Seminar

Rubella

J E Banatvala, D W G Brown

Maternal rubella is now rare in many developed countries that have rubella vaccination programmes. However, in many developing countries congenital rubella syndrome (CRS) remains a major cause of developmental anomalies, particularly blindness and deafness. WHO have provided recommendations for prevention of CRS, and, encouragingly, the number of countries introducing rubella vaccination programmes has risen. However, declining uptake rates due to concerns about the measles-mumps-rubella vaccine in the UK, and increasing numbers of cases in some European countries coupled with poor uptake rates might jeopardise this progress. Surveillance of postnatally and congenitally acquired infection is an essential component of CRS prevention since rubella is difficult to diagnose on clinical grounds alone. Laboratory differentiation of rubella from other rash-causing infections, such as measles, parvovirus B19, human herpesvirus 6, and enteroviruses in developed countries, and various endemic arboviruses is essential. Reverse transcriptase PCR and sequencing for diagnosis and molecular epidemiological investigation and detection of rubella-specific IgG and IgM salivary antibody responses in oral fluid are now available.

Rubella, also known as German measles, was first described by two German physicians in the mid-18th century.[1,2] The disease was initially thought to be generally mild, to occur mostly in childhood, and have few complications. In 1941, however, an Australian ophthalmologist, Norman McAlister Gregg, recognised a group of infants born with congenital cataract.[3] Some of these infants also had congenital heart disease. Most of the mothers had a history of rubella in early pregnancy and illness with rash occurring over a limited time period during an extensive epidemic in New South Wales. Gregg's observations were subsequently confirmed by others.[4] The panel shows the major historical developments in the understanding of rubella, including isolation of virus, vaccine development, and WHO's recommendations for prevention of congenital rubella syndrome (CRS).[3,5,6]

Although a detailed description of the clinical features of postnatally and congenitally acquired infection is available in standard textbooks of clinical virology[4] and infectious diseases,[7] cases of infection acquired in these ways are frequently missed. Today in most industrialised countries, only paediatricians and specialists in infectious diseases who were practising in the 1960s and 1970s will have seen cases. Furthermore, if children present with only deafness, many are likely to be old enough to have rubella antibodies already resulting from the measles-mumps-rubella (MMR) vaccination, making virological confirmation impossible. We, therefore, describe the clinical features and laboratory diagnosis of infection, but also emphasise the changing epidemiological pattern of infection in relation to the achievements and potential of rubella immunisation to control CRS.

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Postnatally acquired rubella
Pathogenesis
Infection is acquired via inhalation of aerosol, and the virus infects cells in the upper-respiratory tract, after which cell entry occurs by receptor-mediated endocytosis. Rubella spreads and replicates in the lymphoid tissue of the nasopharynx and upper-respiratory tract, after which a viraemia leads to systemic infection, involving many organs, including the placenta.

Infected people excrete high concentrations of rubella in nasopharyngeal secretions. Thus, vaccinees may excrete more than 10^5 $TCID_{50}$ per 0·1 mL, although diurnal variations as large as 1000-fold have been reported.[8] Individuals acquiring natural infection probably excrete even higher concentrations of infectious virus.

Clinical features
Figure 1 shows the typical relation between the clinical, virological, and immunological features of infection. Among children, constitutional features are mild or absent but adults might develop fever and malaise associated with viraemia before the development of rash. The rash disappears as humoral immune responses develop, and at this stage viraemia is terminated.

Since rubella-like illnesses can be induced by other viruses that have no teratogenic potential, serological investigation is important in women who might be pregnant and who have been exposed to close contacts who might have rubella or who have rubella-like illness. Rubella virus may continue to be excreted for 1–2 weeks,

Main developments in history of rubella

1881
International Congress on Medicine recognised rubella as a distinct disease

1941
Gregg in Australia recognises teratogenic effects[3]

1962
Rubella virus isolated in cell culture. Neutralisation tests developed[5]

1963–64
Extensive European and USA epidemics. 12·5 million rubella cases, 11 000 fetal deaths, and 20 000 CRS cases in USA

1969 and 1970
Attenuated rubella vaccines licensed in USA and UK (USA universal childhood programme; UK selective vaccination of prepubertal school girls)[6]

1971
MMR licensed in USA

1978, 1979, and 1983
Severe UK rubella epidemics

1988
UK policy augmented by offering MMR to preschool children of both sexes

1989
USA introduced a two-dose measles vaccination at age 12–15 months and at age 4–5 years or 11–12 years

1989–91
Resurgence of rubella in USA

1996
In UK, schoolgirl vaccination discontinued but second dose of MMR introduced for children aged 4–5 years

2000
WHO organises first global meeting on rubella since 1984

2002
123 (57%) of 212 of countries and territories include rubella vaccination in national immunisation programmes

sometimes even longer, and might also be recovered from the nasopharynx during the week preceding the onset of rash. Therefore, the date of first exposure could precede the onset of rash in the contact by 7–10 days.

Complications

Postnatally acquired rubella is seldom associated with complications, apart from joint symptoms. Currently recognised complications are shown in table 1.[9–17] Arthralgia or a frank arthritis, although uncommon among boys and prepubertal girls, occurs in up to 60% of postpubertal women. Symptoms generally persist for 3–4 days, although they occasionally last for 1 month or even longer, sometimes with a fluctuating course. Since rubella virus can be detected in the synovial fluid and the synovium in arthritis related to naturally acquired infection and vaccination, and since symptoms appear as rash subsides and humoral antibody develops, immune complexes might be involved in the pathogenesis. Although some findings suggest that rubella is involved in the pathogenesis of some forms of chronic arthritis,[18,19] this association has not been confirmed in other studies.[20]

Differential diagnosis

Clinical diagnosis of rubella is unreliable and laboratory confirmation essential. Table 2 shows the most frequent causes of febrile rash, their geographical distribution, and main features. Infection with parvovirus B19 is frequently impossible to distinguish clinically from rubella, since fever, rash, and joint symptoms commonly occur in both infections. Pregnant women exposed to or developing non-vesicular rashes should be investigated for both infections.[21] Parvovirus B19 is non-teratogenic but is associated with a high incidence of miscarriage, generally in the second trimester, and, less frequently, fetal hydrops.[22,23] Furthermore, rubella and parvovirus B19 can circulate concurrently.[24] Human herpes virus 6 can also cause rash and fever in children (exanthem subitum), which should be considered as a differential diagnosis.[25,26] In a study in the UK in primary care among children younger than 5 years with rash, only two (3%) of 74 cases were confirmed as rubella.[27]

In many parts of the tropics, alphaviruses[28] and flaviviruses[29] may induce rubella-like illnesses. Dengue (a flavivirus) is the most widely distributed arbovirus infection worldwide, and its prevalence is increasing. In parts of Australia, Ross River fever (epidemic polyarthritis) is a major public-health problem. The results of a Brazilian study show that between 1994 and 1998, maculopapular rashes that were difficult to
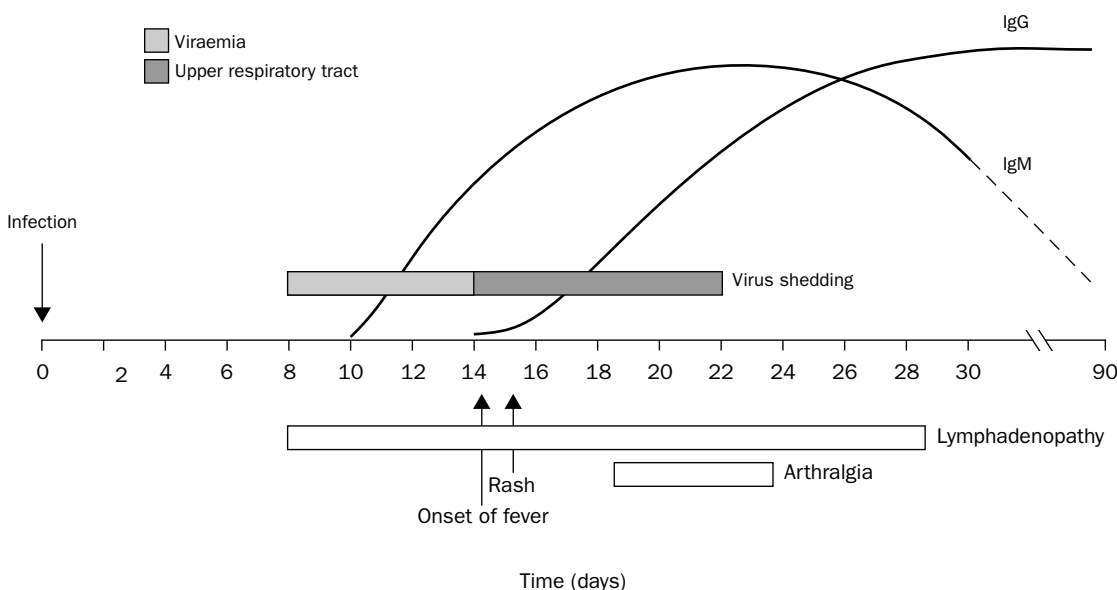

Figure 1: **Timing of key clinical, virological, and immunological features in acquired rubella infection**

	Frequency	
	Wild rubella	Vaccination
Complication		
Arthralgia/arthritis[9,10,11]	Up to 50% of post-pubertal females	Up to 40% of adult women
Post-infections encephalopathy[12–14]	1 in 5000 to 1 in 10 000	1 in 29 000
Guillain-Barré[15]	Very rare	..
Haematological		
Transient thrombocytopenia[14,16]	1 in 3500 but not generally investigated	..
Purpuric rash[14]	1 in 1500	..
Haemolytic anaemia[17]	Rare	..

Table 1: **Complications of postnatally acquired rubella and vaccination**

differentiate clinically were induced by rubella, parvovirus B19, dengue, human herpesvirus 6, and measles, some of which were circulating concurrently.[30] The difficulties of differential diagnosis highlight the need for laboratory confirmation to underpin rubella and measles surveillance.

Congenital rubella syndrome
Pathogenesis
Fetal damage is multifactorial, resulting from a combination of rubella-virus-induced cellular damage and the effect of the virus on dividing cells. Placental infection occurs during maternal viraemia, resulting in focally distributed areas of necrosis in the epithelium of chorionic villae and in the endothelial cells of its capillaries.[31] These cells seem to be desquamated into the lumen of vessels, suggesting that rubella virus is transported into the fetal circulation as infected endothelial cell emboli, which may result in infection and damage of fetal organs. During early pregnancy, fetal defence mechanisms are immature, and a characteristic feature of rubella embryopathy in early gestation is cellular necrosis in the absence of any inflammatory response.

Rubella-virus-infected cells have a reduced life span;[32] in the organs of affected fetuses and infants the number of cells is lower than in healthy infants.[33] Rubella virus can also induce damage by apoptosis. In-vitro studies suggest that this effect is due to a rubella-induced capsase-dependent mechanism.[34,35] The exact mechanism has yet to be determined, but it seems to be dependent on virus replication started within 12 h of infection.[34,36,37] The p53 pathway seems not to be involved.[38] However, in non-

human cells, although viral replication is required to induce apoptosis, it is the non-infected neighbouring cells that undergo this effect.[39]

If maternal infection occurs after the first trimester, the frequency and severity of fetal damage decreases strikingly. This difference occurs because the fetus is protected by the progressive development of fetal humoral and cell-mediated immune responses,[40,41] and by passive transfer of maternal antibodies. As with other enveloped viruses, cytotoxic T cells, natural-killer cells, monocytes, and secretion of lymphokines, are likely to be involved in recognising and eliminating rubella-virus-infected cells.[40]

CRS risks after maternal rubella in first trimester
The range of anomalies can be correlated with gestational age during maternal rubella infection in the first trimester (figure 2). Rubella virus continues to replicate and be excreted by infants with CRS, which may lead to infection in susceptible contacts. Mechanisms of virus persistence, despite the fetus being able to mount a rubella-virus-specific immune response, have not been clearly established. Possible mechanisms include persisting defective cell-mediated immunity,[42,43] limited life span of infected clones of cells termination of virus excretion after their elimination , or both. Selective immune tolerance to the rubella virus E1 protein might also be involved.[44]

The clinical features of CRS, including some of the delayed manifestations of disease, which may not present until adolescence or adulthood, are listed in table 3.[45] These features can be classified as transient, self-limiting, or permanent. Figures 3 and 4 show typical presentations of cataract and purpuric rash. Some developmental defects such as deafness might not become apparent for months or even years, but then can persist indefinitely.

Between ages 3 and 12 months, some infants with CRS develop multisystem disease with a chronic rubella-like rash, persistent diarrhoea, and pneumonitis, which is also, although inappropriately, referred to as late-onset disease. Circulating immune complexes and interstitial pulmonary deposits may be present. This form of disease might respond to treatment with corticosteroids.[46,47]

Cardiovascular anomalies include proliferation and damage of the integral lining of blood vessels, causing obstructive lesions of medium-sized and larger arteries in the systemic and pulmonary circulatory systems. Hypertension might result from renal obstruction.[48,49]

Very rarely, children with clinically stable CRS develop a widespread subacute panencephalopathy that is invariably fatal.[12] Clinical and laboratory features are similar to measles-induced subacute panencephalitis.

	Geographical distribution								Key features
	Africa	Asia	Australia	Europe	North America	Central America	South America	Pacific	
Virus infection									
Rubella	+	+	+	+	+	+	+	+	..
Parvovirus B19	+	+	+	+	+	+	+	+	Erythema infectiosum
Human herpes viruses 6 and 7	+	+	+	+	+	+	+	+	Exanthem subitum, mainly <2 years
Measles	+	+	+	+	+	+	+	+	Prodrome with cough, conjunctivitis, coryza
Enteroviruses	+	+	+	+	+	+	+	+	Echovirus 9, Coxsackie A9 most frequent
Dengue	+	+	+	–	–	+	+	+	Joint and back pain, haemorrhagic complications in children
West Nile fever	+	+	–	+	+	–	–	–	Joint pain
Chickungunya	+	+	–	–	–	–	–	–	Joint pain
Ross River	–	–	+	–	–	–	–	+	Joint pain
Sindbis	+	+	+	+	–	–	–	–	Joint pain

Table 2: **Differential diagnosis of postnatal rubella in different geographical regions**

Rubella virus has been detected in brain tissue and from lymphocytes. A high ratio of cerebrospinal fluid to serum rubella antibody titre is present. The disease might be mediated by immune complexes or rubella-virus-mediated autoreactivity to brain antigens.

The burden of deafness among infants with CRS has certainly been underestimated; deafness is probably the most important cause of non-genetic congenitally acquired hearing loss in countries with no rubella vaccination programme.[50] Methods to assess hearing loss in early infancy, such as otoacoustic emissions and auditory brainstem responses,[51] are now available to screen infants at risk and will detect hearing defects much earlier than previously, even neonatally.[52] The equipment is, however, costly and has not been fully assessed for reliability outside the laboratory or been widely used. This lack of evidence limits the use of such techniques in developing countries where CRS is common.

In addition to the eye defects listed in table 3, aphakic glaucoma can occur after cataract aspiration, and neovascularisation of the retina might be a late-onset manifestation of CRS. In some imaging studies enlargement of lateral ventricles and reduced grey matter,[53] intracranial calcification, and linear hyperechogenicity in the basal ganglia region have been reported; these lesions might predict the development of microcephaly.[54]

The most common manifestation of delayed-onset disease is the development of type 1 diabetes mellitus. Follow-up studies in children born in the 1939–41 Australian epidemic, showed that about 20% had developed diabetes by their third decade.[55] Similar

Figure 3: **Congenital rubella cataract in an infant aged 9 months**

findings have been reported from infants with CRS after the 1963–64 US epidemic; 12·4% developed diabetes, although a higher proportion (20%) had pancreatic-islet-cell cytotoxic surface antibodies, which suggests that many of these patients would develop type 1 diabetes later.[56] The presence of these antibodies in such patients was associated with a significantly increased HLA-DR3 and decreased HLA-DR2 haplotype, which are characteristic of autoimmune phenomena. Data from experimental studies add support to the role of autoimmune mechanisms, thus monoclonal antibodies to rubella-virus capsid protein glutamic acid decarboxylase recognise B cell epitopes on human and rat islet cells[57] and clones of T cells from patients with CRS elicit cytotoxic responses to a β-cell autoantigen glutamic acid decarboxylase 65.[58]
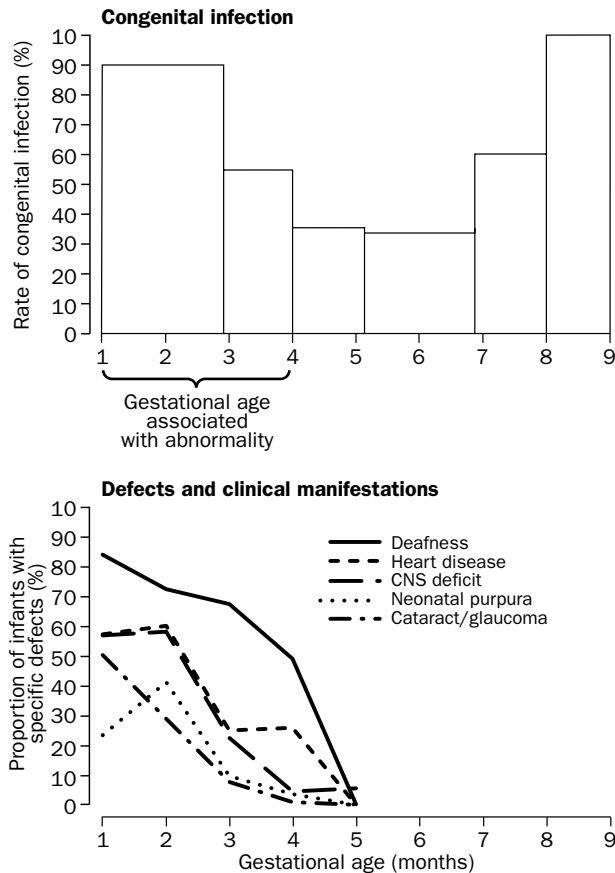

Figure 2: **Rates of congenital infection, congenital defects, and clinical manifestations in CRS by time of maternal infection**
Adapted with permission from references 4 and 41.

Figure 4: **Purpuric rash in infant with CRS**

	Time when signs commonly recognised	Early transient features	Permanent features†
Ocular defects			
Cataracts (unilateral or bilateral)	Early infancy	–	+
Glaucoma	Early infancy	–	+
Pigmentary retinopathy	Early infancy	–	+
Microphthalmia	..	–	+
Iris hypoplasia	..	–	+
Cloudy cornea	..	+	–
Auditory defects			
Sensorineural deafness (unilateral or bilateral)	Early infancy	–	+
Cardiovascular defects			
Persistent ductus arteriosus	Early infancy	–	+
Pulmonary artery stenosis	Early infancy	–	+
Ventricular septal defect	Early infancy	–	+
Myocarditis		+	–
Central nervous system			
Microcephaly	Neonatal	–	+
Pyschomotor retardation	..	–	+
Meningoencephalitis	Neonatal	+	–
Behavioural disorders	..	–	–
Speech disorders			
Intrauterine growth retardation	..	+	–
Thromocytopenia, with purpura	Neonatal	+	–
Hepatitis/hepatosplenomegaly	Neonatal	+	–
Bone lesions	Neonatal	+	–
Pneumonitis	..	+	–
Lymphadenopathy	..	+	–
Diabetes mellitus	..	–	+
Thyroid disorders	..	–	+
Progressive rubella panencephalitis	..	–	+

*Time when signs seen commonly used to clinically confirm CRS cases (reference 45). †Some recognised late.

Table 3: **Clinical features of congenital rubella syndrome**

A further follow-up of the Australian cohort at age 60 years showed an increased prevalence of type 2 diabetes, and that 19% had also experienced thyroid disorders, 73% early menopause, and 13% osteoporosis, these being significantly higher than in the general Australian population.[59] Further investigations on the pathogenesis of rubella-induced type 1 diabetes in patients with CRS are of notable importance since, although other viruses have been implicated in the pathogenesis of type 1 diabetes,[60] so far only rubella has been associated with its pathogenesis, but only after congenitally acquired infection. Studies directed towards an understanding of the pathogenesis of late-onset disease among CRS patients might throw light on the pathogenesis of other chronic diseases.

Infection after first trimester
Rubella is seldom isolated from infants whose mothers acquire infection after the first trimester, although serological studies show that about a third of infants whose mothers were infected with rubella virus between 16 and 20 weeks are infected and have rubella-specific IgM at birth.[61] Studies done in different countries showed that if maternal infection was acquired between 13 and 20 weeks of gestation, 16–18% of infants acquired rubella-induced defects, but after this period, the incidence was less than 2%.[4] Deafness and retinopathy are frequently the only manifestations of congenital infection, although retinopathy does not generally affect sight.

Infection occurring before conception
In occasional reports of individual cases, even if acquired before conception, rubella has induced congenitally acquired infection. However, in a prospective study done in the UK and Germany involving 38 infants delivered of mothers whose rash occurred before conception, rubella virus was not transmitted to the fetus. All 38 infants had no serological evidence of infection, contrasting with ten whose mothers had rash 3–6 weeks after their last menstrual period.[62]

Re-infection
Re-infections with rubella occur more frequently after vaccine-induced than after naturally acquired infection. Re-infections are generally asymptomatic and are recognised by serological investigation of a mother after contact with rubella. Several studies have attempted to define the risk of re-infection during the first trimester, which is put at less than 10% and probably less than 5%,[63,64] but, when counselling mothers who might have experienced re-infection, they should be reassured that the risk of fetal damage is extremely small.

The rarity of congenital malformations after re-infection make it difficult to assess why fetal infection and damage does occur, albeit rarely. However, re-infection, associated with viraemia, does not seem to be due to a lack of neutralising antibodies or a defect in rubella-specific lymphoproliferative responses.[43] Production of epitope-specific antibodies might fail. However, rubella-virus strains from cases of re-infection do not seem to differ from other strains; no sequence changes in the E1 open reading frame have been detected.[65,66]

Long-term prognosis
Reports on long-term outcome have varied. After 25 years, the 40 survivors of the Australian epidemic reported by Gregg in 1941 had adjusted well to their defects and associated difficulties; 58% had married and had children.[67] Follow-up studies on the survivors of the extensive US epidemics in the 1960s were more discouraging. Perhaps advances in management after this outbreak reduced mortality, particularly in infants with congenital heart disease. Although improving prognosis, these benefits might have long-term consequences relating to the cost of institutional care and in survivors developing late-onset sequelae.

Virology

Rubella is classified as a member of the togaviridae. The virus contains single-stranded RNA (9762 nucleotides) and is the only member of a separate genus *Rubivirus*. The virus particle (figure 5) has a diameter of about 60 nm. There is a nucleocapsid exhibiting cubic symmetry surrounded by a lipoprotein envelope with spiky projections consisting of two glycoproteins, E1 and E2.[68] The replication of rubella virus is reviewed in detail elsewhere.[69,70]

Humoral and cell-mediated responses are produced against all three structural proteins, although E1 probably carries the major immunodominant epitopes.[71,72] Antibody titres correlate with protection from challenge. Rubella is antigenically stable[73] and consequently antigenic variation does not pose a risk in the use of rubella vaccines or for serological diagnosis. However, sequencing studies concentrating on the E1 open reading frame have recognised two genotypes, viruses from Europe, North America, and Japan differing from some isolates from India and China.[65,66]

Laboratory diagnosis
Postnatally acquired infection

Various techniques have been used to assess immunity by detecting rubella-specific IgG from naturally acquired or vaccine-induced infection. In the past, tests to detect rubella-specific neutralising antibodies, haemagglutination-inhibition antibodies or single radial haemolysis were widely used.[74] However, laboratories now generally use commercially available enzyme immunoassay for IgG and IgM detection.[75,76] In Britian a national standard serum is available and an antibody concentration of 10 IU/mL is generally seen as indicative of immunity.[77]

The presence of rubella-specific IgM is used to determine whether patients have current or recently acquired rubella. However, when interpreting results of laboratory investigations, particularly in pregnancy and when termination is under consideration, details of rubella vaccination, results of previous antenatal screening tests, and precise details of date and duration of contact should be obtained. Close collaboration between antenatal clinics and the laboratory is essential for appropriate investigation of pregnant women exposed to or who have acquired rubella-like infections. Care of patients is increasingly shared between family practices and hospital clinics, which might occasionally result in the laboratory failing to receive relevant information and do appropriate investigations. Vaccination programmes have made maternal rubella rare in developed countries, but failure to appreciate the importance of a rubella-like illness and to alert the laboratory to its importance in pregnancy, might still result in avoidable CRS[78] and be costly medicolegally.

A notable rise in IgG antibodies can generally be detected within 4–7 days of the onset of symptoms, although occasionally responses are delayed. However, patients frequently present after the acute phase of their illness, by which time rubella-specific IgG antibodies have reached maximum concentrations. Whether or not a rise in rubella-specific IgG is present, tests to detect rubella-specific IgM should be done, since a positive response is strongly suggestive of recently acquired infection. Rubella-specific IgM mostly persists for 8–12 weeks, although, if sensitive tests are used, low concentrations can be seen for much longer after naturally acquired and vaccine-induced infection or re-infection.[79] False-positive results are more likely to occur if indirect rather than antibody capture assays are used and might also result from other IgM antibodies, which cross-react, or from rheumatoid factor. Consequently, a second rubella-specific IgM test with a different format should be done to confirm maternal rubella in the first 20 weeks of pregnancy, before patients have to make a decision as to whether or not they wish to have their pregnancy terminated in countries where this is legal.[21]

For women wishing to continue with the pregnancy various methods can be used to investigate fetal infection, including IgM detection by cordocentesis in fetal blood, viral RNA in amniotic fluid, or testing chorionic-villus samples by reverse transcriptase (RT) PCR.[80–82] The detection of rubella RNA in amniotic fluid by RT-PCR has a sensitivity of 87–100%.[83,84] Amniocentesis should be done at least 8 weeks after onset of maternal rubella, and after 15 weeks' gestation. Occasional false-negative results occur if the fetus does not produce detectable IgM before 22 weeks of gestation, and testing of a second sample at 22–23 weeks' gestation might, therefore, be necessary.[85,86] The presence of virus in chorionic-villus biopsy samples must be interpreted cautiously, since the presence of placental rubella virus might not reflect fetal infection.[85]

Congenitally acquired infection

The immune responses in infants with CRS differ substantially from those in infants with postnatally acquired infection. Rubella-specific IgG and IgM synthesised by the fetus are detectable at birth in CRS. However, since maternally derived rubella-specific IgG is also present in infants' sera, laboratory diagnosis of CRS is almost invariably made by detection of rubella-specific IgM responses. This response is detectable in almost 100% of CRS cases up to age 3 months with the most sensitive antibody-capture assays. The response declines progressively to less than 50% at 12 months, and is rarely detectable after 18 months.[87]

Although rubella virus can be detected in respiratory secretions in 80–90% of infants with CRS during the first month of life, virus excretion
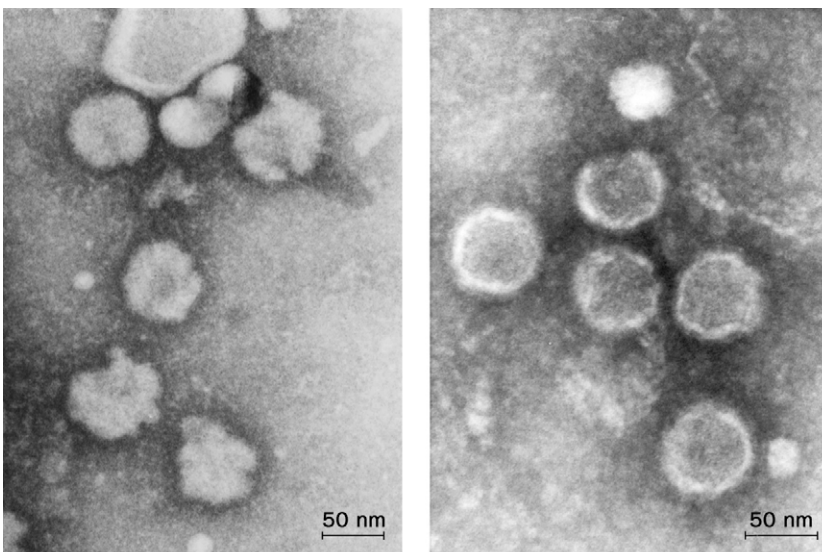

Figure 5: **Electron micrographs of rubella virus**
Courtesy of I Chrystie, St Thomas' Hospital, London, UK.

declines progressively in the first year.[87] Few laboratories now have the techniques or expertise to culture rubella virus, but sensitive RT-PCR tests have been described and, although not yet widely assessed for diagnosis, they are likely to be useful.[82]

Among infants with CRS who have cataracts, rubella virus may be detected by RT-PCR in lens aspirates in the first year of life.[88] Among infants who might have CRS but who present when rubella-specific IgM responses will no longer be present, laboratory diagnosis of CRS may be made by detection of low-avidity IgG 1 rubella antibodies. These antibodies mature more slowly in children with CRS than those present after postnatally acquired infection, and might be present up to age 3 years.[89] In addition, a useful diagnostic tool is to vaccinate children whose rubella antibodies are no longer detectable but who have one or more clinical features compatible with CRS. These children commonly do not respond serologically to rubella vaccination.

Oral-fluid testing for diagnosis and surveillance

Testing of oral-fluid samples as an alternative to serum samples offers many advantages for surveillance. The ease and acceptability of oral-fluid collection is shown in figure 6. Methods for collection, extraction, and preservation of samples have been established.[90–92] Serological tests for detection of rubella-specific IgM in oral-fluid samples are accurate in CRS.[93] The rubella genome has been detected in oral fluid by RT-PCR in a large proportion of cases[94] and the amplicons used for molecular epidemiological studies. Oral-fluid samples are also suitable for detection of antibody avidity.[95] As with all tests, rubella IgM has a low predictive value in periods of low rubella circulation, but tests for low avidity antibody and virus genome by RT-PCR offer a potential confirmatory strategy. The benefits of oral fluid for rubella surveillance are clear, but their full exploitation is likely to depend on widespread availability of suitable commercial assays.

Vaccination

Rubella vaccination makes CRS a preventable disease. Live attenuated rubella vaccines were first licensed in the 1960s (panel). RA27/3, which is grown in human diploid cells, is now used in most of the world, although China and Japan use similar locally developed live attenuated vaccines. Immune responses to rubella vaccine closely resemble those of naturally acquired infection. More than 95% of recipients older than 11 months seroconvert and antibody responses are detectable for more than

Figure 6: Collection of oral fluid from an infant for rubella IgM detection
Courtesy of D M Eckstein and P Vijayalakshmi, Aravind Eye Hospital, Madurai, India.

21 years.[96] Long-term vaccine efficacy is more than 90%. However, in some vaccines, antibody concentrations might wane over time to less than 10 IU/mL. Studies in which volunteers with low or undetectable concentrations of antibody were challenged intranasally with high-titre rubella vaccine showed boosts in antibody, but viraemia was rare, transient, and of low concentration.[97] The duration and degree of viraemia is unlikely to result in fetal damage. Indeed, inadvertent rubella vaccination among susceptible women in early pregnancy does not lead to rubella-induced defects. Thus, analysis of data from several countries identified no CRS cases. The theoretical maximum risk of rubella-induced major malformations among infants whose mothers were susceptible and vaccinated during the first 2 months of pregnancy, was calculated to be 1·3%, which is less than the risk of major malformation occuring in usual pregnancies (3%).[98] In recent rubella campaigns in Brazil, which included women of childbearing age, more than 6000 pregnant women were inadvertently vaccinated.[99]

Vaccination causes few side-effects (table 1),[100] but it is associated with acute joint symptoms in up to 40% of postpubertal females, there being a higher frequency of HLA-DR2 and HLA-DR5 and lower frequencies of HLA-DR4 and HLA-DR6 in RA27/3 vaccinees with arthropathy.[11,101] Hormonal changes are also suggested to be involved.

As with other live vaccines, rubella vaccine should not be given to immunocompromised patients.[102] Nevertheless, since rubella vaccine is generally administered as the MMR vaccine, HIV-positive individuals, particularly children, should benefit from being afforded protection, not only from rubella, but from mumps and measles; measles is life-threatening in such patients. Current US guidelines state that people who are HIV positive, who are asymptomatic or have only mild symptoms can be vaccinated since they do not generally experience complications.[103]

Epidemiology, immunisation, and surveillance

Immunisation programmes have already had a major impact on the epidemiology of rubella in many developed and several developing countries. In some countries in Europe, in the USA, and Australasia, CRS is now very rare, and countries using two doses of the MMR vaccine, such as the USA, have interrupted indigenous transmission of rubella virus.[104]

There is now an impetus to extend vaccination programmes to the developing world. A review of published work sponsored by WHO in 1996 showed that in 45 developing countries, despite substantial variation in rubella susceptibility among women of childbearing age, the proportion (15–20%) was similar to that in industrialised countries in the prevaccination era.[45,105] Indeed, some countries had appreciably higher susceptibility rates at that time (eg, Trinidad and Tobago 68%, and Thailand 30%).[45] In some countries regional variation was considerable; reduced susceptibility rates might reflect recent unrecognised outbreaks in which infection was atypical, subclinical, or merely incorrectly diagnosed.

In the absence of rubella vaccination programmes, if CRS is sought it is found.[106,107] The incidence of CRS is similar to that in developed countries, such as the UK before the vaccination era. Indeed, with use of mathematical modelling techniques, for five WHO regions (excluding Europe) there were estimated to be around 236 000 cases of CRS in developing countries during non-epidemic years. However, during epidemics
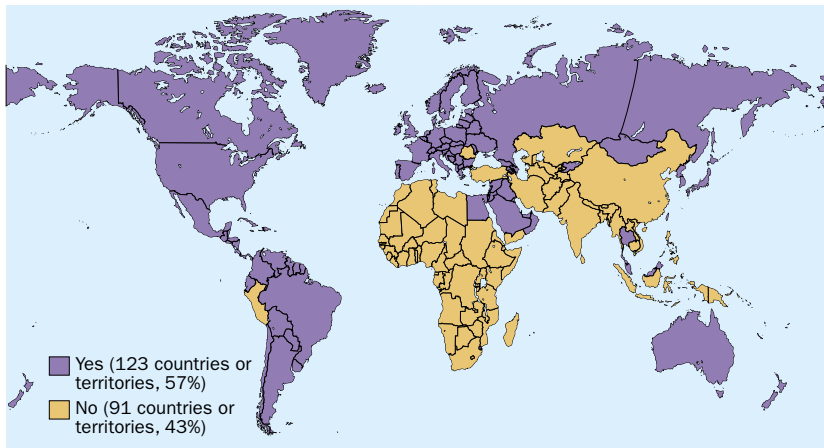
Figure 7: **Countries and territories with rubella vaccine in national immunisation system, 2002**

there could be a ten-fold increase in incidence, and even that might be an underestimate, since many infants with CRS might have been assessed in early infancy before such manifestations as deafness are apparent. The current WHO position is that there are more than 100 000 CRS cases occurring every year.[108,109] The depletion of already scarce health-care resources by rubella in developing countries is still insufficiently appreciated.

In January, 2000, WHO held a meeting in Geneva directed towards prevention of CRS, particularly in developing countries.[110] Strategies recommended included piggy-backing rubella with measles vaccine, or with measles and mumps, ensuring that the vaccination programme covered children of both sexes and adult women. In countries with low measles-vaccine uptake, rubella vaccination of young women is likely to be the most appropriate strategy to reduce CRS, but reduction in the incidence of CRS is unlikely to be achieved for many years if vaccination is directed selectively for schoolgirls. In economic analyses of rubella vaccination strategies in developed and developing countries, rubella vaccination programmes have been proved cost effective, and benefits are similar to those associated with vaccination against hepatitis B and *Haemophilus influenzae* type b.[111]

Encouragingly, rubella vaccination in national immunisation programmes increased from 78 countries or territories in 1996, to 123 by December, 2002 (figures 7 and 8), the most impressive coverage being in the WHO region of the Americas. The European region of WHO
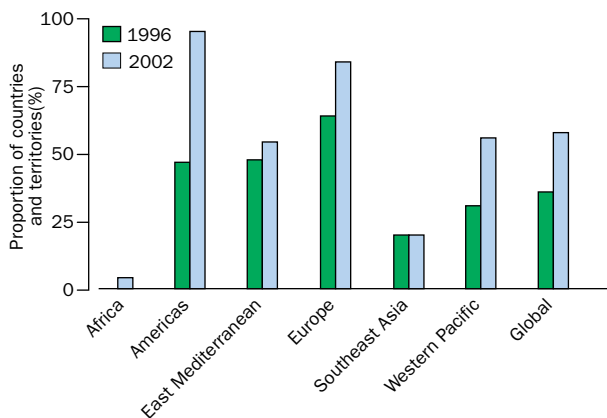

Figure 8: **Proportion of countries and territories, by WHO region, with rubella vaccine included in national immunisation system, 1996 and 2002**

has set a target for the elimination of indigenous measles by 2007, and the reduction of CRS to fewer than one per 100 000 livebirths by 2010.[112]

Unfortunately, rubella prevalence has increased strikingly in central and eastern Europe, particularly in the newly independent states (former Soviet Union), where large epidemics occurred between 1998 and 2000.[113] Such countries do not undertake surveillance for CRS, although clusters of cases have been reported in eastern and southern Europe. A further cautionary episode occurred in Greece. An extensive epidemic of rubella occurred in 1993, followed by the delivery of a high incidence of infants with CRS (24·6 per 100 000 livebirths). Because at that time, rubella vaccination was only optional and before 1990, vaccine coverage was only 50–60%, an upward shift was seen of age susceptibility to rubella, with infection occurring frequently among women of childbearing age.[114]

Although CRS is now rare in the UK, complacency would be unwise. The rubella susceptibility rate among white UK women screened antenatally in north London (1996–99) is low (1·6%), but it is much higher among women from the Indian subcontinent, particularly Sri Lanka (16%).[78,115] Furthermore, one in five of such women had an opportunity for vaccination which was missed in the UK, either prenatally or postpartum, largely due to professional ignorance.[116] Concern about the safety of the MMR vaccine has resulted in a reduced vaccine uptake rate from 92% in 1995 to 84% in 2002.[116] Measles outbreaks should warn that rubella could also reappear. The basis of this concern is a proposed association of the measles component of the multivalent vaccine with development of autism. However the published evidence supporting the association is meagre, scientifically questionable,[117,118] and unconfirmed, and several wide-ranging independent reviews have not supported the association.[119,120]

Future issues

The indigenous circulation of rubella has been interrupted and CRS cases have been virtually eliminated in the USA and several European countries. These achievements indicate that the goal of rubella elimination and CRS control is largely dependent on the establishment of vaccination programmes. Elimination programmes should be supported by appropriate surveillance including molecular epidemiological studies to establish links between cases and outbreaks and provide useful evidence about the circulation of indigenous or the introduction of strains from other countries. Such investigations are of particular importance when approaching stages of rubella elimination.

Immunisation programmes aimed at rubella elimination or CRS should adopt techniques appropriate to local health services, and be accompanied by appropriate training to establish high-quality clinical and laboratory surveillance, which should be regularly monitored. A cheap robust test to detect rubella-virus-specific IgM responses is needed that can be done at ambient temperatures and in field conditions for diagnosis, particularly during surveillance programmes. This aim has been achieved for dengue virus, which has a diagnostic profile similar to rubella.

Currently WHO's major priority for vaccine-preventable diseases is worldwide poliomyelitis eradication. Substantial progress has been made in CRS control and there is also the potential to eliminate CRS and measles worldwide. If this goal is to be achieved, WHO, in conjunction with such organisations as the Global Alliance for Vaccines and Immunisations, must continue to provide resources and direction. Countries with low vaccine uptake rates must be encouraged to improve, ensuring that vaccination programmes are seen as a priority, but within the overall strategy directed towards infectious diseases and other health priorities.

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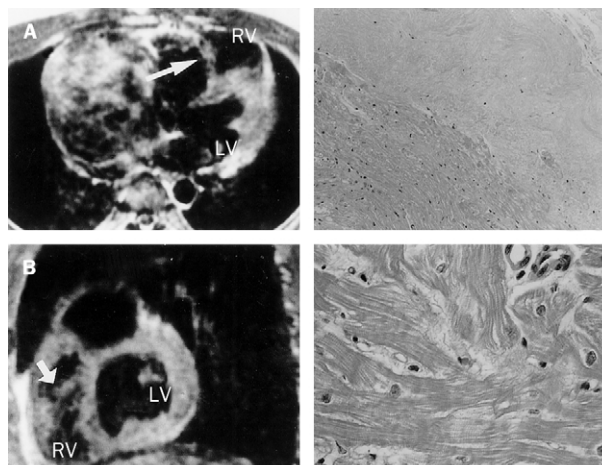107 Banatvala JE. Rubella—could do better. *Lancet* 1998; **351:** 849–50.

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Clinical picture

Double chambered right ventricle

Tomoaki Nakata, Atsuo Hattori, Kazuaki Shimamoto,

Two patients, a 31-year-old man and a 29-year-old man, were admitted to our hospital for further evaluation of heart murmur and exertional dyspnoea. In addition to abnormalities on their chest radiographs and electrocardiograms suggestive of right ventricular overload, two-dimensional Doppler echocardiography revealed enlarged right atrium with severe tricuspid regurgitation, aberrant muscular bands of the right ventricle but no definitive left ventricular abnormality in the patients. MRI clearly demonstrated anomalous muscle bundles that transected the right ventricle from a free wall to ventricular septum, resulting in division of the right ventricle into two chambers (left panels: A, transverse section; B, coronal section). The right ventricles were also haemodynamically separated, and there were two pathways for blood to flow above and below the bundles; initial blood flow was around the lower chamber located at apical and anterior-to-infundibular regions of the right ventricle. The tricuspid valves were surgically repaired, and the anomalous muscle bands were removed. Histopathological examination of the anomalous muscle bundles revealed thickened subendocardium, disarrayed cardiac tissues, heterogeneously stained myofilaments, vacuolisation, irregular sizes of nuclei, and partial replacement of the myocardium by fibrous tissue (right panels). The postoperative courses of both patients were uneventful.

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