Reviews/Analyses

Control of rubella and congenital rubella syndrome (CRS) in developing countries, part 1: burden of disease from CRS

F.T. Cutts,[1] S.E. Robertson,[2] J-L. Diaz-Ortega,[3] & R. Samuel[4]

Congenital rubella syndrome (CRS) can lead to deafness, heart disease, and cataracts, and a variety of other permanent manifestations. In developing countries, the burden of CRS has been assessed as follows: by surveillance of CRS; by surveillance of acquired rubella; by age-stratified serosurveys; and by serosurveys documenting the rubella susceptibility of women of childbearing age. During rubella outbreaks, rates of CRS per 1000 live births were at least 1.7 in Israel, 1.7 in Jamaica, 0.7 in Oman, 2.2 in Panama, 1.5 in Singapore, 0.9 in Sri Lanka, and 0.6 in Trinidad and Tobago. These rates are similar to those reported from industrialized countries during the pre-vaccine era. Special studies of CRS have been reported from all WHO regions. Rubella surveillance data show that epidemics occur every 4–7 years, similar to the situation in Europe during the pre-vaccination era. In developing countries, the estimated average age at infection varies from 2–3 years to 8 years. For 45 developing countries we identified serosurveys of women of childbearing age that had enrolled ≥ 100 individuals. The proportion of women who remained susceptible to rubella (e.g. seronegative) was <10% in 13 countries, 10–24% in 20 countries, and $\geq 25\%$ in 12 countries. Discussed are methods to improve the surveillance of rubella and CRS in developing countries.

Introduction

Rubella is a common cause of childhood rash and fever; its public health importance relates to the teratogenic effects of primary rubella infection in pregnant women (*1*). The worldwide pandemic of rubella in 1962–65 highlighted the importance of congenital rubella syndrome (CRS); and in the USA alone, more than 20 000 cases of CRS were estimated to have occurred (*2*).

Table 1 summarizes the clinical manifestations of congenital rubella. After infection in the first tri-mester, there is an approximately 50% increase in risk of spontaneous abortion (*3*). CRS manifestations in surviving infants may be transient (e.g. purpura); permanent structural manifestations (e.g. deafness, congenital heart disease, cataract); or late-emerging conditions (e.g. diabetes mellitus). Sensorineural deafness may occur following maternal infection up to the 19th week of pregnancy, while cataract and heart disease only occur after infection prior to the ninth gestational week (*4*).

The absolute risk of CRS among children born to mothers infected during pregnancy varies widely in different studies; in part, this reflects the age at follow-up of children, as deafness is most easily detected after 2 years of age (*5*). Among a series of 269 infants born to mothers with rubella infection during pregnancy, Miller et al. (*6*) found that the risk of congenital infection was 81% and that of malformations was 69% after confirmed maternal rubella with rash in the first trimester. The risk of malformation detected by 2 years of age fell rapidly from 90% of nine infants infected prior to 11 weeks' gestation to 33% of four infants infected at 11–12 weeks' gestation. No defects were detected among 63 infants born to mothers in-

[1] Senior Lecturer in Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, England.

[2] Medical Officer, Global Programme for Vaccines and Immunization, World Health Organization, 1211 Geneva 27, Switzerland. Requests for reprints should be sent to this author.

[3] Director, Research, Training, and Supervision, National Vaccination Council, Ministry of Health, Mexico City, Mexico.

[4] Research Officer, Departments of Clinical Virology and Community Health, Christian Medical College and Hospital, Vellore, India; and DSc Fellow, Netherlands Institute for Health Sciences, Erasmus University Medical School, Rotterdam, Netherlands.

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Table 1: Main clinical manifestations of congenital rubella[a]

General
  Fetal loss (spontaneous abortion and stillbirths)
  Low birth weight
  Micrognathia

Ears and central nervous system
  Sensorineural deafness: unilateral or bilateral
  Central auditory deafness
  Mental retardation
  Speech defects

Cardiovascular system
  Patent ductus arteriosus
  Pulmonary arterial stenosis
  Ventricular septal defects

Eyes
  Retinopathy
  Cataracts: pearly, dense, nuclear; 50% bilateral[b]
  Microphthalmos

Transient neonatal manifestations[c]
  Thrombocytopenia, +/− purpura
  Hepatospenomegaly
  Meningoencephalitis
  Bony radiolucencies
  Adenopathies

Late-emerging or developmental
  Late-onset interstitial pneumonitis, age 3–12 months
  Chronic diarrhoea
  Insulin-dependent diabetes mellitus

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[a] Adapted from ref. *4* and *99*.
[b] Cataract is always accompanied by retinopathy.
[c] Extensive infection; high mortality.

fected after 16 weeks' gestation. A study in the USA, however, found a small risk of CRS even among infants born to mothers infected after the 16th week of pregnancy (*7*).

Interest in the burden of disease and global rubella vaccination policies has increased recently for a number of reasons. Rubella outbreaks leading to CRS were documented in Panama (*8*) in the mid-1980s, and in Oman (*9*) and Sri Lanka (*10*) in the 1990s. Measles vaccine coverage of infants is now >80% in many developing countries; thus effective rubella control programmes are feasible. Many countries have introduced rubella-containing vaccines to their national programmes, using a variety of different schedules. In addition, measles–mumps–rubella (MMR) vaccine is distributed in the private sector, even in countries without a national rubella control programme (*11*). There is thus a need to review the principles and practice of control of rubella and CRS.

In this review article, the first of two parts on control of rubella and CRS in developing countries, we present information on the burden of disease related to CRS and make recommendations for surveillance of rubella and CRS. In part 2, we present information on the current use of rubella vaccine in different WHO regions, and summarize the lessons learned from different rubella vaccination policies (*12*).

Methods

Data were obtained from a literature review of CRS and acquired rubella in developing countries. Information on the burden of CRS was available from surveillance data and from serosurveys showing age-specific rubella seroprevalence among pregnant women and/or women of childbearing age. Issues that could affect the validity of these sources of data (*13*) are discussed below.

Surveillance of CRS

CRS may be diagnosed by its classic triad of clinical signs: cataract, heart disease, and deafness (*14*). However, many infants only have one of these manifestations, or may present earlier with neonatal signs; laboratory confirmation of the diagnosis is therefore recommended. Rubella virus may be isolated for 6–12 months following birth, and occasionally longer, from nasopharyngeal swabs, urine specimens, or cerebrospinal fluid, or less commonly from tissues obtained by biopsy, autopsy, or surgical procedures (*14*). Rubella-specific IgM is readily detected in the first 6 months of life, and among a decreasing proportion of cases up to 1 year of age. Its detection usually indicates prenatal rather than postnatal infection (*4*).

The persistence of rubella-specific IgG beyond 6 months (the age when maternally derived IgG would usually have waned) can be detected in 95% of infants with CRS (*15*). However, the presence of IgG in a child over 6 months of age may indicate either prenatal or postnatal infection. The likelihood of it reflecting prenatal infection can be assessed by comparing the IgG prevalence among suspected CRS cases with that among age-matched healthy controls. If sophisticated laboratory services are available, identification of low-avidity IgG1 may indicate prenatal infection (*16*).

Cases of CRS may be identified in hospitals and schools for the deaf and blind; more rarely, they have been identified in community-based disability surveys. The manifestations exhibited by neonates (e.g. purpura, hepatosplenomegaly, low birth weight) or during early infancy (e.g. cataract, congenital heart disease) have been detected most often during investigations that followed rubella outbreaks. Those af-

fecting neonates have also been identified through routine toxoplasmosis, rubella, cytomegalovirus, herpes simplex, and syphilis (TORCHES) screening programmes.

Compared with other manifestations of CRS, there are fewer data on deafness, which may be the only sign in up to 50% of affected children (*13*), perhaps because of the greater difficulty in case detection. In Australia, the contribution of CRS to deafness was studied by comparing time trends in deafness with those of acquired rubella (*17*), but few countries have sufficiently complete data to make such comparisons. Other studies have used clinical and historical data to diagnose rubella-related deafness (*18–20*) or compared the prevalence of rubella-specific IgG among children with deafness and healthy controls (*21, 22*). Occasionally, population-based surveys have been conducted, but these are costly because of the relatively low prevalence of severe sensorineural deafness (1 to 3 per 1000 live births) (*19*).

In this review we present the incidence of CRS per 1000 live births, calculated by the authors of each study, or estimate the rate by comparing the number of reported cases of the syndrome with the estimated birth cohort for the particular location and period. Because of the difficulty in conducting population-based studies of CRS incidence, many investigations have estimated the proportion of defects such as blindness or deafness caused by CRS, rather than the rate per 1000 live births. Such estimates, however, depend on the incidence of other etiological factors; thus, in Africa and Asia a low proportion of blindness due to CRS may in part reflect a high prevalence of measles, vitamin A deficiency and ocular infections, or other common causes of childhood blindness (*23*).

Surveillance of acquired rubella

Acquired (postnatal) rubella causes mild fever and maculopapular rash, often with occipital and post-auricular lymphadenopathy, after an incubation period of 14–21 days. Arthralgia/arthritis is common in adults, particularly women. The differential diagnosis includes measles, dengue, parvovirus B-19, human herpesvirus-6, coxsackievirus, echovirus, adenovirus, and *Streptococcus* group A (beta haemolytic) (*24*). Because of the difficulty in clinical diagnosis, studies that use serological confirmation are the most reliable, either by detecting rubella-specific IgM, which is usually positive for up to 6 weeks after rash onset, or by demonstrating a four-fold rise in rubella-specific IgG antibody titre between acute and convalescent specimens (*14*). Up to 50% of infections occur without a rash, thus

clinical notifications underestimate the incidence of rubella. We examined rubella notifications in developing countries reported in the literature to compare the periodicity of epidemics and age-distribution of acquired rubella with that in industrialized countries in the pre-vaccination era.

Serological surveys

A large number of serological surveys of acquired rubella have been reported, but the data should be interpreted with caution. Few studies have attempted to obtain a random sample of individuals, and many do not state the sampling method used. Most studies were cross-sectional in design, but the serological profile obtained in a given survey may vary depending on the period since the previous epidemic of rubella (*25*). The assays for rubella-specific IgG varied between studies, as did the titre that was considered positive. The haemagglutination inhibition (HI) test, which is considered the reference standard (*26*), was used in most studies, but some employed haemolysis in gel (HIG), single radial haemolysis (SRH), or enzyme-based immunoassays (EIA). Although there is general agreement between these tests, the results obtained using different assays or different commercial kits may not be strictly comparable (*26*). An HI titre of 1:8 is usually taken as the threshold for positivity, but some studies used a threshold of 1:10 and occasionally 1:20.

Age-stratified serosurveys. Age-stratified serosurveys have been used, in conjunction with mathematical models, to estimate the average age at rubella infection and predict the effect of various vaccination strategies (*27, 28*).

Serosurveys of women of child-bearing age. Because the public health burden of rubella relates to the risk of infection of pregnant women, many countries have conducted serosurveys to determine the proportion of women of childbearing age who are susceptible to rubella (negative for rubella-specific IgG). We have included the results from published serosurveys that studied at least 100 healthy women of childbearing age, either at antenatal clinics or selected from the community. If there was more than one survey from the same country, we used the following criteria to determine which survey to include: the widest geographical representation; the most recent study; the largest sample size; and use of HI rather than other assays. If several regions of a country were included, we averaged the results to obtain a national estimate. Excluded were studies conducted on a highly selected group of individuals.

Results

Incidence of CRS

Most data on CRS cover periods when outbreaks of rubella were documented. Rates of CRS per 1000 live births were at least 1.7 in Israel in 1972 (29); 0.7 in Oman in 1993 (9), 2.2 in Panama in 1986 (8), 1.5 in Singapore in 1969 (30), 0.9 in Sri Lanka in 1994–95 (10), and 0.6 in Trinidad and Tobago in 1982–83 (31) (Table 2). These data exclude abortions and are underestimates of congenital malformations, since only anomalies that were manifest at birth or during the first few months of life were included, except in the studies in Israel.

After the 1972 epidemic in Israel, CRS was diagnosed in 15 (31%) children during the neonatal period; in 25 (52%) at 8–12 months of age; and in 8 (20%) at 1–3 years of age (32). The proportion diagnosed in early infancy was similar to the 34% of notified CRS cases diagnosed among under-6-month-olds in the United Kingdom (5). In the Israel epidemic, substantial numbers of therapeutic abortions were also recorded (reports were generally 10-fold higher than those of CRS cases), and among one orthodox religious population that refuses abortion the CRS incidence was 11.8 per 1000 live births (29).

In Oman, 34 cases of CRS (0.5 per 1000 live births) were documented in 1988 (33), but data on the epidemicity of acquired rubella were not available. The only published report from a developing country of CRS incidence that included post-infancy manifestations such as deafness, and spanned both epidemic and non-epidemic years, was from Jamaica (34): the overall incidence of CRS for 1972–81 was 0.4 per 1000 live births (approximately 1.7 per 1000 during epidemic years and 0.2 per 1000 otherwise). The high incidence of CRS in Jamaica is further supported by surveys showing that congenital rubella caused an estimated 22% of childhood blindness (35) and that there was a high proportion of susceptible women of childbearing age (see below).

These data are comparable to the pre-vaccination incidence of CRS in industrialized countries. In Australia, the incidence averaged 0.8 per 1000 live births including epidemic and non-epidemic years over the period 1954–70, estimated from reported rates of rubella-associated deafness, assuming that 50% of cases of deafness were reported and 70% of CRS children were deaf (36). In Norway, CRS incidence per 1000 live births was 1.5 for epidemic years and 0.2 in other years, giving an average incidence of 0.4 (37). In Great Britain, the reported annual incidence of CRS in the early years

Table 2: **Incidence of congenital rubella syndrome (CRS) and rubella susceptibility in pregnant women**

Country, city	CRS incidence	Proportion of adult women susceptible
India, Lucknow	Case–control study showed rubella IgG in 62% of 55 children with CRS-compatible malformations vs 10% of control children (ref. 53)	15–22% (ref. 54, 85)
India, New Delhi	Rubella confirmed in 7–12% of infants with suspect congenital infection (ref. 56, 57)	>30% (ref. 86–88)
Israel	CRS incidence, 1.7 per 1000 live births in 1972 (ref. 29). Among women pregnant in 1972, 4.7% had clinical rubella and 6.4% had subclinical infection (ref. 73)	25% (ref. 73)
Jamaica	Average CRS incidence, 0.4 per 1000 live births over 10 years (ref. 34)	43% (urban), 51% (rural) (ref. 80)
Malaysia	35% of 165 deaf children had rubella pigmentary retinopathy (ref. 18). In infants, 221 cases of CRS were identified through TORCHES screening (ref. 60)	42% (ref. 100)
Oman	CRS incidence, 0.5 per 1000 live births in 1988 (33); 0.7 per 1000 in 1993 (ref. 9)	8% in 1988–89 (4% to 30% in different regions) (ref. 9)
Nigeria, Ibadan	9 of 41 cases of patent ductus arteriosus, CRS-associated (ref. 41)	30% (ref. 84)
Panama	CRS incidence, 2.2 per 1000 live births in 1986 outbreak and 30% of rubella cases in women of childbearing age (ref. 8)	38% (urban), 64% (rural) (ref. 80)
Singapore	CRS incidence, 1.5 per 1000 live births in 1969 outbreak (ref. 30)	47% (ref. 62)
Sri Lanka	CRS incidence, 0.9 per 1000 live births in 1994–95 outbreak (ref. 10)	43% (ref. 101)
Thailand	56% of 49 infants with suspect intrauterine infection were rubella-IgM-positive (ref. 59)	32–36% (ref. 68, 83)
Trinidad and Tobago	CRS incidence, 0.6 per 1000 live births in 1982–83 outbreak (ref. 31)	68% (ref. 80)

of the vaccination programme was approximately 0.14 per 1000 during epidemics, otherwise 0.08 (*38*), although Peckham (*21*) has estimated that the average incidence in non-epidemic years was 0.5 per 1000 live births from data on the incidence of deafness and congenital heart disease, and the proportion of each condition attributed to CRS. In the USA, the incidence of CRS was less than 1 per 1000 in non-epidemic years and 1–4 per 1000 during the 1964 epidemic (*39*). Thus, the incidences after outbreaks in developing countries are similar to those in industrialized countries during the pre-vaccination era, especially since most of the studies in developing countries include only young infants.

CRS case reports, by WHO region

Other reports of CRS identified in the literature did not include information that would permit estimation of incidences, as discussed below.

African Region. Several small studies report the occurrence of clinically diagnosed CRS. Congenital cataract is estimated to account for 3–19% of childhood blindness in Africa (*23*), but there are no reliable estimates of the contribution of rubella to cataract. In the United Republic of Tanzania, 10% of 20 patients with congenital cataract had other signs compatible with CRS in 1980–81, and 12% of 34 patients with congenital heart disease in 1985–86 had CRS-compatible defects (*40*). In Ibadan, Nigeria, 9 of 41 children with patent ductus arteriosus had other manifestations of CRS (*41*). In Harare, Zimbabwe, 18 cases of CRS were detected after a rubella epidemic that followed an influx of refugees from rural, war-affected areas to the city in 1978 (*42*). In South Africa, 10% of the first 200 legal abortions at Johannesburg General Hospital were due to confirmed rubella infection (*43*). Occasional cases of CRS have been reported from Kenya (*44*), Senegal (*45*), and Uganda (*46*). In West Africa, only a small proportion of deafness among children is attributable to rubella: 3% of 267 children in Nigeria (*47*) and 2% of 257 children in the Gambia (*48*). In contrast, in Europe prior to vaccination CRS was responsible for about 15% of moderate-to-severe deafness in schools in non-epidemic years (*21*).

Region of the Americas. In Brazil, 3% of cases of deafness among under-15-year-olds were attributed to CRS (*49*) in one study, while it was stated to be the most important cause in another (*50*). In a necropsy study of 68 infants with acute myocarditis, 4% of cases were attributable to CRS (*51*).

Eastern Mediterranean Region. During the pre-vaccination era in Saudi Arabia, TORCHES screening identified rubella infection among 13 pregnant woman (1.7 per 1000 pregnancies in 1985) and two infants with IgM-positive CRS (*52*).

South-East Asia Region. Most published reports of CRS are from India, with one study from Thailand.

In Lucknow, where 80–85% of women of childbearing age were immune to rubella a case–control study found that 62% of 55 under-3-year-olds who had congenital eye or central nervous system (CNS) malformations, neonatal jaundice, or purpura had rubella-specific IgG, compared with 10% of controls (*53, 54*). The prevalence of rubella IgG was also significantly higher among mothers with a history of spontaneous abortion or stillbirth than among controls. In Calcutta, 49% of 66 children aged 4–59 months with clinical signs of CRS were rubella-IgG-positive, significantly more than 33% of 151 healthy controls (*55*). Over the period 1979–82, the All India Institute for Medical Sciences, New Delhi, found evidence of congenital rubella among 18 (6.7%) of 272 under-1-year-olds with suspected congenital infections (*56*); at the same institute in 1988–89, 12% of 249 infants suspected to have congenital infections and 26% of 90 with congenital malformations were rubella-IgM-positive (*57*). In Madras, 374 children aged 3–19 years at deaf schools were examined in 1987. Of these, 29% had severe sensorineural deafness, no family history of deafness, and retinal stippling (or microphthalmia or cataract) as evidence of CRS (*19*). In a study at a large ophthalmic referral hospital in Madurai in 1993–94, rubella-specific-IgM was detected in the saliva of 26% of 95 infants with congenital cataract but in none of 36 age-matched controls (*58*).

In Thailand, 56% of 49 infants with suspected intrauterine infection in 1980 were rubella-IgM-positive, compared with only 6% of 212 normal infants (*59*).

Western Pacific Region. Studies in Malaysia, and Singapore have documented important numbers of CRS cases, but no population denominator was available. In 1991, among 165 children aged 7–14 years in a Malaysian school for the deaf, 35% had pigmentary retinopathy consistent with CRS (*18*). At the Malaysian National Institute for Medical Research, TORCHES screening is carried out on sera obtained from infants with suspected infection. Among children with congenital heart disease, congenital cataract, deafness, or at least two CRS-compatible deformities, rubella-specific IgM was detected in 80% of 107 infants less than 4 months

old. Rubella-specific IgG was detected in 63% of 225 children aged 6 months to 4 years, compared with only 1% of controls (*60*). In Singapore, TORCHES screening identified a total of 93 CRS cases from the period 1969–77, and 26 from 1978–86 (*61*) after schoolgirl vaccination was implemented in 1976 (*62*).

Surveillance of acquired rubella

Acquired rubella is not a notifiable disease in most countries of south Asia and Africa, but data on its periodicity and the age-distribution of reported cases are available from some islands and from several countries in Latin America. Rubella epidemics have been reported every 6–7 years in Hong Kong (*63*) and São Paulo, Brazil (*64*); every 4–5 years in Panama (*8*); and every 4–7 years in Argentina (*65*) and Bangkok, Thailand (*66–68*). These inter-epidemic intervals are comparable with the 4–6 years in many European countries during the pre-vaccination era (*69*). In small island populations, such as China (Province of Taiwan), rubella may be completely absent in inter-epidemic years (*70*).

The age group 15–44 years accounted for 7.5% of 1588 reported rubella cases in three non-epidemic years in Argentina, and 15% of 5303 cases in 1976 (*65*), an epidemic year when there were 83 confirmed cases among pregnant women in Cordoba State (*71*). Women in this age group accounted for 30% of cases in non-epidemic years and 55% in epidemic years in Cuba (*72*), and for 31% of cases in Panama (*8*). In the 1972 epidemic in Israel, a clinical attack rate of 4.7% was found among 11 460 pregnant women screened serologically, with an additional 6.4% having suspected subclinical infection; 70% and 58% of these women, respectively, elected to terminate their pregnancies (*73*).

Serological surveys

We identified over 100 published seroprevalence studies of rubella in developing countries.[a]

Age-stratified surveys. The average age at infection was 2–3 years in the Gambia in 1976 (*74*), 6 years in Brazil (*28*), and 8 years in Mexico (as derived from case notifications) (*75*). The results from Brazil and Mexico are similar to those in Poland and Scotland

Fig. 1. **Age-specific profiles of rubella seropositivity in selected developing countries in the pre-vaccination era: a) Brazil** (*ref. 80*), **Panama** (*ref. 80*); **b) Gambia** (*ref. 25*), **Togo** (*ref. 102*); **c) Egypt** (*ref. 103*), **Islamic Republic of Iran** (*ref. 104*); **d) China** (*ref. 77*), **Malaysia** (*ref. 100*).
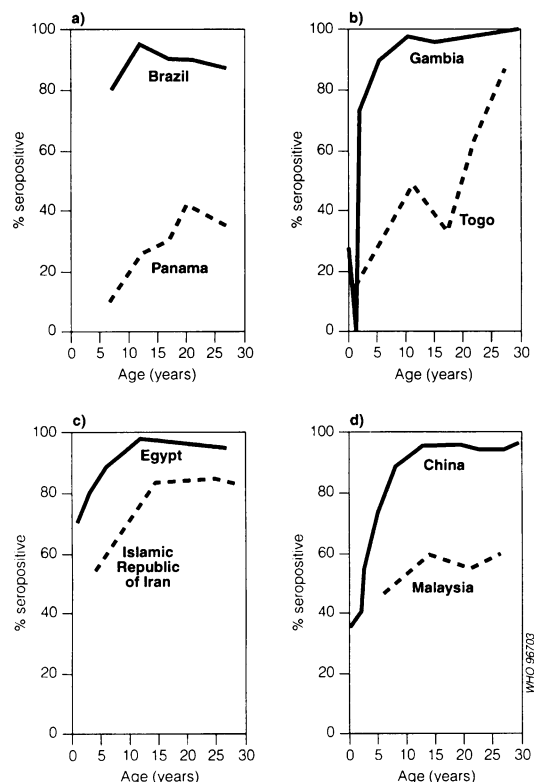
(6–7 years), and somewhat lower than the estimate of 9–12 years in England and Wales, Germany, and the USA during the pre-vaccination era (*74*). The average age at infection with rubella is later than that for measles, reflecting the lower transmissibility of rubella. The basic reproductive rate (R_0), i.e. the average number of secondary cases expected if a single case is introduced into a fully susceptible population, has been estimated to be 6–7 for rubella, as compared with 12–18 for measles (*74*).

Other studies presented age-stratified data but either the age strata were not sufficiently narrow or the sample size was inadequate for the average age at infection to be modelled. As shown in Fig. 1, there is great variation in the age-specific seroprevalence of rubella between countries. In some countries rubella is predominantly a disease of childhood,

Fig. 2. **Rubella susceptibility among women of childbearing age in developing countries prior to the introduction of rubella vaccine.**
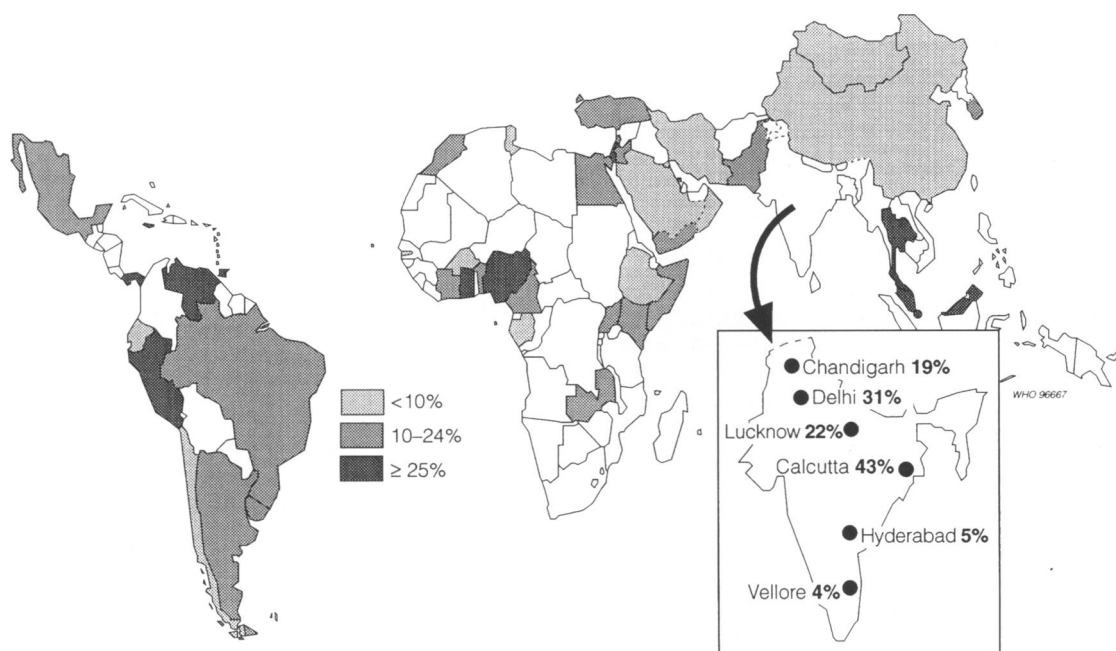
while in others substantial infection continues to be evident among adults.

Serosurveys of women of childbearing age. Surveys from 45 developing countries met our criteria for inclusion; 36% were conducted over the period 1965–74, 36% in 1975–84, and 28% since 1985. Fig. 2 shows the global variation in susceptibility to rubella among women of childbearing age. The proportion of women who were seronegative to rubella was less than 10% in 13 countries (29%), 10–24% in 20 countries (44%), and at least 25% in 12 (27%) countries. Country results are the average values determined using samples from certain areas of each country, except Mexico, where a national survey was conducted in 1990 (76). For some large countries, the national estimate reflects surveys in several different parts of the country. In mainland China, for example, surveys were conducted in 1979–80 in urban and rural areas of 20 provinces on a total of over 16 000 individuals (77). In Nigeria, the results shown are from a study carried out in zones in the north, east, and west of the country (78); and in Brazil three cities and one state were included, with little variation between them (79). For India, it is inappropriate

to present an average estimate because surveys were conducted in specific cities, and results varied widely, as shown in Fig. 2.

In addition to the between-country variations shown in Fig. 2, some studies have identified within-country variations. The WHO Collaborative Study on the Seroepidemiology of Rubella in the Americas in 1967–68, for example, showed urban–rural differences in susceptibility (43% versus 51% in Jamaica; 38% versus 65% in Panama; and 22% versus 40% in Peru) (80). In contrast, results from the same collaborative study in Argentina, Brazil, Chile, Trinidad and Tobago, and Uruguay showed little urban–rural differences, and Gomwalk & Ezeronye (81) found no such differences in Imo State, Nigeria. In Yemen, susceptibility in the highlands (4%) was significantly lower than that in the other four regions studied (18%) (82).

Conclusions

In this review, we have identified more than 100 serosurveys on CRS in developing countries. The strongest evidence for the burden of CRS comes

from countries with more than one source of information that provide consistent results (Table 2). Some large seroprevalence studies have shown susceptibility levels at either extreme (e.g. China, 4% susceptibles (77); Trinidad and Tobago, 68% (80)), which provide an indication of the comparative risk of CRS. For other countries, with less consistent data, or only one study, it is more difficult to draw firm conclusions about the burden of CRS.

Countries with more than one source of information

In countries with the highest susceptibility rates (>25%) among women of childbearing age, including Jamaica, Malaysia, Panama, Singapore and Sri Lanka, serological data are consistent with other data showing a high incidence of CRS and/or a high proportion of acquired rubella among pregnant women (Table 2). In Thailand, CRS incidences are not available, but two surveys have shown that over 30% of pregnant women are susceptible (68, 83). All of these countries now have national rubella vaccination policies, as described in part 2 of this review (12).

In other countries with high or moderate susceptibility rates, such as Brazil, parts of India, and Nigeria, the absolute risk of CRS is difficult to estimate and there may be substantial within-country variation. None the less, serological results are consistent with the documented evidence of CRS in the same areas. In Ibadan, Nigeria, CRS was documented among children with congenital heart defects in 1974 (41), around the time when 30% of 500 women of childbearing age were seronegative (84). In Lucknow, India, a case–control study documenting the risk of CRS (53) was conducted between two serological surveys showing that 15% of 100 pregnant women (54) and 21% (85) of 300 pregnant women were seronegative.

In New Delhi, several case series documented the contribution of rubella to congenital infections over the period 1979–89; and studies conducted in the late 1980s reported that 46% of 160 pregnant women at one hospital (86), 31% at two others (87), and 37% of a random sample of women in the city (88) were seronegative. Previous studies in New Delhi had shown lower rates of susceptibility: 13% in 1969–70 (89) and 22% in 1971 (90). In the absence of data on trends in acquired rubella, it is difficult to determine whether this reflects a secular increase in susceptibility, possibly accompanying demographic changes, or a cyclic variation in rubella incidence. In either case, the recent very high susceptibility rates are of concern.

Countries with moderate or high susceptibility rates in serosurveys but without documented CRS

A large group of countries have susceptibility rates among women of childbearing age that are as high or higher than the 10–25% level (91, 92) reported in the pre-vaccination era in industrialized countries. This group includes Argentina, Bahrain, Benin, Cameroon, Côte d'Ivoire, Egypt, Jordan, Kenya, Lebanon, Mexico, Morocco, Pakistan, Peru, Somalia, Togo, Turkey, Uganda, Uruguay, Venezuela, and Zambia. For Ecuador, Panama, Peru, Yemen, and Uruguay, only one published survey, conducted almost 30 years ago (80), was found. More complete and/or more current data on the burden of CRS are needed before conclusions can be drawn on the magnitude of the problem in these countries.

Countries with relatively low susceptibility rates compared with industrialized countries in the pre-vaccination era

In several countries (Burkina Faso, Chile, China, Ecuador, Ethiopia, Gabon, Gambia, Islamic Republic of Iran, Kuwait, Mongolia, Oman, Saudi Arabia, and Tunisia) at least one survey has been published which suggested that susceptibility in women of childbearing age was somewhat lower than that in industrialized countries during the pre-vaccination era. In some countries, these rates have been documented in large surveys covering wide geographical areas (China, Mongolia) or have been consistently obtained in repeated surveys (Chile, Ethiopia, the Gambia). In such countries, the incidence of CRS incidence is likely to be relatively low but they are not free of risk. In Oman, in 1988–89 an average of only 8% of pregnant women were susceptible. In the 1992–94 outbreak, the CRS incidence was highest (3.5 per 1000 live births) in the Salalah Region of the country, which had 30% susceptibles. However, CRS cases occurred in all regions, with an incidence in 1993 of 0.3 per 1000 live births in Muscat Region, where there were only 4% susceptible pregnant women in 1988–89 (9).

Recommendations

Many countries have already gathered substantial evidence on their burden of CRS. In other countries there is some evidence that CRS may be a hidden problem, and more information should be sought without delay. Appropriate methods for countries to obtain information on the burden of CRS include the following: retrospective or prospective hospital-based register reviews of CRS-compatible defects in

infants; monitoring susceptibility to rubella in pregnancy and/or TORCHES screening in pregnancy; case–control serological studies at institutions such as schools for the deaf and/or blind; integrating CRS studies in general surveys of disability; surveillance of acquired rubella to determine the proportion of cases in women of childbearing age and identify outbreaks; and active surveillance for CRS after a rubella outbreak. Discussion at the national level between epidemiologists, paediatricians, obstetricians, and national laboratory directors will enable the most practicable methods to be selected.

• *Conduct surveillance for CRS*
Data on the incidence of CRS provide the most direct evidence of the burden of disease, and are most useful if there is a defined population denominator. The following case definitions for confirmed and compatible CRS are recommended (*9*, *13*), and confirmation by the detection of rubella-specific IgM is ideal.

— Confirmed CRS: congenital defects and laboratory confirmation.
— Compatible CRS (when laboratory data are not sufficient for confirmation):
  any two complications listed below in (a) or one from (a) and one from (b):
  (a) cataracts/congenital glaucoma, congenital heart disease, loss of hearing, pigmentary retinopathy;
  (b) purpura, splenomegaly, microcephaly, mental retardation, meningoencephalitis, radiolucent bone disease, jaundice with onset within 24 hours of birth.

Most industrialized countries have established surveillance of cases of CRS through national registries and/or birth defects monitoring programmes (*5*, *93*). Even in the richest countries such as the USA, however, CRS reporting has been estimated to be less than 25% complete (*93*). In developing countries, it is most practicable to concentrate on monitoring CRS cases that present in the neonatal period or early infancy, when approximately one-third of CRS cases can be identified (*5*, *32*). During early infancy, the diagnosis should be confirmed by detection of rubella-specific IgM. In countries conducting TORCHES screening of infants, it would be helpful to obtain information on the annual birth cohort in the area from which serum samples are collected in order to estimate rates of confirmed CRS per 1000 live births. An outbreak provides an opportunity to establish CRS surveillance, as described below.

• *Include CRS in disability surveys*
Surveys that are conducted periodically to determine the prevalence of disabilities such as blindness and deafness may offer an opportunity to include investigation of CRS. It is important to be aware that surveys of surviving children with CRS-compatible defects may underestimate the incidence of CRS; at least 50% of children who become blind in developing countries, for example, die within the following 12 months (*94*). The contribution of CRS to these anomalies can be assessed by looking for other clinical manifestations of the syndrome, but the result obtained will be an underestimate. A case–control comparison of rubella-IgG prevalence may provide supportive data. In the United Kingdom, for example, 13% of children aged 6 months to 4 years with probable rubella-associated sensorineural deafness had other manifestations of CRS (*21*). Among cases, 24% were rubella-IgG positive compared with 9% of controls, suggesting that 15% of all cases of sensorineural deafness were due to CRS. The younger the age group of children under study, the more helpful case–control comparisons of rubella-specific IgG are, since a high background incidence of acquired rubella reduces the usefulness of such comparisons in older children.

• *Conduct surveillance of acquired rubella*
Surveillance of acquired rubella is useful for determining the proportion of cases that occur in women of childbearing age and to identify outbreaks. The upgrading of laboratory capacity in developing countries for measles control programmes should include rubella diagnostics, because of the difficulty in distinguishing between these and other causes of rash and fever. Although measles surveillance tends to concentrate on children under 15 years of age, for rubella it is important to include all age groups.

• *Investigate rubella outbreaks*
Rubella outbreaks have frequently continued over two or more years (*65*), a smaller outbreak often heralding a larger one (*95*). It should thus be feasible in most countries to initiate investigation of the outbreak to determine the incidence of acquired rubella among women of childbearing age. Active surveillance for CRS should be initiated early in an outbreak and should continue for at least 9 months after it has ended. Obstetricians and paediatricians should be alerted to the occurrence of an outbreak and its implications, informed of the clinical case definition for suspect CRS, and supplied with an appropriate notification form (*9*). Arrangements should be made to obtain serum samples for IgM assays from as many infants with suspected CRS as possible, and a suitable laboratory identified. During an outbreak, a proportion of acquired rubella cases should ideally be confirmed serologically at regular intervals. Even

if the outbreak is initially confirmed as due to rubella, concurrent outbreaks of rubella and measles have occurred (9, 42) and health workers may continue to label all rash and fever illnesses as rubella after a rubella outbreak has ended.

For low-income countries (defined by the World Bank as having a gross national product per capita of ≤US$ 695 (96)), CRS, even if underdetected, is of lower priority than the major causes of childhood mortality and morbidity. For example, most estimates of CRS incidence in countries without active rubella vaccination have been lower than the goal of the neonatal tetanus elimination programme (<1 case of neonatal tetanus per 1000 live births) (97). In countries where CRS currently appears to be a relatively low priority, there will none the less be an opportunity to establish surveillance, at least of acquired rubella, as part of the activities in progress to improve measles surveillance and control. This would provide valuable baseline trends in age-specific rubella incidence that could assist in making decisions about future vaccination policies. Should a rubella outbreak be detected, especially if it involves cases in women of childbearing age, outbreak investigations should be conducted to the extent that resources allow.

Conclusions

This review has highlighted that the importance of CRS is already well documented in several developing countries. Data from many other developing countries suggest that they have a risk of CRS at least as high as that in industrialized countries during the pre-vaccination era. Although several of these countries have already introduced rubella vaccine, others have not, and may be at risk of epidemics such as that seen recently in Sri Lanka (10). Further information on the burden of CRS is needed, particularly for countries that already have some data indicating that they have substantial hidden morbidity. A number of methods to model the incidence of CRS have been proposed. The data required for these models range from reported incidence of rubella in women of childbearing age and age-specific fertility rates (13), to the serologically confirmed incidence of rubella in pregnancy (37, 98), to finely stratified community-based studies of age-specific seroprevalence (27). In part 2 of this review (12), we present information on current global vaccination policies and discuss the need for studies of the cost–benefit of rubella vaccination in developing countries and the cost–effectiveness of different approaches to control rubella and CRS.

Résumé

Lutte contre la rubéole dans les pays en développement, première partie: fardeau représenté par la rubéole congénitale

L'importance de la rubéole du point de vue de la santé publique tient à ses effets tératogènes chez la femme enceinte. La rubéole congénitale peut entraîner des incapacités permanentes en provoquant surdité, cardiopathies, cataracte, et diverses autres manifestations, notamment l'arriération mentale et le diabète sucré insulino-dépendant. Depuis peu, on s'intéresse davantage au fardeau que représente cette maladie dans les pays en développement, où l'étude des épidémies de rubéole révèle souvent l'existence de cas de rubéole congénitale. La couverture vaccinale contre la rougeole dépasse maintenant 80% dans nombre de ces pays, ce qui montre qu'il est possible de mettre en oeuvre des programmes efficaces de lutte contre la rubéole. D'ailleurs, beaucoup de pays en développement pratiquent déjà la vaccination antirubéolique dans le cadre de leur programme national de vaccination.

Quatre types d'étude ont été menées pour évaluer le fardeau représenté par la rubéole congénitale dans les pays en développement: rapports ou études sur la surveillance de la rubéole congénitale; surveillance de la rubéole acquise; enquêtes sérologiques montrant la distribution de la séroprévalence en fonction de l'âge; enquêtes sérologiques établissant la possibilité de contracter la maladie pour les femmes en âge de procréer.

En période d'épidémie, on a observé que le taux de rubéole congénitale pour mille naissances vivantes était d'au moins 1,7 en Israël, 1,7 à la Jamaïque, 0,7 à Oman, 2,2 au Panama, 1,5 à Singapour, 0,9 à Sri Lanka et 0,6 à Trinité-et-Tobago. Ces taux sont analogues à ceux des pays industrialisés avant la vaccination. Des études spéciales portant sur la rubéole congénitale (y compris des études concernant les enfants sourds ou aveugles) ont été menées dans toutes les Régions OMS.

Les données de surveillance de la rubéole ont montré que des épidémies se produisaient tous les 6 à 7 ans à Hong Kong et São Paulo (Brésil), tous les 4 à 5 ans au Mexique et à Panama et tous les 4 à 7 ans en Argentine et à Bangkok (Thaïlande). L'âge moyen au moment de l'infection, estimé à partir des données d'enquêtes sérologiques stratifiées en fonction de l'âge, était de 2 à 3 ans en Gambie et de 6 ans au Brésil; au Mexique, l'âge moyen déterminé à partir des notifications de cas cliniques était de 8 ans. En moyenne, l'infection survient plus tardivement que pour la rougeole, ce qui traduit la contagiosité plus faible de la rubéole.

Pour les besoins de notre étude, nous avons retenu les enquêtes sérologiques effectuées dans 45 pays en développement sur un minimum de 100 femmes en âge de procréer. La proportion des femmes susceptibles de contracter la rubéole (c'est-à-dire séronégatives) était inférieure à 10% dans 13 pays, comprise entre 10 et 24% dans 20 pays et égale ou supérieure à 25% dans 12 pays. Dans les pays où cette proportion est inférieure à 10%, le fardeau de la rubéole congénitale peut être relativement léger; toutefois, une flambée en Oman (où seulement 8% des femmes étaient séronégatives) a été suivie de 68 cas confirmés de rubéole congénitale.

Pour obtenir plus d'informations sur le fardeau que représente la rubéole congénitale, on peut utiliser les méthodes suivantes: recherche dans les registres d'hôpitaux de malformations compatibles avec cette maladie chez les nourrissons; études dans les institutions pour sourds et aveugles; surveillance de la rubéole acquise pour déterminer la proportion de cas chez les femmes en âge de procréer et pour détecter les épidémies; surveillance active des flambées de rubéole congénitale. Si les deux premières de ces méthodes sont certainement de la plus grande importance pour les pays où une forte proportion des femmes en âge de procréer sont séronégatives, les deux dernières devraient être applicables dans la plupart des pays.

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