 1983 introduction of routine infant rubella immunization, epidemics of rubella continued to occur every 3 to 10 years. Many of these outbreaks, including one involving over 3,900 cases in Manitoba in 1997, differentially affected males aged 15 to 24 years of age who were not immunized because of pre-1983 selective rubella immunization programs of girls only in some jurisdictions. Since the late 1990s, outbreaks have largely been restricted to isolated clusters of unimmunized people, including those who decline immunization for religious or philosophical reasons.

In 2005, there was a rubella outbreak involving 309 laboratory confirmed cases in an unimmunized southwestern Ontario community. The outbreak was attributed to under-vaccination of persons in a community that is philosophically opposed to immunization. Over 60% of the cases were in unimmunized children aged 5 to 14 years. Ten cases involved pregnant women, but no cases of CRS were reported. As a result of high immunization rates in the general population, spread of the outbreak to the surrounding community was limited.

Figure 1: Reported number of cases and incidence rates of rubella in Canada, 1979 to 2010



PREPARATIONS AVAILABLE FOR USE IN CANADA

RUBELLA-CONTAINING VACCINES

- **M-M-R® II** (live, attenuated combined measles, mumps and rubella vaccine), Merck Canada Inc. (MMR)
- **PRIORIX®** (live, attenuated, combined measles, mumps and rubella vaccine), GlaxoSmithKline Inc. (MMR)
- **PRIORIX-TETRA®** (live, attenuated combined measles, mumps, rubella and varicella vaccine), GlaxoSmithKline Inc. (MMRV)

In Canada, rubella vaccine is only available in combination with measles and mumps vaccine (MMR) or measles, mumps and varicella vaccine (MMRV). In many countries outside of Canada, measles vaccine alone is given and rubella vaccination is not offered.

For complete prescribing information, consult the product leaflet or information contained within the product monograph available through Health Canada's Drug Product Database. (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php) Refer to Contents of Immunizing Agents Available for Use in Canada in Part 1 for a list of vaccines available for use in Canada and their contents.

EFFICACY, EFFECTIVENESS, AND IMMUNOGENICITY

EFFICACY AND EFFECTIVENESS

The duration of protection following immunization with rubella-containing vaccine is not known, but studies indicate that the duration of both cellular and humoral immunity exceeds 20 years. Asymptomatic rubella re-infection, manifest by a rise in antibody, has been observed in some vaccinees. Asymptomatic re-infection has also been observed in women with naturally acquired immunity associated with very low antibody titres. There are no data regarding the efficacy of MMRV vaccine.

IMMUNOGENICITY

In clinical trials, 95% or more of vaccinees aged 12 months and older developed serologic evidence of rubella immunity after a single dose of rubella-containing vaccine. Antibody titres are generally lower than those observed in natural rubella infection. Long-term persistence of anti-measles, anti-mumps, anti-rubella and anti-varicella antibodies following MMRV vaccinations are under evaluation.

RECOMMENDATIONS FOR USE

CHILDREN (12 months to 17 years of age)

One dose of rubella-containing vaccine should be given for routine immunization of children and for immunization of children and adolescents who missed rubella immunization on the routine schedule. MMRV vaccine may be used in children aged 12 months to 12 years.

ADULTS (18 years of age and older)

Adults who do not have documented evidence of receiving rubella-containing vaccine on or after their first birthday, or laboratory evidence of immunity, or a history of laboratory confirmed rubella infection should be immunized with one dose of MMR vaccine.

Rubella immunization recommendations differ from measles and mumps recommendations. Because the available preparations all contain measles, mumps and rubella, extra rubella vaccinations may be administered when following the recommendations for measles and mumps vaccination.

Susceptibility and immunity

Individuals who have one or more of the following are considered immune to rubella. Individuals who do not have ANY of the following are considered susceptible to rubella:

- Documented evidence of immunization with a rubella-containing vaccine on or after the first birthday
- A history of laboratory confirmed rubella infection
- Laboratory evidence of immunity

PRIORITY GROUPS

The following groups are priorities for rubella immunization:

- **Susceptible women of childbearing age** should be vaccinated before pregnancy or post-partum. Refer to Pregnancy and breastfeeding.
- **Susceptible non-pregnant, foreign-born women of childbearing age** from countries where rubella vaccine is not in use should be immunized with MMR vaccine as soon as possible after entry to Canada. Refer to Persons new to Canada.
- **Susceptible non-pregnant women of childbearing age in educational settings** (e.g., schools, colleges, and universities) should be immunized with MMR vaccine because of their relatively high risk of exposure.
- **Susceptible people who work with children** (e.g., child care workers, teachers) should be immunized with MMR vaccine because of their relatively high risk of exposure.
- **Susceptible health care workers** should receive one dose of MMR vaccine. Refer to Workers.
- **Susceptible travellers** to rubella-endemic areas should receive one dose of rubella-containing vaccine. Refer to Travellers.

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SECOND DOSE OF VACCINE

A second dose of MMR or MMRV vaccine (as appropriate for age and risk factors) may be recommended for measles and mumps protection (MMR and MMRV) and varicella protection (MMRV) in certain people. Although a second dose of the rubella component is not considered necessary for elimination of CRS, it is not harmful and may benefit the 1% to 5% of people who do not respond to primary immunization. Refer to Measles Vaccine, Mumps Vaccine and Varicella (Chickenpox) Vaccine in Part 4 for additional information and to Schedule.

PERSONS WITH INADEQUATE IMMUNIZATION RECORDS

Children and adults lacking adequate documentation of immunization should be considered unimmunized and started on an immunization schedule appropriate for their age and risk factors, unless known to be immune based on laboratory testing. MMR or MMRV vaccine as appropriate may be given regardless of possible previous receipt of the vaccine because additional adverse events associated with repeated immunization have not been demonstrated. Refer to Immunization of Persons with Inadequate Immunization Records in Part 3 for additional general information.

PREGNANCY AND BREASTFEEDING

Immunity to measles, mumps and rubella should be reviewed in women of reproductive age, and vaccination should be recommended to non-pregnant susceptible women. Ideally, the immunization status of women intending to become pregnant should be reviewed and vaccines updated as necessary prior to conception. Women should delay pregnancy by at least 28 days following vaccination with a live vaccine.

MMR and MMRV vaccines should generally not be given during pregnancy because of the theoretical risk of disease transmission to the fetus; however, there is no evidence demonstrating a teratogenic or other risk from such vaccines. In one study, there was no evidence of CRS in any of the offspring of 226 women inadvertently vaccinated during pregnancy. Inadvertent immunization with MMR vaccine is not a reason for pregnancy termination. In some situations, potential benefits of MMR vaccination may outweigh risks such as during measles or rubella outbreaks, in which case vaccination may be considered.

Women who are breastfeeding can be vaccinated with MMR vaccine.

Refer to Contraindications and Precautions. Refer to Immunization in Pregnancy and Breastfeeding in Part 3 for additional general information.

PERSONS/RESIDENTS IN HEALTH CARE INSTITUTIONS

Susceptible residents of long-term care facilities should receive measles, mumps and rubella-containing vaccine as well as all routine immunizations appropriate for their age and risk factors. Refer to Immunization of Persons/Residents in Health Care Institutions in Part 3 for additional general information.

IMMUNOCOMPROMISED PERSONS

In general, immunocompromised persons should not receive live vaccines because of the risk of disease caused by the vaccine strains. When considering immunization of an immunocompromised person with a live vaccine, **approval from the individual's attending physician should be obtained before vaccination.** For complex cases, referral to a physician with expertise in immunization or immunodeficiency or both is advised. Refer to Immunocompromised persons in Measles Vaccine in Part 4 for additional information.

Household contacts

Susceptible household contacts of immunocompromised people should receive a rubella-containing vaccine as appropriate for age and risk factors.

Refer to Contraindications and Precautions. Refer to Immunization of Immunocompromised Persons in Part 3 for additional information.

PERSONS WITH CHRONIC DISEASES

Neurologic disorders

People with conditions such as autism spectrum disorders or demyelinating disorders (including multiple sclerosis) should receive all routinely recommended immunizations, including MMR or MMRV vaccine. Refer to Immunization of Persons with Chronic Diseases in Part 3 for additional general information.

TRAVELLERS

Protection against rubella is important for people planning travel to rubella-endemic areas. Susceptible travellers should receive one dose of rubella-containing vaccine.

Refer to rubella incidence rates in WHO member countries for additional information. (http://www.who.int/immunization/monitoring_surveillance/en/)

Refer to Immunization of Travellers in Part 3 for additional general information.

PERSONS NEW TO CANADA

Health care providers who see persons newly arrived in Canada should review the immunization status and update immunization for these individuals. In many countries outside of Canada, mumps and rubella vaccines are in limited use and measles vaccine alone is given. A Canadian study showed that more than one-third of new immigrants and refugees, particularly women, were susceptible to measles, mumps, or rubella.

Unless known to be immune to rubella because of prior serology or documentation of a dose of rubella-containing vaccine, rubella-containing vaccine should be given to persons new to Canada; pre-immunization serology is not needed. Unless there is a contraindication to use, rubella-susceptible people should be immunized with one dose of a measles-mumps-rubella-containing vaccine as soon as possible after entry to Canada. Foreign-born women of childbearing age from countries where rubella-containing vaccine is not in use should be a priority. Susceptible women who are pregnant should receive MMR vaccine after delivery. Refer to Immunization of Persons New to Canada in Part 3 for additional general information.

WORKERS

It is recommended that all health care workers be immune to rubella. Health care workers who do not have documented evidence of receiving one dose of rubella-containing vaccine on or after their first birthday, or laboratory evidence of immunity, or a history of laboratory confirmed rubella disease should receive one dose of MMR vaccine. Non-immune people who work with children (e.g., child care workers, teachers) and non-immune, non-pregnant female workers of childbearing age in educational settings are priorities for rubella immunization. Refer to Immunization of Workers in Part 3 for additional general information.

POST-EXPOSURE IMMUNIZATION

Post-exposure MMR vaccination does not prevent or alter the clinical severity of rubella after exposure; however, if exposure to rubella does not cause infection, post-exposure vaccination with MMR vaccine should induce protection against subsequent infection. There is no evidence of increased risk of adverse reactions from immunization with MMR vaccine if an individual is already immune to one or more components of the vaccine or infected by rubella virus.

Passive immunization with human immune globulin (Ig) is not effective in preventing rubella. Ig given soon after exposure to rubella may modify or suppress symptoms but may not prevent infection, including

congenital infection. Therefore, the routine use of Ig in susceptible women exposed to rubella early in pregnancy is not recommended.

OUTBREAK CONTROL

During rubella outbreaks, susceptible people should be given MMR vaccine promptly without prior serologic testing. In consultation with public health officials, it may be appropriate to vaccinate pregnant women.

VACCINE ADMINISTRATION

DOSE, ROUTE OF ADMINISTRATION, AND SCHEDULE

Dose

Each dose is 0.5 mL.

Route of administration

MMR vaccine should be administered subcutaneously; MMRV can be administered subcutaneously or intramuscularly. Refer to Vaccine Administration Practices in Part 1 for additional information.

Schedule

Children (12 months to 12 years of age)

For routine immunization of children aged 12 months to 12 years, one dose of rubella-containing vaccine (MMR or MMRV) should be administered at 12 to 15 months of age.

Adolescents (13 to 17 years of age)

Rubella-susceptible adolescents should receive one dose of MMR vaccine.

Adults (18 years of age and older)

Rubella-susceptible adults should receive one dose of MMR vaccine.

BOOSTER DOSES AND RE-IMMUNIZATION

Re-immunization with rubella-containing vaccine after documented receipt of one dose of rubella-containing vaccine is not necessary. However, if a booster dose is given, it is not harmful and may benefit individuals who do not respond to primary immunization.

SEROLOGICAL TESTING

Serologic testing is not routinely recommended before or after receiving rubella-containing vaccine.

Pregnant women without documented evidence of prior immunization with a rubella-containing vaccine should be serologically screened for rubella antibodies, unless there is documented evidence of receipt of a rubella-containing vaccine. Those found to be non-immune serologically should be vaccinated with one dose of MMR vaccine in the immediate post-partum period, before discharge from hospital (unless they have received Rh immune globulin [RhIg] – refer to *Rh immune globulin and MMR vaccine in Immunization in Pregnancy and Breastfeeding* in Part 3). Women who have been appropriately immunized post-partum do not need to be serologically screened for rubella antibodies either post-immunization or in subsequent pregnancies. Women who have been found to be serologically positive in one pregnancy do not need to be screened again in subsequent pregnancies.

STORAGE REQUIREMENTS

M-M-R® II: Maintain vaccine at +10°C or colder during shipment. Freezing during shipment will not affect potency of the vaccine. Protect the vaccine from light. Before reconstitution, store the vial of vaccine at +2°C to +8°C or colder. The diluent may be stored in the refrigerator or at room temperature and must not be frozen.

PRIORIX®: Store in a refrigerator at +2°C to +8°C. The diluent may be stored separately at room temperature. Protect from light

PRIORIX-TETRA®: Store the vaccine and diluent in a refrigerator at +2°C to +8°C and do not freeze. Protect the vaccine from light.

Refer to Storage and Handling of Immunizing Agents in Part 1 for additional general information.

SIMULTANEOUS ADMINISTRATION WITH OTHER VACCINES

Live vaccines given by the parenteral route may be administered concomitantly with all other vaccines during the same visit using different injection sites and separate needles and syringes. In general, if two live parenteral vaccines are not administered concomitantly, there should be a period of at least 4 weeks before the second live parenteral vaccine is given. Exceptions are varicella-containing vaccines, such as MMRV vaccine:

- Administer doses of varicella-containing vaccine at least 3 months apart for children 1 to 12 years of age. If rapid, complete protection against varicella is required, a minimum interval of 6 weeks between 2 doses may be used for children 1 to 12 years of age.
- Do not concomitantly administer varicella-containing vaccines with smallpox vaccine; administer varicella-containing vaccine and smallpox vaccine at least 4 weeks apart.

Oral and intranasal vaccines can be given at the same time as, or any time before or after any other live vaccine, regardless of the route of administration of the other live vaccine.

Refer to Timing of Vaccine Administration in Part 1 for additional general information.

VACCINE SAFETY AND ADVERSE EVENTS

Refer to Vaccine Safety Part 2 for additional general information.

COMMON AND LOCAL ADVERSE EVENTS

MMR vaccine

Adverse events following MMR immunization occur less frequently and are less severe than those associated with natural disease. Adverse reactions are less frequent after the second dose of vaccine and tend to occur only in those not protected by the first dose. Six to 23 days after MMR immunization, approximately 5% of immunized children experience malaise and fever (with or without rash) lasting up to 3 days. Parotitis, rash, lymphadenophy, and joint symptoms also occur occasionally after MMR immunization.

MMRV vaccine

Pain and redness at the injection site or low-grade fever or both occur in 10% or more of vaccinees. Rash, including measles-like, rubella-like and varicella-like rash, as well as swelling at the injection site and moderate fever (greater than 39°C) occur in 1% to less than 10% of vaccinees. As varicella-like rashes that occur within the first two weeks after immunization may be caused by wild-type virus,

health care providers should obtain specimens using viral transport media from a lesion of the vaccinee to ensure varicella disease is not confused with a reaction to vaccination.

Rubella-containing vaccines

Acute transient arthritis or arthralgia may occur 1 to 3 weeks after immunization with rubella-containing vaccine, lasts for about 1 to 3 weeks, and rarely recurs. This is more common in post-pubertal females, among whom arthralgia develops in 25% and arthritis in 10% after immunization with rubella-containing vaccine. There is no evidence of increased risk of new onset, chronic arthropathies or neurologic conditions.

LESS COMMON AND SERIOUS OR SEVERE ADVERSE EVENTS

MMR and MMRV vaccines

Serious adverse events are rare following immunization and, in most cases, data are insufficient to determine a causal association. As with other vaccines, anaphylaxis following vaccination with MMR or MMRV vaccine may occur but is very rare.

Immune Thrombocytopenic Purpura (ITP)

Rarely, ITP occurs within 6 weeks after immunization with MMR or MMRV vaccine. In most children, post-immunization thrombocytopenia resolves within three months without serious complications. In individuals who experienced ITP with the first dose of MMR or MMRV vaccine, serologic status may be evaluated to determine whether an additional dose of vaccine is needed. The potential risk to benefit ratio should be carefully evaluated before considering vaccination in such cases.

Encephalitis

Encephalitis has been reported in association with administration of measles vaccine in approximately 1 per million doses distributed in North America which is much lower than that observed with natural measles disease (1 per 1,000 cases).

Febrile seizures

Recent studies have found a higher risk of febrile seizures with the first dose of a MMRV vaccine (ProQuad®, not authorized for use in Canada) when compared to the concomitant administration of MMR and univalent varicella vaccine. Data from the United States (US) estimated that the risk of febrile seizures in the 5 to 12 days following the first dose of this MMRV vaccine is 1 for every 2,600 vaccinated children aged 12 to 23 months. Experience with the MMRV vaccine available in Canada is more limited; however, one study showed an additional risk of febrile seizures with MMRV vaccine compared to MMR and univalent varicella vaccines given as two separate products administered concomitantly. The risk with the Canadian vaccine was smaller than the risk found with the US product. Close surveillance and further investigation are underway.

OTHER REPORTED ADVERSE EVENTS AND CONDITIONS

In the mid to late 1990s, researchers from the United Kingdom reported an association between MMR vaccine and inflammatory bowel disease, and MMR vaccine and autism. Rigorous scientific studies and reviews of the evidence have been done worldwide, and there is now considerable evidence to refute those claims. In 2010, the original study suggesting a link between the MMR vaccine and autism was retracted.

GUIDANCE ON REPORTING ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)

Vaccine providers are asked to report the following AEFI in particular, through local public health officials:

- Febrile seizures within 30 days after vaccination with MMR or MMRV vaccine.

- Varicella that is moderate (50 to 500 lesions) or severe (more than 500 vesicular lesions or associated complications or hospital admission) and occurs 7 to 21 days after vaccination with MMRV vaccine.
- Any serious or unexpected adverse event felt to be temporally related to vaccination. An unexpected AEFI is an event that is not listed in available product information but may be due to the immunization, or a change in the frequency of a known AEFI.

Refer to *Reporting Adverse Events Following Immunization (AEFI) in Canada* and Vaccine Safety in Part 2 for additional information about AEFI reporting. (http://www.phac-aspc.gc.ca/im/aefi-essi_guide/index-eng.php)

CONTRAINDICATIONS AND PRECAUTIONS

MMR and MMRV vaccines are contraindicated in persons with a history of anaphylaxis after previous administration of the vaccine and in persons with proven immediate or anaphylactic hypersensitivity to any component of the vaccine (with the exception of egg allergy [refer below]) or its container. Refer to *Contents of Immunizing Agents Available for Use in Canada* in Part 1 for a list of vaccines available for use in Canada and their contents. For rubella-containing vaccines, potential allergens include:

- M-M-R®II: neomycin, phenol red, porcine gelatin, residual components of chick embryo cell cultures
- PRIORIX®: egg protein, neomycin
- PRIORIX-TETRA® egg protein, neomycin

In situations of suspected hypersensitivity or non-anaphylactic allergy to vaccine components, investigation is indicated which may involve immunization in a controlled setting. Consultation with an allergist is advised.

The measles and mumps components of MMR and MMRV vaccines are produced in chick embryo cell culture and may contain traces of residual egg and chicken protein. The trace amount of egg protein in the vaccine appears to be insufficient to cause an allergic reaction in egg-allergic individuals. Skin testing is not recommended prior to vaccination as it does not predict reaction to the vaccine. MMR or MMRV vaccine can be administered in the routine manner to people who have a history of anaphylactic hypersensitivity to hens' eggs. Prior egg ingestion is not a prerequisite for immunization with egg protein-containing vaccine. For all vaccines, immunization should always be performed by personnel with the capability and facilities to manage adverse events post-vaccination. Refer to Anaphylactic Hypersensitivity to Egg and Egg-Related Antigens in Part 2 for additional information.

Children with a known or suspected family history of congenital or hereditary immunodeficiency that is a contraindication to vaccination with live vaccine should not receive live vaccines unless their immune competence has been established.

MMRV vaccine is contraindicated in persons with impaired immune function, including primary or secondary immunodeficiency disorders. Refer to Immunocompromised persons.

MMR and MMRV vaccines are contraindicated during pregnancy. Refer to Pregnancy and breastfeeding.

MMR vaccine is contraindicated in individuals with active, untreated tuberculosis. While tuberculosis may be exacerbated by natural measles infection, there is no evidence that measles, such as MMR or MMRV, vaccine has such an effect.

A history of febrile seizures or a family history of convulsions is not a contraindication for the use of MMRV vaccine.

Administration of MMR or MMRV vaccine should be postponed in persons with a severe acute illness. Persons with a minor acute illness (with or without fever) may be vaccinated.

It is recommended to avoid the use of salicylates (e.g., acetylsalicylic acid [ASA]) for 6 weeks after

immunization with MMRV vaccine because of an association between wild-type varicella, salicylate therapy and Reye's syndrome.

Refer to Contraindications, Precautions and Concerns in Part 2 for additional general information.

DRUG INTERACTIONS

Systemic antiviral therapy (such as acyclovir, valacyclovir, famciclovir) should be avoided in the peri-immunization period, as it may reduce the efficacy of varicella-containing vaccine such as MMRV. On the basis of expert opinion, it is recommended that people taking long-term antiviral therapy should discontinue these drugs, if possible from at least 24 hours before administration of MMRV vaccine and should not restart antiviral therapy until 14 days after.

The measles component in measles-containing vaccines can temporarily suppress tuberculin reactivity, resulting in false-negative results. If tuberculin skin testing or an Interferon Gamma Release Assay (IGRA) test is required, it should be done on the same day as immunization or delayed for at least 4 weeks after measles vaccination. Vaccination with measles-containing vaccine may take place at any time after tuberculin skin testing has been performed and/or read.

Passive immunization with human immune globulin (Ig) or receipt of most blood products can interfere with the immune response to MMR and MMRV vaccines. These vaccines should be given at least 14 days prior to administration of an Ig preparation or blood product, or delayed until the antibodies in the Ig preparation or blood product have degraded. If the interval between administration of vaccine and subsequent administration of an Ig preparation or blood product is less than 14 days or before the antibody has degraded, repeat the vaccine dose after the recommended interval. The recommended interval between administration of an Ig preparation or blood product and subsequent immunization varies, depending on the Ig preparation or blood product. Palivizumab (RSVAb) and washed red blood cell transfusion do not interfere with the antibody response to MMR or MMRV vaccines. Refer to Blood Products, Human Immune Globulin and Timing of Immunization in Part 1 for additional general information.

OTHER CONSIDERATIONS

INTERCHANGEABILITY OF VACCINES

On the basis of expert opinion, the MMR vaccines authorized in Canada may be used interchangeably. Refer to Principles of Vaccine Interchangeability in Part 1 for additional general information.

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