Rubella

Amy K Winter, William J Moss

Lancet 2022; 399: 1336–46

Department of Epidemiology and Biostatistics, College of Public Health, University of Georgia, Athens GA, USA (A K Winter PhD); **International Vaccine Access Center, Department of International Health** (Prof W J Moss MD), **and Department of Epidemiology** (Prof W J Moss), **Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA**

Correspondence to: Prof William J Moss, Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD 21205, USA
wmoss1@jhu.edu

Rubella is an acute illness caused by rubella virus and characterised by fever and rash. Although rubella is a clinically mild illness, primary rubella virus infection in early pregnancy can result in congenital rubella syndrome, which has serious medical and public health consequences. WHO estimates that approximately 100 000 congenital rubella syndrome cases occur per year. Rubella virus is transmitted through respiratory droplets and direct contact. 25–50% of people infected with rubella virus are asymptomatic. Clinical disease often results in mild, self-limited illness characterised by fever, a generalised erythematous maculopapular rash, and lymphadenopathy. Complications include arthralgia, arthritis, thrombocytopenic purpura, and encephalitis. Common presenting signs and symptoms of congenital rubella syndrome include cataracts, sensorineural hearing impairment, congenital heart disease, jaundice, purpura, hepatosplenomegaly, and microcephaly. Rubella and congenital rubella syndrome can be prevented by rubella-containing vaccines, which are commonly administered in combination with measles vaccine. Although global rubella vaccine coverage reached only 70% in 2020 global rubella eradiation remains an ambitious but achievable goal.

Introduction

Rubella is an acute illness caused by rubella virus and characterised by fever and rash. Although rubella is a clinically mild illness, primary rubella virus infection in early pregnancy can result in congenital rubella syndrome, which has serious medical and public health consequences. The name rubella is derived from the Latin word *rubellus*, the diminutive for red (ie, little red) and was first used in 1866 by Henry Veale.[1] Rubella has also been referred to as German measles (*rötheln*) because it was first described as a separate disease by German clinicians. Alfred Hess suspected that rubella was caused by a filterable virus in 1914 after he did not observe bacteria in the blood of children with rubella, despite identifying the ability to transfer infection to monkeys.[2] Hiro and Tasaka confirmed this observation in 1938 by infecting children with rubella virus using filtered nasal washings from acute cases.[3] However, it was not until 1941 that the Australian ophthalmologist Norman Gregg[4] first reported the association between congenital cataracts and rubella during the first trimester of pregnancy. This report was the earliest recognition that an environmental exposure, and specifically a virus, could cause birth defects. Rubella virus was first isolated in tissue culture in 1962 by two research groups, creating the foundation for the development of attenuated rubella virus vaccines. A massive rubella outbreak in the USA that lasted from 1964 to 1965 resulted in an estimated 12·5 million cases of rubella, 20 000 cases of congenital rubella syndrome, and more than 2000 deaths. This outbreak prompted research on the clinical spectrum of congenital rubella syndrome and vaccine development. Between 1965 and 1967, Stanley Plotkin[5] developed the RA27/3 rubella vaccine that is the most used vaccine in the world today. Much progress has been made in the control of rubella and the prevention of congenital rubella syndrome via widespread vaccination with rubella-containing vaccines, including efforts to reach and sustain both country-wide and regional rubella elimination, which has generated hope for global rubella eradication.

Search strategy and selection criteria

We searched PubMed for publications in English from inception up to August, 2021, using the terms "rubella", "rubella virus", "rubella vaccine", "rubella and epidemiology", "rubella and pathophysiology", "rubella and immunity", "rubella and diagnosis", "rubella and management", "rubella and prevention", and "rubella and elimination". Our search focused on, but was not restricted to, publications in since 2016. We also searched the Cochrane Database of Systematic Reviews using the term "rubella" and our own database of references, as well as those of linked articles in the searched journals. When more than one article illustrated a specific point, the most representative article was chosen.

Disease burden

Rubella virus infection is typically asymptomatic or results in mild symptoms, making disease surveillance challenging and insensitive.[6] Rubella virus infection among pregnant women, particularly during the first 16 weeks of gestation, can result in miscarriage, stillbirth, or the birth of a child with congenital rubella syndrome. The multiple possible causes of miscarriage, stillbirth, and congenital abnormalities mean that surveillance for congenital rubella syndrome is difficult. Laboratory confirmation is needed for greater specificity. The type and quality of rubella and congenital rubella syndrome surveillance systems differ greatly by country.[7,8] WHO criteria for minimum standard surveillance for rubella have been reached in 122 of 194 WHO member countries, and in 95 of 194 countries for congenital rubella syndrome.[7] For rubella, WHO criteria includes national case-based surveillance that is integrated into measles surveillance systems because of the diseases's similar clinical presentations with fever and rash.[9] For congenital rubella syndrome, they represents sentinel site case-based surveillance (panel). Because of the surveillance challenges, global numbers of rubella and congenital rubella syndrome cases are vastly underreported, with

Panel: **WHO case definitions for congenital rubella syndrome[10,11]**

Suspected case

Any infant younger than 12 months of age who presents with any of the following:

- Congenital heart disease
- Suspicion of hearing impairment
- One or more of the following eye signs: cataract, congenital glaucoma (larger eyeball), or pigmentary retinopathy

Any infant younger than 12 months of age who a health worker suspects has congenital rubella syndrome, even without apparent signs of congenital rubella syndrome, including maternal history of suspected or confirmed rubella during pregnancy.

Final case classification

Final classification of congenital rubella syndrome cases depends—in part—on identifying Group A or Group B clinical signs of congenital rubella syndrome.

- Group A clinical signs: cataracts, congenital glaucoma, pigmentary retinopathy, congenital heart disease (most commonly peripheral pulmonary artery stenosis, patent ductus arteriosus, or ventricular septal defects), hearing impairment.
- Group B clinical signs: purpura, splenomegaly, microcephaly, developmental delay, meningoencephalitis, radiolucent bone disease, jaundice that begins within the first 24 h after birth.

Using these clinical signs, one of these final classifications can be made:

- Laboratory-confirmed congenital rubella syndrome: an infant who is suspected of having congenital rubella syndrome with at least one sign from group A and who meets the laboratory criteria for confirmation of congenital rubella syndrome.
- Clinically compatible congenital rubella syndrome: an infant who is suspected of having congenital rubella syndrome with no adequate specimen available, and in whom a qualified clinician detects at least two of the clinical signs from group A or one from group A and one from group B.
- Congenital rubella infection: an infant who has none of the clinical signs of congenital rubella syndrome from group A, but who meets the laboratory criteria for congenital rubella syndrome.
- Discarded: an infant who is suspected of having congenital rubella syndrome with an adequate specimen that does not meet the laboratory-confirmed case definition; or an infant who is suspected of having congenital rubella syndrome with no adequate laboratory specimen and who does not meet the clinically compatible case definition.

Laboratory confirmation

Laboratory confirmation of congenital rubella infection or syndrome in an infant must meet one of the following criteria:

- Infants younger than 6 months: rubella IgM antibody detected
- Infants aged 6–12 months: rubella IgM and IgG antibody detected or a sustained rubella IgG antibody concentration as determined on at least two occasions at least 1 month apart in the absence of receipt of rubella vaccine or exposure to wild-type rubella virus
- Infants younger than 12 months: rubella virus detection by viral culture or RT-PCR in an appropriate clinical sample (throat, nasopharyngeal, or nasal swabs, blood, urine, or cerebrospinal fluid specimens).

Although IgM antibodies can persist for up to 1 year, about 50% of congenital rubella syndrome cases are IgM negative at 6 months of age, depending on test sensitivity.

Because IgM might not be detectable in some infants tested shortly after birth, IgM-negative infants with suspected congenital rubella syndrome should be retested at 1 month of age or shortly thereafter.

Laboratory confirmation of congenital rubella syndrome in an infant older than 6 months of age should not rely on the IgM test alone if the IgM result is negative. Serial IgG testing should be done after at least 1 month to check for a sustained concentration of IgG antibody over several months.

only 10 194 rubella cases and 603 congenital rubella syndrome cases reported to WHO in 2020.[12,13,14]

Due to the under-reporting of rubella and congenital rubella syndrome cases, rubella serological data are frequently combined with models of rubella virus transmission to estimate the number of rubella cases and the resulting congenital rubella syndrome cases.[15] In 2016, the most recent year such analyses were done, model outputs estimated that the global burden of congenital rubella syndrome in 2010 was 105 000 cases (95% CI 54 000–158 000),[15] driven by countries that had not yet introduced rubella-containing vaccines.[15] The case fatality ratio for congenital rubella syndrome has been reported to be as low as 5% and as high as 34% in different settings,[16,17] resulting in an estimated 5000–34 000 annual deaths attributable to congenital rubella syndrome. Although these rigorously modelled estimates are over 10 years old, WHO still reports that the current global congenital rubella syndrome burden is 100 000 cases annually.[6] A modelling study estimated that rubella vaccination would avert 1·2 million deaths from congenital rubella syndrome (95% credible interval 0·47–2·1) and 86 million disability-adjusted life-years (95% credible interval 56–170) across 112 countries from 2000 to 2030.[18]

Epidemiology

Before the development and introduction of rubella-containing vaccines, low-level endemic circulation of rubella virus was interrupted by outbreaks occurring every 3–8 years,[19–24] although annual outbreaks occurred in some

countries such as Mexico and Peru.[25,26] In the absence of vaccination, rubella cases are seasonally distributed, coinciding with school terms,[25,27] and most individuals are infected as children.[28–31] However, there can be a wide age distribution of cases such that some women of reproductive age remain susceptible to infection. The proportion of susceptible women of reproductive age in a population varies widely.[32] Before the introduction of rubella-containing vaccines, congenital rubella syndrome incidence ranged from 0·1 to 0·2 cases per 1000 livebirths during endemic periods and from 0·8 to 4·0 cases per 1000 livebirths during rubella epidemics.[32] Demographic factors play an important role in determining the transmission dynamics and number of congenital rubella syndrome cases. For example, higher birth rates decrease the average age of infection and the risk of congenital rubella syndrome,[33] whereas limited mobility across geographical areas increases the average age of infection and thus the risk of congenital rubella syndrome cases.[27] Populations smaller than the critical community size for rubella (around 1 million) are unable to maintain endemic transmission but are at risk of larger interannual variations in rubella virus infections and thus at higher risk of congenital rubella syndrome cases during outbreak years.[25]

The introduction of vaccination creates complex transmission dynamics that are highly influenced by population demographics. A level of vaccination coverage in children that does not result in the elimination of rubella virus transmission increases the average age of infection by reducing virus circulation in the population so that individuals avoid infection in early childhood and are older when infected. Increased vaccination coverage lowers the number of effective contacts between infectious and susceptible individuals; this therefore lowers rubella incidence. If vaccination coverage is sufficiently high (estimated >80%),[33] incidence will decrease in all age groups, including people of reproductive age, which will result in the decline of congenital rubella syndrome cases.[34] If vaccination coverage is insufficient, for example as a result of only being available through the private sector or because of an underperforming vaccination programme, then it is possible that rubella incidence will increase among people of reproductive age, thereby resulting in an increased risk of a child being born with congenital rubella syndrome.[33,35] This adverse and counterintuitive impact of vaccination has only been observed in the short term within a single epidemic cycle, with overall rates of congenital rubella syndrome declining in subsequent years.[36–38] Insufficient vaccination that directly targets women of reproductive age is unlikely to increase congenital rubella syndrome cases; however, targeting by gender has been shown to leave men susceptible later in life and therefore at risk of infection. These susceptible men can drive rubella outbreaks, placing susceptible women of childbearing age at risk of rubella, as seen in Japan in 2013–14 and 2018–19.[39] Vaccination strategies that target all children through routine immunisation programmes by adding rubella vaccines to measles-containing vaccines is WHO's preferred method of vaccination for rubella.[34] To ensure sufficient rubella vaccination coverage and minimise the risk of increasing congenital rubella syndrome cases, WHO recommends that countries introduce rubella-containing vaccines only if measles vaccination coverage through routine immunisation or vaccination campaigns is at least 80%. Introduction of rubella-containing vaccines should begin with a catch-up programme consisting of a wide age-range vaccination campaign (eg, up to 15 years of age) before the measles vaccine is replaced with a measles-and-rubella-containing vaccine within the routine immunisation schedule. Subsequent vaccination campaigns should use a combined vaccine.[6]

Virology

Rubella virus is an enveloped, positive-sense, non-segmented RNA virus in the genus *Rubivirus* and the family Matonaviridae. Before 2018, rubella virus was classified as part of the family Togaviridae. Rubella virus exists as a single stable serotype, so vaccines developed in the 1960s remain protective today. Humans are the only known host of rubella virus, but two relatives in the genus *Rubivirus* were recently identified in mammals: ruhugu virus from asymptomatic cyclops roundleaf bats in Uganda and rustrela virus from a marsupial and two placental mammals with acute encephalitis in a German zoo.[40] Highly conserved regions of the envelope protein across the three viruses suggest that these recently identified viruses could potentially infect humans.

The viral genome consists of approximately 10 000 nucleotides that encode for two non-structural polypeptides and three structural proteins (the capsid protein and two envelope proteins).[41] The glycosylated envelope proteins E1 and E2 combine to form spikes that protrude from the lipid envelope and are crucial to viral adhesion, fusion, and entry into host cells. Neutralising antibody responses are directed against the E1 glycoprotein. The host cellular receptors for rubella virus are largely unknown, although myelin oligodendrocyte glycoprotein was reported to be a cellular receptor for rubella virus in the CNS.[42]

Rubella viruses are classified into two clades and 13 genotypes that differ by about 8–10% in the nucleotide sequence of 3□ proximal third of the genome, which codes for the structural proteins. Genotyping requires sequencing of 739 nucleotides in the E1 protein coding region. The Global Measles and Rubella Laboratory Network, which was established by WHO in 2000, supports molecular epidemiology studies of measles and rubella. From 2016 to 2018, the genetic diversity of both measles and rubella viruses decreased due to elimination strategies that were used in some countries.[43] Of the 1296 rubella virus sequences submitted to the global rubella nucleotide surveillance database during this period, the number of

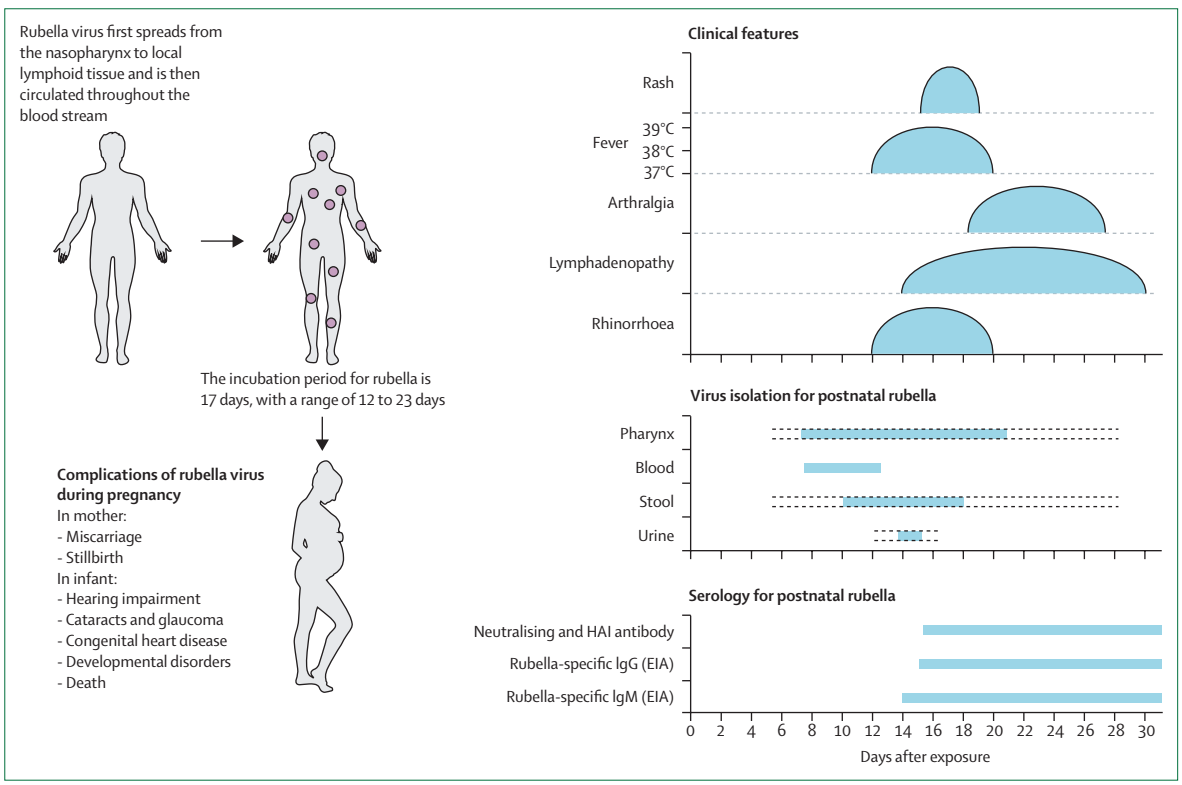

Figure 1: **Rubella disease course and complications**
The panel of clinical features, virus isolation and serology is adapted from WHO.[44] EIA=enzyme immunoassay. HAI=serum haemagglutination-inhibition.

rubella virus genotypes decreased from five in 2016, to two in 2018. However, rubella virus sequences are under-reported, as global surveillance for rubella viruses is not comprehensive. The two regions with large numbers of reported confirmed rubella cases in 2018, the African and Eastern Mediterranean regions, were not represented.

Pathophysiology

Rubella virus is transmitted through respiratory droplets and direct contact, with initial virus replication occurring in the nasopharyngeal mucosa, followed by spread to regional lymph nodes (figure 1). Viraemia results in systemic infection. In pregnant women, infection of the placenta occurs during viraemia, leading to transplacental infection of the fetus. Some of the complications of rubella result from host immune responses, including arthralgia, arthritis, thrombocytopenic purpura, and encephalitis, although the pathophysiology is not fully understood.

Infection with rubella virus during pregnancy can result in miscarriage, stillbirth, and birth defects. The risk of congenital infection and birth defects is highest during the first 12 weeks of gestation as this is when most organ development takes place. 85% of primary maternal infections occurring during this time result in congenital defects. This risk decreases to 50% during gestational weeks 13–16, and 25% if infection occurs in the second trimester through week 26. Excess risk of miscarriage or stillbirth because of rubella infection during the first 20 weeks of pregnancy is as high as 3%.[45] Congenital rubella syndrome is rare when rubella virus infection occurs at 20 weeks of gestation or later, even though transplacental infection can occur.[46] Fetal infection can be persistent, with damage resulting from cell death and impaired cellular division during the essential period of organ development. Examination of aborted fetuses infected with rubella virus shows widespread cellular damage with non-inflammatory necrosis in the eyes, ears, heart, and brain.[47] Pathological examination of the lens in fetuses with cataracts showed pyknotic nuclei, cytoplasmic vacuoles, and inclusion bodies in primary lens cells. Cellular necrosis has also been observed in the epithelium of the cochlear duct, the myocardium, and in endothelial cells in blood vessels within the heart and brain.

Clinical presentation, complications, outcomes

A quarter to half of people infected with rubella virus are asymptomatic.[48] Clinical disease often results in mild illness characterised by fever, a generalised erythematous maculopapular rash, and lymphadenopathy (figure 1). Fever is typically low grade and can be accompanied by headache, malaise, mild conjunctivitis (particularly in adults), sore throat, cough, and rhinorrhoea. These signs and symptoms can occur up to 5 days before the rash. The lymphadenopathy might also start before the rash and characteristically involves posterior auricular,

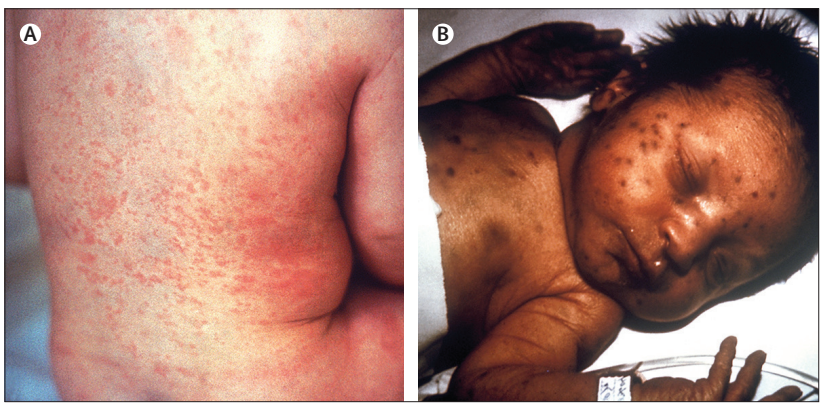

Figure 2: **Dermatologic features of rubella and congenital rubella syndrome**
(A) The erythematous maculopapular rash of rubella;[49] (B) the purpuric rash of congenital rubella syndrome.[50,51]

posterior cervical, and suboccipital lymph nodes, and lasts 5–8 days. The rash typically starts on the face, an average of 17 days after exposure to the virus (range 12–23 days) and spreads to the trunk and extremities over 24 h, lasting a median of 3 days (figure 2). Joint signs and symptoms are more common in adolescent girls and adult women, with up to 70% of adult women with rubella developing transient polyarthralgia or polyarthritis. Rubella is rarely associated with thrombocytopenic purpura (approximately one in 3000 cases) and encephalitis (approximately one in 6000 cases). An analysis of 4116 rubella cases during a large rubella outbreak in Tokyo, Japan, from January, 2012 to December, 2013 identified arthralgia and arthritis in 19·4% of cases, thrombocytopenic purpura in 0·5%, hepatic dysfunction in 0·3%, and encephalitis in 0·1%.[52] Progressive rubella panencephalitis is a rare and usually fatal neurodegenerative disorder that develops months to years after primary infection, which is most commonly congenital rubella syndrome, and is analogous to subacute sclerosing panencephalitis following measles. A high concentration of IgG antibodies against rubella virus is present in cerebrospinal fluid and is diagnostic.[53]

Common presenting signs and symptoms of congenital rubella syndrome include cataracts, sensorineural hearing impairment, congenital heart disease, hepatosplenomegaly, hepatitis with jaundice, thrombocytopenia with purpura, interstitial pneumonitis, meningoencephalitis, and microcephaly (panel; figure 2).[51] Hearing impairment is most common, occurring in 60–90% of cases, with cataracts occurring in approximately 30% of cases, heart defects in 45%, and other signs of generalised disease (eg, hepatosplenomegaly and thrombocytopenia) in 10–15% of cases.[53] Dermal erythropoiesis results in the so-called blueberry muffin skin lesions, which are characteristic. Other ocular defects include glaucoma, microphthalmia, pigmentary retinopathy, and chorioretinitis. Patent ductus arteriosus, peripheral pulmonary artery stenosis, and ventricular septal defects are the most common congenital heart defects. Radiolucency of the long bones can also be observed. Infants with congenital rubella syndrome often present with multiple congenital abnormalities but can also present with a single abnormality, which is most commonly hearing impairment following transplacental infection that occurs between 13 and 20 weeks of gestation.[54] Hearing impairment and developmental delays can be first diagnosed after infancy.

Diagnosis

Postnatal rubella can be suspected clinically, particularly during an outbreak or with a history of travel to a country with endemic rubella virus transmission in a patient without documentation of rubella vaccination, but should be confirmed through laboratory testing. Other acute infections that can be confused with rubella include scarlet fever and infection with measles virus, human herpes virus type 6, parvovirus B19, and dengue virus. Medical history and physical examination should focus on the clinical features of rubella, particularly posterior auricular, posterior cervical, and suboccipital lymphadenopathy in the presence of fever and rash, as well as the presence of arthralgias and arthritis in adolescent girls and women.

Following postnatal rubella virus infection, antibodies are detectable within 2 weeks and are concurrent with the rash (figure 1). IgM antibody concentrations reach their peak around 5 days after rash onset and decline rapidly until becoming undetectable about 8 weeks after infection, but IgG antibodies are believed to persist over an individual's lifetime.[55,56] Infants born to immune mothers have maternally derived antirubella virus IgG antibodies at a protective concentration that wanes after birth,[57] and is typically undetectable by 9 months of age.[58]

The most commonly used diagnostic test is detection of IgM antibodies against rubella virus by enzyme immunoassay, although commercial kits can have low sensitivity and specificity, which results in false positive and false negative test results. False positive IgM enzyme immunoassays can result from cross-reacting rheumatoid factor, parvovirus IgM antibodies, and heterophile antibodies. If serum is collected fewer than 5 days after rash onset and tests for IgM antibodies are negative, a second sample should be obtained to confirm rubella. A minimum 400% increase in IgG antibody concentration between acute and convalescent samples is also diagnostic, and both IgM and IgG antibody testing can be helpful. However, in low-incidence settings these tests can have low positive predictive value. A study from the French national reference laboratory of 5398 serum samples collected from 4104 pregnant women between 2013 and 2019 found that the positive predictive value of IgG seroconversion to assess primary maternal rubella virus infection was as low as 0·2% (95% CI 0·0–0·5%) and the positive predictive value for a positive rubella IgM test only 1·4% (95% CI 0·99–1·81%).[59] In some circumstances, IgG avidity assays could be helpful, with high avidity consistent with past infection and low avidity with recent infection. Acute rubella also can be confirmed

by viral isolation in cell culture and the detection of rubella virus RNA by RT-PCR in nasal, throat, and urine specimens up to 10 days after rash onset. However, detection of rubella virus is most successful within 3 days of rash onset. Droplet precautions are recommended in health-care settings for 7 days after rash onset by the US Centers for Disease Control and Prevention.[60]

Congenital rubella syndrome should be suspected clinically on the basis of the constellation of abnormalities, particularly with the triad of cataracts, sensorineural hearing impairment, and congenital heart disease, with or without a history of maternal rubella or exposure in early pregnancy, but laboratory confirmation is necessary (table 1). Echocardiography and rubella testing should be performed for children with cataracts or sensorineural hearing impairment in appropriate clinical and epidemiological settings (eg, susceptible mother and potential rubella virus exposure). Serological assays to detect IgM antibodies against rubella virus were first developed in the 1960s to guide pregnancy termination decisions and so needed to be highly accurate. Both IgM antibodies and rubella virus can persist for months following congenital rubella virus infection.[58] Detection of rubella virus-specific IgM antibodies within the first 6 months of life is confirmatory, as are stable or increasing rubella virus-specific IgG antibodies over the first 7–11 months of life before rubella vaccination. Nasopharyngeal swabs and urine should be collected as soon as possible after birth in infants suspected of having congenital rubella syndrome; this can be used for detection of rubella virus by RT-PCR or virus isolation in cell culture. Rubella virus can also be identified in blood and cataract specimens in children with congenital rubella syndrome. Confirmation of congenital rubella syndrome can be challenging in children who have been vaccinated against rubella and are older than 12 months of age. Infants with congenital rubella syndrome should be placed on contact isolation if admitted to hospital before 1 year of age unless they are shown to be non-infectious by two negative viral molecular tests or cultures after 3 months of age.

Management

Management of patients with postnatal rubella consists of supportive therapy, including bed rest, antipyretics, and anti-inflammatory drugs. There are no specific antiviral therapies available for rubella. Thrombocytopenia is usually self-limiting but use of intravenous immunoglobulin could be considered in rare severe cases, as with immune thrombocytopenia. Treatment of encephalitis includes seizure management with anticonvulsants. Although no supportive data exist, treatment of rubella post-infectious encephalitis with corticosteroids or immunoglobulin could be considered on the basis of treatment of measles-related acute disseminated encephalomyelitis.[61]

Management of a child with congenital rubella syndrome often requires the care of a multidisciplinary team under the direction of a paediatrician or other primary care provider and is determined by the range of systems involved. Treatment options are more limited in low-resource settings where most cases of congenital rubella syndrome occur, particularly for complex surgical procedures. Management of susceptible pregnant women exposed to rubella virus before 18 weeks gestation includes counselling, ultrasonography to identify fetal abnormalities, detection of rubella virus RNA in amniotic fluid for diagnostic confirmation, and consideration of pregnancy termination.[62] Counselling susceptible and exposed pregnant women includes explanation of the potential increased risk of miscarriage, stillbirth, and severe birth defects, ideally by a trained counsellor. Given that the risk of congenital rubella infection and birth defects is highest in the first trimester and then quickly decreases with gestational age, time of exposure is a crucial consideration during counselling. Routine use of immunoglobulin in exposed pregnant women is not recommended, although consideration could be given for susceptible, exposed women at high risk of having a child with severe congenital anomalies who chose not to terminate the pregnancy.[63]

Cataracts and other ocular problems require the care of an ophthalmologist. Cataracts that interfere with vision should be surgically removed by a skilled team and the aphakia corrected with eyeglasses, contact lenses, or intraocular lenses as early in life as possible to prevent amblyopia and preserve vision. Congenital glaucoma requires early diagnosis, drugs to lower intraocular pressure, and surgery. Hearing impairment requires the care of an audiologist and otolaryngologist, with hearing screening ideally conducted in the first month of life by measuring otoacoustic emissions or auditory brainstem responses.[64] Treatment of hearing impairment includes amplification with hearing aids or cochlear implants. Children with congenital heart disease should be managed by a paediatric cardiologist and cardiac surgeon.[65] Small cardiac defects might not require surgical intervention but a large patent ductus arteriosus can result in pulmonary hypertension and congestive heart failure and requires transcatheter or surgical closure. Severe peripheral pulmonic stenosis can be treated with balloon dilatation via cardiac catheterisation. Developmental delays often require a child development specialist and tailored educational environment. The family of a child with congenital rubella syndrome might require a social worker to assist with comprehensive care and family issues.

Prevention

Rubella and congenital rubella syndrome are prevented primarily through vaccination. There are no guidelines on post-exposure vaccination for rubella as there are for measles. Unvaccinated individuals should be vaccinated

against rubella as the vaccine results in direct and generally lifelong protection to the individual who is successfully immunised, and indirect protection to individuals who remain susceptible to rubella virus infection.[6] If population immunity acquired from vaccination and natural infection is high enough (estimated >80%) then herd immunity can be reached.

Rubella-containing vaccines can be monovalent formulations but are typically administered in combination with measles vaccine or combined with the measles and mumps vaccine or with the measles, mumps, and varicella vaccine. Rubella vaccine effectiveness is high, ranging from 99·3% (95% CI 95·3–99·9%)[66] for the RA27/3 vaccine to 100% (95% CI 35–100%)[67] for the BRD-II vaccines. Although a single dose of a rubella-containing vaccine is highly immunogenic and effective, a second dose is offered for protection against measles as part of a measles-containing vaccine.

The most widely administered rubella-containing vaccines use the attenuated RA27/3 strain. Other less widely used attenuated rubella vaccine strains include Takahashi, TO-336, and Matsuura, which are primarily used in Japan, and BRD-II, which is used in China. The number of countries that have introduced rubella-containing vaccines has increased substantially between 1970 and 2020. By 2021, 173 of 194 (89%) WHO member countries had rubella-containing vaccines in their childhood immunisation programmes; most commonly as measles–mumps–rubella or measles–mumps–rubella–varicella vaccines (123 of 173 countries), but also as a bivalent measles–rubella vaccine (50 of 173 countries). Global coverage with a first dose of rubella-containing vaccines was 70% in 2020 and was lowest in the African and Eastern Mediterranean regions.[68]

Rubella-containing vaccines elicit both humoral and cellular immune responses. A meta-analysis of 26 studies assessing the RA27/3 vaccine in those aged 9–18 months found that 99% (95% CI 98–99%) seroconverted after administration of one dose, and 100% (95% CI 99–100%) after two doses.[69] A second meta-analysis of 50 studies (43 using the RA27/3 vaccine) found no significant difference in seroconversion between one or two doses, with seroconversion in 98·3% (95% CI 97·3–99·2%) of vaccine recipients.[70]

Despite high rates of seroconversion and vaccine effectiveness, individual variation in immune responses to vaccination has been observed.[71–73] Several characteristics have been associated with the development and durability of immune responses following rubella vaccination, including age at vaccination, nutritional status, and genetic background.[74,75] Some studies have explored genetic differences in HLA alleles and single nucleotide polymorphisms that are associated with individual variability in immune response.[76–79] However, most people vaccinated with a rubella-containing vaccine develop a protective immune response.

Adverse events following receipt of rubella-containing vaccines are typically mild and include soreness or redness at the injection site. Fever occurs in 5–15% of individuals from 6 to 12 days after vaccination and rash in 5%. Rubella vaccination can sometimes cause mild rubella, including rash, lymphadenopathy, fever, sore throat, and headache. The incidence of these side effects generally increases with age. Up to half of women older than 30 years might experience side effects but infants typically do not.[80] Transient arthropathy is a more serious side effect of rubella vaccine among adults. The incidence of acute arthralgia or arthritis is 14% (95% CI 13–15%) in adult women who received the RA27/3 vaccine, most commonly involving the knees and fingers.[81] There is no epidemiological evidence to accept (or reject) a causal association between the measles–mumps–rubella vaccine and chronic arthralgia or arthritis.[82]

A review conducted in 2020 found no severe adverse events that were causally linked to rubella-containing vaccines among 49 randomised controlled trials and six observational studies.[69] A 2012 Cochrane review of the safety of measles–mumps–rubella vaccine found no significant association between measles–mumps–rubella vaccination and autism, asthma, leukaemia, hay fever, type 1 diabetes, gait disturbance, Crohn's disease, demyelinating diseases, or secondary bacterial or viral infections,[83] but did report an association with febrile seizures among children, and potentially with thrombocytopenic purpura. The risk of febrile seizures is higher among children younger than 2 years in the second week following receipt of the measles–mumps–rubella–varicella vaccine compared to the measles–mumps–rubella vaccine.[84] Approximately 25–34 additional febrile seizures for every 100 000 vaccinations are attributable to the measles–mumps–rubella vaccine.[85] In a systematic review, the incidence of immune thrombocytopenic purpura following measles–mumps–rubella vaccination was 2·6 (range 0·087–4) cases per 100 000 vaccine doses.[86]

As an attenuated viral vaccine, rubella vaccine should not be administered to individuals with severe immunosuppression, although members of their household should be vaccinated.[80] Individuals receiving short-term systemic immunosuppressive therapy should wait 3 months after ceasing treatment before being vaccinated.[80] Measles–mumps–rubella vaccination of people living with HIV is safe unless they are severely immunocompromised, but might result in a lower seroconversion rate than in HIV-uninfected individuals.[80] Pregnancy is a contraindication to rubella vaccination and women are advised to take precautions to avoid pregnancy for 1 month (28 days) after vaccination.[80] However, some pregnant women have inadvertently been vaccinated. A systematic review of adverse events following rubella vaccination during pregnancy concluded that there is no evidence that congenital rubella syndrome is caused by rubella vaccine, although

transplacental infection with the vaccine virus can occur.[87] Breastfeeding is not a contraindication to rubella vaccination.[80]

Elimination

With the burden of rubella and congenital rubella syndrome declining over the past decade because of the widespread introduction of rubella-containing vaccines,[34] regional rubella elimination appears possible. Rubella elimination is defined as the absence of endemic rubella virus transmission in a defined spatial area (eg, region or country) for at least 12 months in the presence of a well performing surveillance system.[14] In 2012, the World Health Assembly endorsed the Global Vaccine Action Plan 2011–2020 target to eliminate rubella in at least five of the six WHO regions by 2020, but this goal was not met.[88] The region of the Americas was the first to declare a rubella elimination goal in 2003 following confirmation of the last endemic measles case in 2002. It achieved rubella elimination in 2009, which was officially verified in 2015, and has maintained its elimination status through 2021 despite losing its measles elimination status.[89] It is the only WHO region to have eliminated rubella. The Eastern Mediterranean and African regions have yet to establish rubella elimination goals, although country-specific elimination goals have been set.[83] As of January, 2021, rubella has been eliminated in 93 of 194 WHO member countries, 35 of which are in the region of the Americas.

Prospects for rubella elimination are intertwined with measles elimination as the rubella vaccine is administered in combination with the measles vaccine and the two diseases share the same surveillance systems. The measles vaccine has been introduced in every country and national efforts to reduce the burden of measles will positively impact rubella control. The most important challenges for rubella elimination are: (1) increasing measles vaccination coverage (ie, to at least 80% through routine immunisation and campaigns) to introduce rubella-containing vaccines in the remaining 21 countries,[83] (2) increasing measles–rubella vaccination coverage in countries that have introduced rubella-containing vaccines,[90] and (3) improving surveillance to enable rapid outbreak detection and response to achieve and maintain elimination.[68,75] The reasons for insufficient measles–rubella vaccination coverage are diverse and complex but include challenges in both vaccine access (eg, remote or conflict-affected areas) and demand (eg, vaccine refusal and hesitancy).[91]

Future of rubella

The future of rubella eradication is uncertain, but progress made towards reducing the burden of rubella and congenital rubella syndrome offers hope.[92] New microarray patches used for vaccine delivery offer many operational advantages over traditional needles and syringes, including thermostability with a reduced need for cold chain transportation, ease of administration by lower level health-care workers, reduced supply chain requirements and medical waste, potential for reduced vaccine hesitancy or refusal, and dose sparing.[93] As a result, hard-to-reach populations, including zero-dose children and missed communities, might be more easily vaccinated.

Point-of-contact rapid diagnostic tests for rubella-specific IgM antibodies could improve surveillance to identify rubella outbreaks and trigger vaccination campaigns faster, thereby reducing outbreak size and duration. Point-of-contact diagnostic tests for rubella-specific IgG antibodies could be used to identify age-specific immunity gaps, particularly among women of childbearing age, or at school entry to identify susceptible children and inform vaccination strategies. Such tests could also be used in early prenatal appointments to identify susceptible pregnant women and provide guidance on how best to avoid exposures to reduce the risk of infection. These tests would also reduce the cost and difficulty of conducting population-based serosurveys, which are invaluable to estimating rubella disease burden and creating national and sub-national vaccination plans to control and eliminate rubella.[94]

WHO and partners launched the Immunization Agenda 2030 based on four core principles and seven strategic priorities to ensure that everyone, everywhere, at every age, fully benefits from vaccines to improve health and wellbeing.[95] Aligned with the Immunization Agenda 2030, WHO's Measles and Rubella Strategic Framework 2021–2030 outlines seven strategic priorities to achieve and sustain regional measles and rubella elimination goals.[96] Achieving these strategic priorities will advance the Immunization Agenda 2030 and help to secure a world free from measles and rubella.

Contributors

AKW and WJM equally contributed to this work by conducting the literature reviews and writing the manuscript.

Declaration of interests

AKW receives funding from the Bill and Melinda Gates Foundation and Gavi, the Vaccine Alliance. AKW is a member of the Vaccine Impact Modelling Consortium. The views expressed in this Seminar reflect those of the author and are not necessarily those of the Vaccine Impact Modelling Consortium. WJM was a member of WHO's Strategic Advisory Group of Experts on Immunization Working Group on Measles and Rubella from 2011 to 2018 and is currently a member of the WHO Measles-containing vaccine Microarray patches Product Development Working Group. The views expressed in this Seminar reflect those of the author and are not necessarily those of WHO or the Strategic Advisory Group of Experts on Immunization Working Group on Measles and Rubella.

Acknowledgments

We are grateful to the anonymous reviewers for their thoughtful comments and suggestions.

References

1 Cooper LZ. The history and medical consequences of rubella. *Rev Infect Dis* 1985; **7** (suppl 1)**:** S2–10.

2 Hess AF. German measles (rubella): an experimental study. *Arch Intern Med* 1914; **8:** 913–16.

3 Hiro Y, Tasaka S. Die Röteln sind eine Viruskrankheit. *Mschr Kinderheilk* 1938; **76:** 328–32.

4 Gregg NM. Congenital cataract following German measles in the mother. *Trans Ophthal Soc Aust* 1941; **3:** 35–41.

5 Plotkin SA, Farquhar JD, Katz M, Buser F. Attenuation of RA 27–3 rubella virus in WI-38 human diploid cells. *Am J Dis Child* 1969; **118:** 178–85.

6 World Health Organization. Rubella vaccines: WHO position paper. *Wkly Epidemiol Rec* 2020; **95:** 306–24.

7 Patel MK, Gibson R, Cohen A, Dumolard L, Gacic-Dobo M. Global landscape of measles and rubella surveillance. *Vaccine* 2018; **36:** 7385–92.

8 WHO. JRF supplementary questionnaire on surveillance. 2017. https://cdn.who.int/media/docs/default-source/immunization/vpd_surveillance/jrf-supplementary-questionnaire-surveillance-18mar.pdf?sfvrsn=61578f6_2 (accessed Feb 14, 2021).

9 WHO. Rubella: vaccine-preventable diseases surveillance standards. 2018. https://www.who.int/publications/m/item/vaccine-preventable-diseases-surveillance-standards-rubella (accessed Feb 7, 2021).

10 WHO. Congenital rubella syndrome: vaccine-preventable diseases surveillance standards. 2018. https://www.who.int/publications/m/item/vaccine-preventable-diseases-surveillance-standards-crs (accessed Feb 7, 2021).

11 WHO. Congenital rubella syndrome. 2018. https://www.who.int/immunization/monitoring_surveillance/burden/vpd/WHO_SurveillanceVaccinePreventable_03_CRS_R2.pdf?ua=1 (accessed Feb 12, 2022).

12 WHO. Rubella reported cases and incidence. 2021. https://immunizationdata.who.int/pages/incidence/rubella.html (accessed Sept 19, 2021).

13 WHO. Congenital rubella syndrome (CRS) reported cases and incidence. 2021. https://immunizationdata.who.int/pages/incidence/crs.html (accessed Sept 19, 2021).

14 Zimmerman LA, Knapp JK, Antoni S, Grant GB, Reef SE. Progress toward rubella and congenital rubella syndrome control and elimination – worldwide, 2012–2020. *MMWR Morb Mortal Wkly Rep* 2022; **71:** 196–201.

15 Vynnycky E, Adams EJ, Cutts FT, et al. Using seroprevalence and immunisation coverage data to estimate the global burden of congenital rubella syndrome, 1996–2010: a systematic review. *PLoS One* 2016; **11:** e0149160.

16 Toizumi M, Motomura H, Vo HM, et al. Mortality associated with pulmonary hypertension in congenital rubella syndrome. *Pediatrics* 2014; **134:** e519–26.

17 Miller E, Cradock-Watson JE, Pollock TM. Consequences of confirmed maternal rubella at successive stages of pregnancy. *Lancet* 1982; **2:** 781–84.

18 Toor J, Echeverria-Londono S, Li X, et al. Lives saved with vaccination for 10 pathogens across 112 countries in a pre-COVID-19 world. *eLife* 2021; **10:** e67635.

19 Ueda K. Epidemiology of rubella and congenital rubella syndrome in Japan before 1989. *Vaccine* 2016; **34:** 1971–74.

20 Witte JJ, Karchmer AW, Case G. Epidemiology of rubella. *Amerj DisChild* 1969; **118:** 107–11.

21 Plotkin SA, Ingalls TH, Farquhar JD, Katz M. Intranasally administered rubella vaccine. *Lancet* 1968; **2:** 934–36.

22 Plotkin SA, Orenstein WA, Offit PA. Vaccines, 6th ed. Philadelphia, PA: Elsevier, 2013.

23 Edmunds WJ, Gay NJ, Kretzschmar M, Pebody RG, Wachmann H, Esen Project. The pre-vaccination epidemiology of measles, mumps and rubella in Europe: implications for modelling studies. *Epidemiol Infect* 2000; **125:** 635–50.

24 Rozhnova G, Metcalf CJE, Grenfell BT. Characterizing the dynamics of rubella relative to measles: the role of stochasticity. *J R Soc Interface* 2013; **10:** 20130643.

25 Metcalf CJE, Bjornstad ON, Ferrari MJ, et al. The epidemiology of rubella in Mexico: seasonality, stochasticity and regional variation. *Epidemiol Infect* 2011; **139:** 1029–38.

26 Rios-Doria D, Chowell G, Munayco-Escate C, Witthembury A, Castillo-Chavez C. Spatial and temporal dynamics of rubella in Peru, 1997–2006: geographic patterns, age at infection and estimation of transmissibility. In: Chowell G, Hyman J, Bettencourt LA, Castillo-Chavez C, eds. Mathematical and statistical estimation approaches in epidemiology. Dordrecht: Springer, 2009: 325–41.

27 Metcalf CJE, Munayco CV, Chowell G, Grenfell BT, Bjornstad ON. Rubella metapopulation dynamics and importance of spatial coupling to the risk of congenital rubella syndrome in Peru. *J R Soc Interface* 2011; **8:** 369–76.

28 Durowade KA, Mus, OI, Jimoh MA, et al. Burden, epidemiological pattern, and surveillance gap of rubella in Nigeria: a call for routine vaccination policy. *Indian J Health Sci Biomed Res* 2021; **14:** 31–37.

29 Getahun M, Beyene B, Gallagher K, et al. Epidemiology of rubella virus cases in the pre-vaccination era of Ethiopia, 2009–2015. *BMC Public Health* 2016; **16:** 1168.

30 Tushabe P, Bwogi J, Abernathy E, et al. Descriptive epidemiology of rubella disease and associated virus strains in Uganda. *J Med Virol* 2020; **92:** 279–87.

31 Chimhuya S, Manangazira P, Mukaratirwa A, et al. Trends of rubella incidence during a 5-year period of case based surveillance in Zimbabwe. *BMC Public Health* 2015; **15:** 294.

32 Cutts FT, Robertson SE, DiazOrtega JL, Samuel R. Control of rubella and congenital rubella syndrome (CRS) in developing countries, part 1: burden of disease from CRS. *Bull World Health Organ* 1997; **75:** 55–68.

33 Metcalf CJE, Lessler J, Klepac P, Cutts F, Grenfell BT. Impact of birth rate, seasonality and transmission rate on minimum levels of coverage needed for rubella vaccination. *Epidemiol Infect* 2012; **140:** 2290–301.

34 Patel MK, Antoni S, Danovaro-Holliday MC, et al. The epidemiology of rubella, 2007–18: an ecological analysis of surveillance data. *Lancet Glob Health* 2020; **8:** e1399–407.

35 Vynnycky E, Gay NJ, Cutts FT. The predicted impact of private sector MMR vaccination on the burden of congenital rubella syndrome. *Vaccine* 2003; **21:** 2708–19.

36 Panagiotopoulos T, Antoniadou I, Valassi-Adam E. Increase in congenital rubella occurrence after immunisation in Greece: retrospective survey and systematic review. *BMJ* 1999; **319:** 1462–67.

37 Panagiotopoulos T, Georgakopoulou T. Epidemiology of rubella and congenital rubella syndrome in Greece, 1994–2003. *Euro Surveill* 2004; **9:** 17–19.

38 Jimenez G, Avila-Aguero ML, Morice A, et al. Estimating the burden of congenital rubella syndrome in Costa Rica, 1996–2001. *Pediatr Infect Dis J* 2007; **26:** 382–86.

39 Oishi K, Satoh H, Tanaka-Taya K. Re-emerging rubella epidemic and public health measures in Japan. *Yakugaku Zasshi* 2020; **140:** 901–04 (in Japanese).

40 Bennett AJ, Paskey AC, Ebinger A, et al. Relatives of rubella virus in diverse mammals. *Nature* 2020; **586:** 424–28.

41 Das PK, Kielian M. Molecular and structural insights into the life cycle of rubella virus. *J Virol* 2021; **95:** e02349–20.

42 Cong H, Jiang Y, Tien P. Identification of the myelin oligodendrocyte glycoprotein as a cellular receptor for rubella virus. *J Virol* 2011; **85:** 11038–47.

43 Brown KE, Rota PA, Goodson JL, et al. Genetic characterization of measles and rubella viruses detected through global measles and rubella elimination surveillance, 2016–2018. *MMWR Morb Mortal Wkly Rep* 2019; **68:** 587–91.

44 WHO. Chapter 1: manual for the laboratory-based surveillance of measles, rubella, and congenital rubella syndrome. In: Measles and rubella: an overview. Geneva: WHO, 2018.

45 Thompson KM, Simons EA, Badizadegan K, Reef SE, Cooper LZ. Characterization of the risks of adverse outcomes following rubella infection in pregnancy. *Risk Anal* 2014; **36:** 1315–31.

46 South MA, Sever JL. Teratogen update: the congenital rubella syndrome. *Teratology* 1985; **31:** 297–307.

47 Lee JY, Bowden DS. Rubella virus replication and links to teratogenicity. *Clin Microbiol Rev* 2000; **13:** 571–87.

48 CDC. Rubella (German measles, three-day measles). Dec 31, 2020. https://www.cdc.gov/rubella/hcp.html (accessed Nov 8, 2021).

49 Centers for Disease Control and Prevention. Public health mage ID 712. 1978. https://phil.cdc.gov/Details.aspx?pid=712 (accessed Nov 8, 2021).

50 Lebrun AJ. Public health image ID 713. 1978. https://phil.cdc.gov/Details.aspx?pid=713 (accessed Nov 8, 2021).

51 Cooper LZ, Green RH, Krugman S, Giles JP, Mirick GS. Neonatal thrombocytopenic purpura and other manifestations of rubella contracted in utero. *Am J Dis Child* 1965; **110:** 416–27.

52 Sugishita Y, Shimatani N, Katow S, Takahashi T, Hori N. Epidemiological characteristics of rubella and congenital rubella syndrome in the 2012–2013 epidemics in Tokyo, Japan. *Jpn J Infect Dis* 2015; **68:** 159–65.

53 Johnson RT. Editorial: Progressive rubella encephalitis. *N Engl J Med* 1975; **292:** 1023–24.

54 Reef SE, Plotkin S, Cordero JF, et al. Preparing for elimination of congenital rubella syndrome (CRS): summary of a workshop on CRS elimination in the United States. *Clin Infect Dis* 2000; **31:** 85–95.

55 Salonen EM, Hovi T, Meurman O, Vesikari T, Vaheri A. Kinetics of specific IgA, IgD, IgE, IgG, and IgM antibody responses in rubella. *J Med Virol* 1985; **16:** 1–9.

56 Best JM, Reef S, Immunization vaccines and biologicals, World Health Organization. Immunological basis for immunization: module 11: rubella. 2008.

57 Leuridan E, Hens N, Hutse V, Aerts M, Van Damme P. Kinetics of maternal antibodies against rubella and varicella in infants. *Vaccine* 2011; **29:** 2222–26.

58 Thomas HIJ, Morgan-Capner P, Cradock-Watson JE, Enders G, Best JM, O'shea S. Slow maturation of IgG1 avidity and persistence of specific IgM in congenital rubella: implications for diagnosis and immunopathology. *J Med Virol* 1993; **41:** 196–200.

59 Bouthry E, Perillaud-Dubois C, Lebraud P, Soutière MP, Grangeot-Keros L, Vauloup-Fellous C. Positive predictive value of seroconversion or positive rubella IgM in diagnosis of maternal rubella infection: seven-years review of French National Reference Laboratory for Rubella. *J Clin Virol* 2021; **134:** 104708.

60 US Centers for Disease Control and Prevention. Rubella information for healthcare professionals. March 31, 2021. https://www.cdc.gov/rubella/hcp.html (accessed Nov 8, 2021).

61 Noorbakhsh F, Johnson RT, Emery D, Power C. Acute disseminated encephalomyelitis: clinical and pathogenesis features. *Neurol Clin* 2008; **26:** 759–80, ix.

62 Bouthry E, Picone O, Hamdi G, Grangeot-Keros L, Ayoubi J-M, Vauloup-Fellous C. Rubella and pregnancy: diagnosis, management and outcomes. *Prenat Diagn* 2014; **34:** 1246–53.

63 Young MK, Cripps AW, Nimmo GR, van Driel ML. Post-exposure passive immunisation for preventing rubella and congenital rubella syndrome. *Cochrane Database Syst Rev* 2015; **9:** CD010586.

64 Bento RF, Castilho AM, Sakae FA, Andrade JQ, Zugaib M. Auditory brainstem response and otoacoustic emission assessment of hearing-impaired children of mothers who contracted rubella during pregnancy. *Acta Otolaryngol* 2005; **125:** 492–94.

65 Oster ME, Riehle-Colarusso T, Correa A. An update on cardiovascular malformations in congenital rubella syndrome. *Birth Defects Res A Clin Mol Teratol* 2010; **88:** 1–8.

66 Hahné S, Macey J, van Binnendijk R, et al. Rubella outbreak in the Netherlands, 2004–2005: high burden of congenital infection and spread to Canada. *Pediatr Infect Dis J* 2009; **28:** 795–800.

67 Xu H, Gao X, Bo F, et al. A rubella outbreak investigation and BRD-II strain rubella vaccine effectiveness study, Harbin city, Heilongjiang province, China, 2010–2011. *Vaccine* 2013; **32:** 85–89.

68 WHO. Immunization Coverage Fact Sheet. July 15, 2021 https://www.who.int/news-room/fact-sheets/detail/immunization-coverage (accessed Sept 19, 2021).

69 van den Boogaard J, de Gier B, de Oliveira Bressane Lima P, et al. Immunogenicity, duration of protection, effectiveness and safety of rubella containing vaccines: a systematic literature review and meta-analysis. *Vaccine* 2021; **39:** 889–900.

70 Schenk J, Abrams S, Theeten H, et al. Immunogenicity and persistence of trivalent measles, mumps, and rubella vaccines: a systematic review and meta-analysis. *Lancet Infect Dis* 2021; **21:** 286–95.

71 Haralambieva IH, Ovsyannikova IG, Kennedy RB, et al. Rubella virus-specific humoral immune responses and their interrelationships before and after a third dose of measles-mumps-rubella vaccine in women of childbearing age. *Vaccine* 2020; **38:** 1249–57.

72 Seagle EE, Bednarczyk RA, Hill T, et al. Measles, mumps, and rubella antibody patterns of persistence and rate of decline following the second dose of the MMR vaccine. *Vaccine* 2018; **36:** 818–26.

73 Crooke SN, Haralambieva IH, Grill DE, Ovsyannikova IG, Kennedy RB, Poland GA. Seroprevalence and durability of rubella virus antibodies in a highly immunized population. *Vaccine* 2019; **37:** 3876–82.

74 Savy M, Edmond K, Fine PEM, et al. Landscape analysis of interactions between nutrition and vaccine responses in children. *J Nutr* 2009; **139:** 2154S-218S.

75 O'Connor D, Png E, Khor CC, et al. Common genetic variations associated with the persistence of immunity following childhood immunization. *Cell Rep* 2019; **27:** 3241–53.e4.

76 Voigt EA, Haralambieva IH, Larrabee BL, et al. Polymorphisms in the wilms tumor gene are associated with interindividual variations in rubella virus-specific cellular immunity after measles-mumps-rubella ii vaccination. *J Infect Dis* 2018; **217:** 560–66.

77 Ovsyannikova IG, Salk HM, Larrabee BR, Pankratz VS, Poland GA. Single nucleotide polymorphisms/haplotypes associated with multiple rubella-specific immune response outcomes post-MMR immunization in healthy children. *Immunogenetics* 2015; **67:** 547–61.

78 Lambert ND, Haralambieva IH, Kennedy RB, Ovsyannikova IG, Pankratz VS, Poland GA. Polymorphisms in HLA-DPB1 are associated with differences in rubella virus-specific humoral immunity after vaccination. *J Infect Dis* 2015; **211:** 898–905.

79 Ovsyannikova IG, Pankratz VS, Larrabee BR, Jacobson RM, Poland GA. HLA genotypes and rubella vaccine immune response: additional evidence. *Vaccine* 2014; **32:** 4206–13.

80 Reef S, Plotkin S. Rubella vaccines. In: Orenstein W, Offit PA, Edwards, KM, Plotkin SA, eds. Vaccines, 7th ed. Philadelphia, PA: Elsevier, 2017.

81 Polk BF, Modlin JF, White JA, DeGirolami PC. A controlled comparison of joint reactions among women receiving one of two rubella vaccines. *Am J Epidemiol* 1982; **115:** 19–25.

82 Institute of Medicine, Stratton K, Ford A, Rusch E, Clayton EW, Committee to Review Adverse Effects of Vaccines. Measles, mumps, and rubella vaccine. In: Committee to review adverse effects of vaccines, institute of medicine, eds. Adverse effects of vaccines: evidence and causality. Washington DC: National Academies Press, 2012: 103–238.

83 Demicheli V, Rivetti A, Debalini MG, Pietrantonj CD. Vaccines for measles, mumps and rubella in children. *Cochrane Database of Syst Rev* 2012; **2012:** CD004407.

84 Ma S-J, Xiong Y-Q, Jiang L-N, Chen Q. Risk of febrile seizure after measles–mumps–rubella–varicella vaccine: a systematic review and meta-analysis. *Vaccine* 2015; **33:** 3636–49.

85 Barlow WE, Davis RL, Glasser JW, et al. The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine. *N Engl J Med* 2001; **345:** 656–61.

86 Mantadakis E, Farmaki E, Buchanan GR. Thrombocytopenic purpura after measles-mumps-rubella vaccination: a systematic review of the literature and guidance for management. *J Pediatr* 2010; **156:** 623–28.

87 Mangtani P, Evans SJW, Lange B, et al. Safety profile of rubella vaccine administered to pregnant women: a systematic review of pregnancy related adverse events following immunisation, including congenital rubella syndrome and congenital rubella infection in the foetus or infant. *Vaccine* 2020; **38:** 963–78.

88 WHO. Global vaccine action plan 2011–2020. 2013. https://apps.who.int/iris/bitstream/handle/10665/78141/9789241504980_eng.pdf;jsessionid=1FCD8BDCCCAACC8E89F9BCB89D15C5B8?sequence=external (accessed March 9, 2021).

89 Kirby T. Rubella is eliminated from the Americas. *Lancet Infect Dis* 2015; **15:** 768–69.

90 Bankamp B, Hickman C, Icenogle JP, Rota PA. Successes and challenges for preventing measles, mumps and rubella by vaccination. *Curr Opin Virol* 2019; **34:** 110–16.

91 Datta SS, O'Connor PM, Jankovic D, et al. Progress and challenges in measles and rubella elimination in the WHO European Region. *Vaccine* 2018; **36:** 5408–15.

92 Moss WJ, Shendale S, Lindstrand A, et al. Feasibility assessment of measles and rubella eradication. *Vaccine* 2021; **39:** 3544–59.
93 Richardson LC, Moss WJ. Measles and rubella microarray array patches to increase vaccination coverage and achieve measles and rubella elimination in Africa. *Pan Afr Med J* 2020; **35:** 3.
94 Winter AK, Martinez ME, Cutts FT, et al. Benefits and challenges in using seroprevalence data to inform models for measles and rubella elimination. *J Infect Dis* 2018; **218:** 355–64.
95 WHO. Immunization agenda 2030: a global strategy to leave no one behind. April 1, 2020. https://www.who.int/teams/immunization-vaccines-and-biologicals/strategies/ia2030 (accessed March 19, 2021).
96 WHO. Measles and rubella strategic framework: 2021–2030. Nov 8, 2020. https://www.who.int/publications-detail-redirect/measles-and-rubella-strategic-framework-2021-2030 (accessed March 19, 2021).