Research

Active surveillance for congenital rubella syndrome in Yangon, Myanmar

Kyaw-Zin-Thant,[a] Win-Mar-Oo,[a] Thein-Thein-Myint,[b] Than-Nu-Shwe,[b] Aye-Maung-Han,[b] Khin-Mar-Aye,[a] Kay-Thi-Aye,[a] Kyaw-Moe,[a] Soe-Thein,[c] & Susan E Robertson[d]

Objective Rubella vaccine is not included in the immunization schedule in Myanmar. Although surveillance for outbreaks of measles and rubella is conducted nationwide, there is no routine surveillance for congenital rubella syndrome (CRS). Therefore, we organized a study to assess the burden of CRS.

Methods From 1 December 2000 to 31 December 2002 active surveillance for CRS was conducted among children aged 0–17 months at 13 hospitals and 2 private clinics in Yangon, the capital city. Children with suspected CRS had a standard examination and a blood sample was obtained. All serum samples were tested for rubella-specific IgM; selected samples were tested for rubella-specific IgG and for rubella RNA by reverse transcriptase–polymerase chain reaction (RT–PCR).

Findings A total of 81 children aged 0–17 months were suspected of having CRS. Of these, 18 children had laboratory-confirmed CRS (7 were IgM positive; 7 were RT–PCR positive; and 10 were IgG positive at ⩾ 6 months of age). One additional child who tested positive by RT–PCR and whose mother had had rubella during pregnancy but who had a normal clinical examination was classified as having congenital rubella infection. During 2001–02 no rubella outbreaks were detected in Yangon Division. In the 31 urban townships of Yangon Division, the annual incidence was 0.1 laboratory-confirmed cases of CRS per 1000 live births.

Conclusion This is the first population-based study of CRS incidence from a developing country during a rubella-endemic period; the incidence of CRS is similar to endemic rates found in industrialized countries during the pre-vaccine era. Rubella-specific IgG tests proved practical for diagnosing CRS in children aged ⩾ 6 months. This is one of the first studies to report on the use of rubella-specific RT–PCR directly on serum samples; further studies are warranted to confirm the utility of this method as an additional means of diagnosing CRS.

Keywords Rubella syndrome, Congenital/epidemiology/diagnosis; Epidemiologic surveillance; Reverse transcriptase polymerase chain reaction; Infant; Cohort studies; Myanmar (*source: MeSH, NLM*).

Mots clés Rubéole congénitale/épidémiologie/diagnostic; Surveillance épidémiologique; Réaction polymérisation en chaîne par transcriptase inverse; Nourrisson; Etude cohorte; Myanmar (*source: MeSH, INSERM*).

Palabras clave Síndrome de rubéola congénita/epidemiología/diagnóstico; Vigilancia epidemiológica; Reacción en cadena de la polimerasa de transcriptasa reversa; Lactante; Estudios de cohortes; Myanmar (*fuente: DeCS, BIREME*).

الكلمات المفتاحية: متلازمة الحميراء (الحصبة الألمانية)، متلازمة الحميراء (الحصبة الألمانية) الخلقية، وبائيات متلازمة الحميراء (الحصبة الألمانية)، تشخيص متلازمة الحميراء (الحصبة الألمانية)، الترصُّد الوبائي، إنزيم الناسخة العكسية التفاعل السلسلي للبوليميراز، دراسات أتراب، ميانمار. (المصدر: رؤوس الموضوعات الطبية، المكتب الإقليمي لشرق المتوسط)

Bulletin of the World Health Organization 2006;84:12-20.

Voir page 18 le résumé en français. En la página 18 figura un resumen en español.

يمكن الاطلاع على الملخص بالعربية في صفحة 19.

Introduction

Rubella is a common cause of rash and fever during childhood. However, its public health importance relates to the teratogenic effects of primary rubella infection occurring in pregnant women, which can lead to fetal death with spontaneous abortion or to congenital defects in surviving infants. The association between birth defects and rubella infection during pregnancy was first reported in 1941 by Gregg, an Australian ophthalmologist.[1] A later prospective study in the United Kingdom found that 85% of infants born to women who had had rubella during the first 11 weeks of pregnancy had birth defects.[2] Manifestations of congenital rubella syndrome (CRS) in surviving infants may be transient (e.g., low birth weight, purpura), may

[a] Virology Research Division, Department of Medical Research (Lower Myanmar), Yangon, Myanmar.
[b] Yangon Children's Hospital, Yangon, Myanmar.
[c] Department of Medical Research (Lower Myanmar), Yangon, Myanmar.
[d] Department of Immunization, Vaccines and Biologicals, World Health Organization, 1211 Geneva 27, Switzerland. Correspondence to this author (email: robertsons@who.int).

Ref. No. **05-022814**
(*Submitted: 4 April 2005 – Final revised version received: 31 August 2005 – Accepted: 1 September 2005*)

be permanent structural manifestations (e.g., deafness, congenital heart disease, cataracts, mental retardation) or may be late-emerging conditions (e.g., diabetes, thyroid disorders).[3]

WHO estimates that worldwide more than 100 000 children are born with CRS each year, mostly in developing countries.[4,5] Studies of CRS have been conducted in many parts of the world, including several south-east Asian countries.[6]

In Myanmar, several rubella seroprevalence studies from the 1970s that were conducted in urban settings showed high immunity (> 92%) among women of childbearing age, although one study showed only 80% immunity among women aged 15–19 years.[7,8] While this suggests that rubella infections occurred mostly prior to childbearing age in the 1970s, a case series of children with congenital anomalies seen at a tertiary referral centre that has Yangon's largest neonatal intensive care unit during 1975–78 found that 21 (11%) of 196 children had signs clinically compatible with CRS.[8]

The National Immunization Programme in Myanmar provides one dose of measles vaccine to all children when they are aged 9 months; however, the routine immunization schedule does not include rubella vaccine. Measles–mumps–rubella vaccine is available privately but uptake is limited because of the cost. In 2000, Myanmar implemented enhanced surveillance procedures for measles and rubella; these consist of investigating outbreaks of febrile illnesses with maculopapular rash in people of all ages. The National Health Laboratory tests serum specimens from 5–10 cases for each outbreak: specimens are tested for measles-specific IgM and if they are negative, they are tested for rubella-specific IgM.[9] Given the lack of information on the burden of CRS in Myanmar, a prospective surveillance study was undertaken, using both molecular and serological tests to confirm the diagnosis.

Methods

Active surveillance

From 1 December 2000 to 31 December 2002, active surveillance for CRS occurring in children aged 0–17 months was conducted in Yangon, Myanmar, at all 13 hospitals providing paediatric services, including: specialist ophthalmology; ear, nose and throat; and obstetric hospitals, and at two private clinics. Meetings were held with administrators and physicians at each study site, and a study coordinator (usually a paediatrician) was appointed. The coordinators were provided with posters that displayed the definitions of CRS cases, study forms, information on the availability of laboratory tests, and details on how to contact the study laboratory. Each month the study coordinators were contacted to ensure that all suspected CRS cases had been reported. In August 2001 and July 2002, one-day workshops on CRS were held for physicians at participating hospitals. In addition, information on CRS was presented at national and regional medical conferences, and a briefing on rubella and CRS was included in continuing education materials for physicians provided by the National Medical Association.

Ethical procedures

The study protocol was reviewed and approved by the Ethical Committee on Medical Research Involving Human Subjects, Department of Medical Research (Lower Myanmar), Yangon, and the WHO Secretariat Committee on Research Involving Human Subjects, Geneva, Switzerland. Parents of children meeting the case definition for suspected CRS were provided with information about the study. If parents provided informed consent, children were enrolled. Each child enrolled had a standard clinical examination and a 1 ml blood sample was obtained. A questionnaire was administered to the mother asking about the child's medical history as well as her pregnancy history, including whether rubella had been diagnosed during the first trimester of pregnancy.

Case definitions

Case definitions were modified from WHO guidelines.[10]

Suspected CRS

A child aged 0–17 months was defined as having suspected CRS if there was a maternal history of suspected or confirmed rubella during pregnancy and/or a physician detected at least one of the following clinical signs: congenital heart disease, suspicion of deafness, cataract, glaucoma, pigmentary retinopathy, purpura, splenomegaly or microcephaly.

Clinically confirmed CRS

A child aged 0–17 months was defined as having clinically confirmed CRS if a physician detected two of the clinical signs in group (a) or one from group (a) and one from group (b). Group (a) consists of: cataract(s), congenital glaucoma, pigmentary retinopathy, congenital heart disease or hearing loss. Group (b) consists of: purpura, splenomegaly, microcephaly, mental retardation, meningoencephalitis, radiolucent bone disease, or jaundice occurring within 24 hours after birth.

Laboratory-confirmed CRS

A child aged 0–17 months was defined as having laboratory-confirmed CRS if the child was suspected of having CRS and a serum sample was positive for rubella-specific IgM; and/or positive for rubella-specific IgG at age 6–17 months (only if the child had not received rubella vaccine and had no history of febrile rash illness); and/or positive for rubella RNA by reverse transcriptase–polymerase chain reaction (RT–PCR).

Congenital rubella infection

A child aged 0–17 months was defined as having congenital rubella infection if there was a positive serum test for rubella but there were no clinical signs of CRS.

Clinical examination

Each child was examined clinically by the attending paediatrician; this examination was based on a standard protocol. At Yangon Children's Hospital all children with suspected congenital heart disease had echocardiography. Hearing was tested by determining whether the child responded to sound; otoacoustic hearing testing equipment was not available.

Laboratory methods

Blood samples were kept at the study hospitals for a few hours at 4–8 °C before being transferred to the Virology Research Division, Department of Medical Research (Lower Myanmar), Yangon. Serum samples were separated and stored at –70 °C until further procedures were performed.

All 81 serum samples from suspected cases were tested for rubella IgM with a commercially available ELISA kit (Human GmbH, Germany), which was used according to the manufacturer's instructions.

A subset of 57 specimens (70%) that had sufficient serum was tested for rubella IgG using a commercially available ELISA kit (bioMérieux, Netherlands). A subset of 39 specimens (48%) that had serum remaining was tested for the presence of rubella virus genome using the

reverse transcription–nested polymerase chain reaction method at the National Institute of Infectious Diseases, Tokyo, Japan.[11] Specimens were shipped from Yangon packed in dry ice and stored at –70 °C in Tokyo prior to testing. DNA fragments covering the whole E1 gene of the rubella virus genome were synthesized using RT–PCR. The resulting products were purified and directly sequenced, and the phylogenetic tree constructed.

Data analysis

Data were entered and analysed using Epi Info software, version 6.04b (United States Centers for Disease Control and Prevention, Atlanta, GA, USA, and WHO, Geneva, Switzerland).

Yangon is the capital of Myanmar and the capital of Yangon Division, one of 14 administrative states/divisions in the country. Yangon Division had a population of approximately 5.7 million in 1999.[12] Yangon Division is administratively divided into 45 townships; the 33 urban townships of Yangon Division were included in the active surveillance system since residents in these townships had easy access to one or more hospitals participating in the study. We calculated the incidence of suspected and laboratory-confirmed CRS cases among children aged 0–11 months occurring per 1000 live births.

Findings

From 1 December 2000 to 31 December 2002, active surveillance for CRS detected 81 children aged 0–17 months who were suspected of having CRS; all were enrolled in the study. Of these, 37 (46%) were reported by the Yangon Children's Hospital, the tertiary referral centre for paediatrics (Table 1). Seventeen of the suspected cases (21%) were reported by the Central Women's Hospital, a tertiary referral centre with the largest neonatal intensive care unit in Yangon. Six suspected cases (7%) were reported by the private clinics. Among the 81 children with suspected CRS, 54 (67%) were aged 0–5 months at enrolment; 20 children (25%) were aged 6–11 months; and 7 children (9%) were aged 12–17 months. Three sets of twins were enrolled.

Laboratory-confirmed cases

There were 18 laboratory-confirmed cases: 7 tested positive for rubella IgM; 10 tested positive for rubella IgG when they were aged ⩾ 6 months, and 7 tested positive by RT–PCR (Table 2). The seven children who tested positive for rubella IgM were aged 1, 2, 3 (2 children), 6, 8 and 17 months, respectively. Among the 10 children who had IgG present when they were aged ⩾ 6 months, only one child (aged 6 months) tested positive for IgM. Four of the children who tested positive by RT–PCR also tested positive for IgM and had unique rubella virus sequences. The remaining three children who tested positive by RT–PCR tested negative for IgM: one child was positive for rubella IgG at the age of 10 months; the other two children had unique rubella virus sequences.

Of the 18 laboratory-confirmed cases of CRS, 11 met the definition for a clinically confirmed case (Fig. 1). Seven laboratory-confirmed cases did not meet the definition of a clinically confirmed case: two children with congenital heart disease (one had a maternal history of rubella), two children with bilateral cataracts (only one of whom had a maternal history of rubella), one child with hearing impairment (and a maternal history of rubella), one child with microcephaly and cleft palate, and one child with splenomegaly.

There were three pairs of twins with suspected CRS (Table 3). In the first pair, one child was classified as having congenital rubella infection; this twin had no clinical signs but had a positive maternal history, negative IgM, positive RT–PCR test and a unique virus sequence. The sibling had clinically-confirmed CRS with a negative IgM test; the RT–PCR test was not done. In the second pair of twins, one child had clinically-confirmed and laboratory-confirmed CRS while the sibling was asymptomatic and laboratory tests were negative. The third pair of twins presented with splenomegaly alone and CRS was not confirmed by laboratory tests.

Congenital rubella infection

One child with congenital infection tested positive by RT–PCR but had no obvious signs of CRS, although there was a positive maternal history of rubella. This child was classified as having congenital rubella infection.

Table 1. **Sources reporting 81 suspected cases of congenital rubella syndrome, Yangon, Myanmar, December 2000–December 2002**

Source	No. (%) of suspected cases	No. (%) of cases confirmed by laboratory testing
Yangon Children's Hospital	37 (46)	7 (39)
Central Women's Hospital	17 (21)	4 (22)
Private clinics	6 (7)	1 (6)
Thingangyun Sanpya General Hospital	5 (6)	2 (11)
North Okkalapa General Hospital	4 (5)	1 (6)
Eye Hospital (Yangon)	3 (4)	1 (6)
South Okkalapa Women and Children's Hospital	3 (4)	0
No.2 Military Hospital	2 (3)	0
Ear, Nose and Throat Hospital (Yangon)	1 (1)	0
Insein General Hospital	1 (1)	1 (6)
Defence Services Obstetrics, Gynaecological and Children's Hospital	1 (1)	1 (6)
East Yangon General Hospital	1 (1)	0
West Yangon General Hospital	0	0
Yangon General Hospital	0	0
Total	**81**	**18**

Table 2. **Clinical presentation of children with laboratory confirmation of congenital rubella syndrome (*n* = 18) or congenital rubella infection (*n* = 1), Yangon, Myanmar, December 2000–December 2002**

Clinical signs	Maternal history of rubella	Age (months)	Laboratory results			
			IgM	RT–PCR[a]	Virus sequence[b]	IgG at ⩾ 6 months
Hearing impairment, mental retardation	Yes	3	Positive	Positive	AY 280706	ND[c]
VSD,[d] cataract (bilateral)	No	2	Positive	Positive	AB 080199	ND
PDA,[e] splenomegaly, microcephaly	Yes	8	Positive	Positive	AB 080200	ND
VSD, cataract, splenomegaly, purpura	Yes	1	Positive	Positive	AB 080198	ND
CHD,[f] purpura, microcephaly, mental retardation	No	15	Negative	Positive	AB 080197	ND
PDA, splenomegaly, hepatomegaly	No	0	Negative	Positive	AY 280707	Negative
PDA, cataract, purpura	No	10	Negative	Positive	ND	Positive
No abnormalities identified[g]	Yes	0	Negative	Positive	ND	ND
Cataract (bilateral)	No	17	Positive	Negative	ND	ND
Splenomegaly	No	3	Positive	Negative	ND	ND
PDA, cataract and microphthalmos (right eye), nystagmus, splenomegaly, hepatomegaly	No	6	Positive	Negative	ND	Positive
Cataract (bilateral)	Yes	6	Negative	ND	ND	Positive
VSD, cataract, pigmentary retinopathy, purpura, splenomegaly, mental retardation	No	7	Negative	ND	ND	Positive
Microcephaly, cleft palate	No	9	Negative	ND	ND	Positive
VSD	Yes	10	Negative	ND	ND	Positive
CHD, hearing impairment,cataract (bilateral), microcephaly, purpura, possible mental retardation, syndactyly (left)	Yes	10	Negative	Negative	ND	Positive
VSD, PS,[h] purpura, microcephaly	No	11	Negative	Negative	ND	Positive
Hearing impairment	Yes	14	Negative	Negative	ND	Positive
VSD	No	17	Negative	ND	ND	Positive

[a] RT–PCR = reverse transcriptase–polymerase chain reaction.
[b] Each rubella virus sequence has been registered with GenBank. The GenBank accession number is listed in the table.
[c] ND= not done.
[d] VSD = ventricular septal defect.
[e] PDA = patent ductus arteriosus.
[f] CHD = congenital heart disease.
[g] This child was classified as having congenital rubella infection.
[h] PS = pulmonary stenosis.

Fig. 2 shows the distribution of 18 laboratory-confirmed cases of CRS and the case of congenital infection by month of birth. Nearly half of these children were born during the cool season (October–December) but there was no obvious clustering of cases.

Virus sequencing

For six of the RT–PCR products, rubella virus strains were identified (manuscript in preparation). Five strains were genotype I, and all of these were from children living in central Yangon. One strain was genotype II, and this came from a child whose mother had lived in western Myanmar during the first trimester of pregnancy. The six strains differed from each other by 0.2–6.4% in their nucleotide sequences.

Population-based incidence among children

A total of 66 000 births occurred annually in the 33 urban townships of Yangon Division. During the 25-month surveillance period there were 59 suspected cases of CRS and 11 laboratory-confirmed cases among children aged 0–11 months in central Yangon. Thus, the annual incidence per 1000 live births was 0.4 suspected cases and 0.1 laboratory-confirmed cases.

Measles and rubella surveillance

The nationwide surveillance of measles and rubella outbreaks was conducted by the National Immunization Programme in collaboration with the National Health Laboratory. The surveillance showed that most outbreaks of febrile rash illnesses during 2001–02 were caused by measles. In only one outbreak were 4/6 specimens found to be positive for rubella IgM. This small rubella outbreak occurred in the Southern Shan State (in the eastern part of Myanmar, more than 450 km from Yangon) during mid-2001, and there was no evidence of spread to other areas of the country. The active laboratory-linked surveillance for febrile rash illness did not detect any rubella outbreaks in Yangon during the study period.

Discussion

This is the first report from a developing country to implement active surveillance for congenital rubella syndrome during a rubella-endemic period. The annual incidence of 0.1 confirmed cases of CRS per 1000 live births found in central

Yangon is similar to the annual incidence of 0.1/1000 reported in Canada[13] and 0.2/1000 reported in Norway[14] during endemic periods prior to the introduction of rubella vaccine. Rubella is an endemic disease with epidemics occurring every 5–9 years. Most population-based assessments of the incidence of CRS occurred after large-scale outbreaks of rubella, and the annual incidence has ranged from 1–4 cases per 1000 live births in the epidemic setting.[4]

CRS surveillance is difficult during endemic periods because it is a relatively rare disease. The success of this study reflects the ongoing efforts that were made to keep clinicians alert to the disease using a variety of strategies, such as making monthly inquiries about suspected cases at each participating hospital, presenting information on the disease at medical conferences and preparing a briefing on rubella and CRS as part of continuing education materials for physicians.

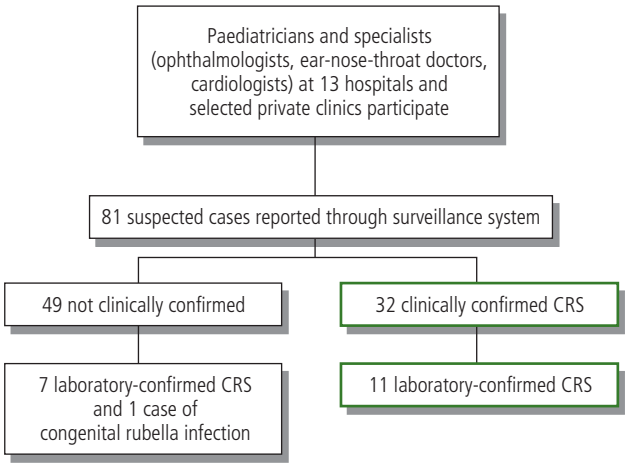
It was unclear whether children born at home who had CRS would be identified by hospital-based surveillance. The 1997 Fertility and Reproductive Health Survey found that 25% of births in the Yangon Division occurred at home.[15] Among the 81 children classified as suspected cases of CRS and identified by the hospital-based surveillance, 17 (21%) had been born at home but eventually were seen by paediatricians and reported to the surveillance system. There is a strong incentive to register infants born at home because a birth certificate is required to obtain health care, including vaccinations.

This study identified three pairs of twins suspected of having CRS. In one pair of twins, one sibling had CRS confirmed both clinically and by laboratory testing while the other child was not infected. This is consistent with other reports in the medical literature that have found only one twin may be affected.[16–18]

Among the 18 laboratory-confirmed cases in this study, congenital heart disease was the most common sign of CRS. It was seen in 13 children (72%). Other common signs were cataract (8 children; 44%), purpura (6 children; 33%) and splenomegaly (6 children; 33%). The proportions of various CRS signs and symptoms identified in Myanmar are similar to those reported in studies from Mexico,[19] Panama[20] and the United States,[21] although surveillance methods varied among studies (Table 4). The proportion of children who were deaf was lower in Myanmar and Mexico but this most likely relates to the younger age at which children were examined and the limited ability to assess hearing loss in very young children in most developing countries. Recently, some higher-income countries have introduced new technologies to diagnose hearing loss in infants. In Singapore, for example, traditional childhood screening detected deafness at a median age of 20.8 months but during the period 2002–04 the age at detection fell to 2.7 months at hospitals that screened neonates using otoacoustic testing and other new technologies.[22] Given that 50–70% of infants with CRS have impaired hearing and in many children this is the only sign,[2, 3] the annual incidence of CRS in Yangon may have been twice the level reported in this study.

A number of modifications in the

Fig. 1. **Flow of active surveillance for congenital rubella syndrome (CRS) among children aged 0–17 months, Yangon, Myanmar, December 2000–December 2002**



WHO 05.152

Table 3. **Clinical signs and results of laboratory tests from twins suspected of having congenital rubella syndrome during a period of active surveillance, Yangon, Myanmar, December 2000–December 2002**

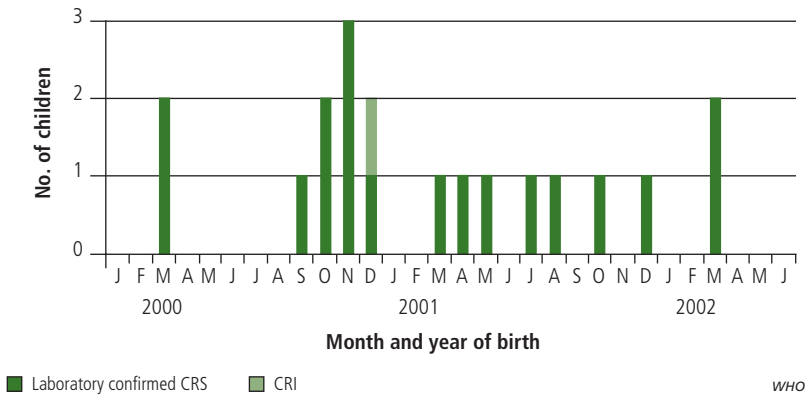
Twin (sex)	Age	Clinical signs	Laboratory results
Twin 1A (male)	4 days	No obvious signs; maternal history of rubella	IgM negative, RT–PCR[a] positive, genotype I sequenced
Twin 1B (female)	4 days	Patent ductus arteriosus, splenomegaly; maternal history of rubella	IgM negative, RT–PCR not done
Twin 2A (female)	12 days	No obvious signs	IgM negative, RT–PCR negative, IgG positive at age 12 days, IgG negative at age 9 months
Twin 2B (male)	12 days	Patent ductus arteriosus, splenomegaly, hepatomegaly	IgM negative, RT–PCR positive, genotype I sequenced, IgG positive at age 12 days, IgG negative at age 9 months
Twin 3A (female)	4 days	Splenomegaly; died in hospital aged 51 days	IgM negative, RT–PCR negative
Twin 3B (female)	4 days	Splenomegaly; died at home aged 54 days	IgM negative, RT–PCR negative

[a] RT–PCR = reverse transcriptase–polymerase chain reaction.

surveillance scheme in Myanmar allowed us to confirm CRS by laboratory testing for 18 patients, whereas only 6 cases would have been confirmed by laboratory tests if we had followed the routine surveillance guidelines recommended by WHO. The WHO guidelines call for CRS surveillance of children aged < 12 months and for testing only for rubella IgM.[10] IgM testing alone will underestimate the burden of CRS depending on the age at which infants are screened. Chantler et al. found that among children with virologically-confirmed CRS, serum IgM was positive by ELISA in 100% of those aged 0–2 months, in 57% of those aged 3–5 months and in only 29% of those aged 6–11 months.[23] In the present study IgG testing of serum specimens from children aged ⩾ 6 months led to identification of 9 additional cases: 7 in children aged 6–11 months and 2 in children aged 12–17 months. Maternal IgG antibody is transmitted to the infant transplacentally; it decays gradually, having a half-life of about 1.3 months.[24] Infants with CRS also produce their own rubella-specific IgG. A study in the United States of America undertaken during the pre-vaccine era assessed whether the persistence of neutralizing antibody could be used as a test for CRS: among 18 children with virologically-confirmed CRS, 17 had neutralizing antibody when they were aged ⩾ 6 months.[25]

Rubella IgG testing using commercially available ELISA kits is relatively inexpensive; however, there are a number of practical limitations to its use in diagnosing CRS in children aged 6–17 months. First, IgG antibody in children in this age group may represent seroconversion following receipt of rubella vaccine. In the present study, none of the children had received rubella vaccine. Second, IgG antibody in this age group may represent exposure to wild rubella virus. Active outbreak surveillance with laboratory confirmation identified no rubella outbreaks in Yangon during the study period; moreover, none of the children in the study had a history of febrile rash illness. Among the children in this age group with positive IgG in this study, 3 met the full clinical case definition for CRS, 4 had only one major sign (3 of these also had a maternal history of rubella occurring during the first trimester of pregnancy), and one child had one minor sign. In our study, only a single serum sample was available from each child; serial specimens demonstrating a sustained titre of IgG and low-avidity IgG would have provided further confirmation of the diagnosis.

Fig. 2. **Number of children with laboratory-confirmed congenital rubella syndrome (CRS) (*n* = 18) and congenital rubella infection (CRI) (*n* = 1), by month and year of birth, Yangon, Myanmar**



The RT–PCR test is a well established method for diagnosing CRS and is usually performed on nasopharyngeal specimens or urine.[26,27] This is one of the first studies to report rubella testing using RT–PCR on serum specimens from children. Further systematic studies in infants are warranted to confirm the utility of using serum specimens for RT–PCR as an additional means of diagnosing CRS. Two of the children who tested positive by RT–PCR were aged < 1 month and tested negative for IgM. This finding is consistent with a statement from Dr LZ Cooper that "approximately 20% of infected infants tested for rubella IgM might not have detectable titres before age 1 month" (oral communication, 1998, reported in reference.[28]

Table 4. **Clinical characteristics of children with laboratory-confirmed cases of congenital rubella syndrome in Myanmar and comparison with findings and characteristics of studies in Mexico, Panama and the United States**

Clinical and study characteristics	Place of study			
	Yangon, Myanmar (*n* = 18)	Mexico City, Mexico[19] (*n* = 42)	Panama[20] (*n* = 54)	USA[21] (*n* = 122)
Congenital heart disease	13/18 (72)[a]	28/42 (67)	34/54 (69)	86/122 (70)
Cataract	8/18 (44)	29/42 (69)	16/54 (30)	52/122 (43)
Splenomegaly	6/18 (33)	8/42 (19)	NA	42/122 (34)
Purpura	6/18 (33)	NA[b]	16/54 (30)	45/122 (37)
Microcephaly	5/18 (28)	7/42 (17)	11/54 (20)	28/122 (23)
Deafness	3/18 (17)	8/42 (19)	16/54 (30)	73/122 (60)
Type of study	Active surveillance	Retrospective review	Active surveillance	Passive surveillance
Years of study	2000–02	1991–98	1986–87	1985–96
Mean age at last examination	8.4 months	5.0 months	15 months	NA

[a] Values are numerator/denominator (percentage) unless otherwise indicated.
[b] NA = not available.

The findings on the rubella virus sequences indicate that two genotypes of rubella virus were circulating in Myanmar during the study period. Five strains — all from children living in central Yangon — were genotype I, a universal genotype comprising rubella viruses from Europe, Japan and North America.[29, 30] One strain was genotype II; this came from a child whose mother had lived in western Myanmar during her pregnancy. This genotype is an Asian prototype comprising mainly strains from China and India. Co-circulation of more than one rubella virus genotype has been reported previously.[31]

During 2003, a rubella serosurvey conducted among 100 schoolgirls in central Myanmar found that 16% of those aged 11–12 years and 18% of those aged 15–16 years tested negative for rubella IgG using a commercial ELISA kit (bioMérieux, Netherlands).[32] These are moderately high rates of rubella susceptibility, suggesting that the situation for women in Myanmar is different from the 1970s when serosurveys in various parts of the country showed that only a low proportion of women remained susceptible. Further serosurveys among schoolgirls and women of childbearing age would be helpful to demonstrate the level of risk in other parts of the country. Such data would aid health administrators in selecting an appropriate vaccine strategy to prevent rubella infection and CRS in Myanmar. If resources permit, it may be advisable to start immunizing adolescent girls and women of childbearing age, or both, against rubella as an initial step towards preventing CRS in Myanmar.[33] ■

Acknowledgements

Thanks to Professor Mya Oo, Deputy Minister, Ministry of Health; Professor Dr Paing Soe, Director General, Department of Medical Research (Lower Myanmar); Dr Mon Mon, Statistician, Department of Medical Research (Lower Myanmar); the hospital study coordinators; and all study participants. Thanks to Dr Shigetaka Katow, National Institute of Infectious Disease, Tokyo, Japan, for inviting the principal investigator to Japan as a Visiting Research Fellow to perform PCR tests. Scientific oversight was provided by the WHO/IVB Steering Committee on Epidemiology and Field Research (Professor Timo Vesikari, Chair). Also thanks to two anonymous reviewers for their insightful comments.

Funding: The RT–PCR testing was funded by the Takeda Science Foundation, Osaka, Japan. Funding for the remainder of the study was provided by WHO, Geneva, Switzerland.

Competing interests: none declared.

Résumé

Surveillance active du syndrome de rubéole congénitale à Yangon (Myanmar)

Objectif Le vaccin antirubéoleux ne fait pas partie du programme de vaccination du Myanmar. Les flambées de rougeole et de rubéole font l'objet d'une surveillance au niveau national, mais il n'y a aucune surveillance systématique du syndrome rubéoleux congénital (SRC). Une étude a donc été organisée pour évaluer la charge de SRC.

Méthodes Du 1er décembre 2000 au 31 décembre 2002, le SRC a fait l'objet d'une surveillance active chez les enfants de 0 à 17 mois dans 13 hôpitaux et 2 établissements privés de Yangon. Les enfants suspectés de SRC ont été soumis à un examen standard et à un prélèvement sanguin. Tous les échantillons de sérum ont été analysés à la recherche des IgM spécifiques de la rubéole ; on a recherché les IgG spécifiques de la rubéole et l'ARN du virus rubéoleux par RT-PCR dans des échantillons sélectionnés.

Résultats Au total, 81 enfants âgés de 0 à 17 mois étaient suspectés de SRC; 18 de ces cas ont été confirmés en laboratoire (7 cas de positivité des IgM, 7 de positivité de la RT-PCR et 10 de positivité des IgG touchant des enfants de 6 mois ou plus). Un autre enfant présentant un test RT-PCR positif, dont la mère avait eu la rubéole pendant sa grossesse mais dont l'examen clinique s'était révélé normal, a été classé comme atteint d'une infection rubéoleuse congénitale. Au cours de la période 2001-2002, aucune flambée de rubéole n'a été détectée dans la Division de Yangon. Dans les 31 arrondissements urbains de la Division de Yangon, l'incidence annuelle était de 0,1 cas de SRC confirmé en laboratoire pour 1000 naissances vivantes.

Conclusion Il s'agit de la première étude en population de l'incidence du SRC menée dans un pays en développement au cours d'une période d'endémie rubéoleuse ; l'incidence du SRC est proche des taux d'endémie rencontrés dans les pays industrialisés avant l'introduction de la vaccination systématique. Les tests reposant sur la détection des IgG spécifiques de la rubéole se sont avérés pratiques pour diagnostiquer le SRC chez les enfants de 6 mois et plus. Cette étude est l'une des premières à présenter des données sur l'utilisation de la RT-PCR spécifique du virus rubéoleux directement sur des échantillons de sérum ; d'autres études sont nécessaires pour confirmer l'utilité de cette méthode comme moyen supplémentaire pour diagnostiquer le SRC.

Resumen

Vigilancia activa del síndrome de rubéola congénita en Yangon, Myanmar

Objetivo La vacuna contra la rubéola no figura en el calendario de vacunación en Myanmar. Aunque la vigilancia de los brotes de sarampión y rubéola se realiza a nivel nacional, no existe un sistema de vigilancia sistemática del síndrome de rubéola congénita (SRC), lo cual nos llevó a organizar un estudio para evaluar la carga de esa enfermedad.

Métodos Entre el 1 de diciembre de 2000 y el 31 de diciembre de 2002 se implantó un sistema de vigilancia activa del SRC entre los niños de 0 a 17 meses de edad en 13 hospitales y 2 consultorios privados de Yangon, capital del país. Los niños con presunto SRC fueron sometidos a una exploración ordinaria, incluida la extracción de una muestra de sangre. Todas las muestras séricas fueron analizadas para determinar las IgM específicas de la rubéola; y en algunos casos se determinaron las IgG de rubéola y el ARN de rubéola mediante la reacción en cadena de la polimerasa dirigida por ARN (transcriptasa inversa) (RT–RCP).

Resultados Del total de 81 niños de 0-17 meses con presunto SRC, las pruebas de laboratorio confirmaron el diagnóstico en 18 casos (7 eran IgM-positivos; 7 RT–RCP-positivos; y 10 IgG- positivos a los 6 meses o más de edad). Otro niño que dio positivo en la prueba de RT–RCP y cuya madre había sufrido rubéola durante el embarazo, pero con resultados normales en la exploración clínica, fue clasificado como un caso de rubéola congénita. Durante 2001–2002 no se detectó ningún brote de rubéola en la división de Yangon. En los 31 municipios urbanos de esa división, la incidencia anual fue de 0,1 casos de SRC confirmados en laboratorio por 1000 nacidos vivos.

Conclusión Éste es el primer estudio basado en la población sobre la incidencia de SRC en un país en desarrollo durante un periodo de rubéola endémica; la incidencia de SRC es similar a las tasas endémicas que presentaban los países industrializados antes del comienzo de las vacunaciones. Las pruebas de IgG específicas para la rubéola fueron útiles para diagnosticar el SRC en los niños con 6 o más meses de edad. Este estudio es asimismo uno de los primeros en que se informa del uso de la prueba RT–RCP específica para la rubéola directamente en muestras séricas; es necesario emprender nuevos estudios para confirmar la utilidad de este método como un nuevo medio de diagnóstico del SRC.

ملخص

الترصُّد الفاعل لمتلازمة الحميراء (الحصبة الألمانية) الخلقية في يانغون، ميانمار

الهدف: إن لقاح الحميراء (الحصبة الألمانية) غير مشمول بالمخطط التمنيعي في ميانمار. ورغم إجراء الترصُّد لفاشيات من الحصبة ومن الحميراء (الحصبة الألمانية) في جميع أنحاء ميانمار، فإنه ليس هناك ترصُّد روتيني لمتلازمة الحميراء (الحصبة الألمانية) الخلقية مما دفعنا لتنظيم دراسة العبء الذي تسببه.

الطريقة: بدئ بتنفيذ الترصُّد الفعَّال لمتلازمة الحميراء (الحصبة الألمانية) الخلقية منذ أول كانون الأول/ديسمبر عام 2000 واستمر حتى الحادي والثلاثين من نفس الشهر عام 2002، بين الأطفال الذين تـتراوح أعمارهم بين ساعة الولادة وحتى سبعة شهور، وذلك في 13 مستشفى وعيادتين في يانغون، المدينة الرئيسية. وقد أجري للأطفال الذين يشتبه أن لديهم متلازمة الحميراء (الحصبة الألمانية) الخلقية فحصاً معيارياً مع أخذ عينات من الدم، واختبرت جميع العينات لتحري الغلوبولين المناعي M النوعي للحصبة الألمانية (الحميراء) كما اختبرت عينات مختارة منها لتحري كل من الغلوبولين المناعي (G) النوعي للحصبة ودنا الحميراء (الحصبة الألمانيـــة) باستخدام اختبار إنزيم الناســخة العكسية التفاعل السلسلي للبوليميراز.

الموجودات: بلغ عدد الأطفال الذين تـتراوح أعمارهم بين ساعة من الولادة وسبعة شهور والمشتبه بإصابتهم بمتلازمة الحميراء (الحصبة الألمانية) الخلقية 81 طفلاً، تأكَّد لدى 18 منهم الإصابة بهذه المتلازمة مختبرياً (فقد كان 7 منهم إيجابيـــين للغلوبولين المناعي M، و7 آخرون إيجابيـــين لاختبار إنزيم الناسخة العكسية التفاعل السلسلي للبوليميراز، و10 ممن تزيد أعمارهم عن ستة شهور إيجابيـــين للغلوبولين المناعي G). وقد صُنِّف طفل آخر كان لديه اختبار إنزيم الناسخة العكسية التفاعل السلسلي للبوليميراز إيجابياً، وكانت أمه مصابة بالحصبة الألمانية (الحميراء) أثناء الحمل به، إلا أن الفحص السريري (الإكلينيكي) لديه كان سوياً باعتباره مصاباً بالحصبة الألمانية (الحميراء) الخلقية. ولم يكشف عن أي فاشية للحميراء (الحصبة الألمانية) في يانغون خلال عامي 2001 – 2002. أما في القرى المحيطة بيانغون والبالغ عددها 31 قرية فقد كان معدل الحدوث السنوي 0.1 حالة مؤكدة مختبرياً من حالات متلازمة الحميراء (الحصبة الألمانية) الخلقية بين كل ألف مولود حي.

الاستنتاج: تُعد هذه الدراسة الأولى من حيث كونها مرتكزة على المجتمع للتعرُّف على معدل حدوث متلازمة الحميراء (الحصبة الألمانية) الخلقية في البلدان النامية خلال فترة توطُّن الحميراء (الحصبة الألمانية). إن معدل حدوثها مشابه للمعدلات التوطنية المصادفة في البلدان الصناعية قبل عهد اللقاحات. وقد أثبت اختبار الغلوبولين المناعي G النوعي للحميراء (الحصبة الألمانيـــة) أنه عملي لتشخيص متلازمة الحميراء (الحصبة الألمانية) الخلقية لدى الأطفال الذين تتجاوز أعمارهم ستة شهور. تُعد هذه الدراسة من أولى الدراسات التي أبلغت عن استخدام اختبار إنزيم الناسخة العكسية التفاعل السلسلي للبوليميراز على عينات مأخوذة مباشرة من المصل. وتمس الحاجة إلى دراسات أخرى للتأكيد على استخدام هذه الطريقة كأسلوب إضافي لتشخيص متلازمة الحميراء (الحصبة الألمانية) الخلقية.

References

1. Gregg NM. Congenital cataract following German measles in the mother. *Trans Ophthal Soc Aust* 1941;3:35-46.
2. Miller E, Cradock-Watson JE, Pollock TM. Consequences of confirmed maternal rubella at successive stages of pregnancy. *Lancet* 1982;2:781-4.
3. Cooper LZ. The history and medical consequences of rubella. *Rev Infect Dis* 1985;7 Suppl 1:S2-10.
4. Robertson SE, Featherstone DA, Gacic-Dobo M, Hersh BS. Rubella and congenital rubella syndrome: global update. *Rev Panam Salud Publica* 2003; 14:306-15.
5. Cutts FT, Vynnycky E. Modelling the incidence of congenital rubella syndrome in developing countries. *Int J Epidemiol* 1999;28:1176-84.
6. Cutts FT, Robertson SE, Diaz-Ortega 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.
7. Ming CK, Thein S, Thaung U, Tin U, Nwe K, Diwan AR. Serologic survey for certain childhood viral infections in Rangoon in 1971. *J Trop Med Hyg* 1974; 77:260-6.
8. Kyaw-Wynn. *Rubella antibody survey in Burmese pregnant women* [dissertation]. Rangoon: Institute of Medicine; 1978.
9. World Health Organization, Myanmar and Ministry of Health, Union of Myanmar. *Accelerating measles control in Myanmar. Measles Bulletin.* Geneva: WHO; 2001. WHO document WHO/V&B/01.23.
10. Cutts FT, Best J, Siqueira MM, Engstrom K, Robertson SE. *Guidelines for surveillance of congenital rubella syndrome and rubella: field test version.* Geneva: World Health Organization; 1999. WHO document WHO/V&B/99.22.
11. Kyaw-Zin-Thant, Katow S, Nakajima S, Kato H, Umino Y, Thein-Thein-Myint, et al. Molecular epidemiology of Myanmar rubella virus strains at the beginning of the 21st century. *J ClinVirol* 2003;28 Suppl 1:S72.
12. Central Statistical Organization, *Myanmar. Myanmar statistical yearbook 2001*. Yangon (Myanmar): Central Statistical Organization; 2001.
13. Furesz J, Varughese P, Acres SE, Davies JW. Rubella immunization strategies in Canada. *Rev Infect Dis* 1985;7 Suppl 1:S191-3.
14. Stray-Pedersen B. Economic evaluation of different vaccination programmes to prevent congenital rubella. *NIPH Ann* 1982;5:79-83.
15. Myanmar Ministry of Immigration and Population, UNFPA. *Fertility and reproductive health survey, 1997*. Yangon (Myanmar): Ministry of Immigration and Population; 1999.
16. Fitzpatrick C. Rubella cataracts in one set of twins. *Trans Ophthal Soc U K* 1972;92:811-3.
17. Montgomery RC, Stockdell K. Congenital rubella in twins. *J Pediatr* 1970; 76:772-3.
18. Wang L-N, Wang Y-F, Horne C-C, Shiao L-C. Congenital rubella infection: escape of one monozygotic twin with two amnions, one chorion, and single placenta. *J Formos Med Assoc* 1990,89:30-3.

19. Solorzano-Santos F, Lopez-Kirwan A, Alvarez y Munoz MT, Miranda-Novales MG, Gadea-Alvarez T, Vazquez-Rosales G. [Congenital rubella syndrome in infants treated at a pediatrics hospital]. *Gac Med Mex* 2001;137:105-9. In Spanish.
20. Saad de Owens CS, Tristan de Espino RT. Rubella in Panama: still a problem. *Pediatr Infect Dis* J 1989;8:110-5.
21. Schluter WW, Reef SE, Redd SC, Dykewicz CA. Changing epidemiology of congenital rubella syndrome in the United States. *J Infect Dis* 1998; 178:633-41.
22. Low WK, Pang KY, Ho LY, Lim SB, Joseph R. Universal newborn hearing screening in Singapore: the need, implementation and challenges. *Ann Acad Med Singapore* 2005;34:301-6.
23. Chantler S, Evans CJ, Mortimer PP, Cadock-Watson JE, Ridehalgh MK. A comparison of antibody capture radio- and enzyme immunoassays with immunofluorescence for detecting IgM antibody in infants with congenital rubella. *J Virol Methods* 1982;4:305-13.
24. Kebede S, Nokes DJ, Cutts FT, Nigatu W, Sanderson F, Beyene H. Maternal rubella-specific antibody prevalence in Ethiopian infants. *Trans R Soc Trop Med Hyg* 2000,94:333-40.
25. Plotkin SA, Cochran W, Lindquist JM, Cochran GG, Schaffer DB, Scheie HG, et al. Congenital rubella syndrome in late infancy. *J Am Med Assoc* 1967; 200:435-41.
26. Bosma TJ, Corbett KM, Eckstein MB, O'Shea S, Vijayalakshmi P, Banatvala JE, et al. Use of PCR for prenatal and postnatal diagnosis of congenital rubella. *J Clin Microbiol* 1995;33:2281-7.
27. Tanemura M, Suzumori K, Yagami Y, Katow S. Diagnosis of fetal rubella infection with reverse transcription and nested polymerase chain reaction: a study of 34 cases diagnosed in fetuses. *Am J Obstet Gynecol* 1996; 174:578-82.
28. Centers for Disease Control and Prevention. Control and prevention of rubella: evaluation and management of suspected outbreaks, rubella in pregnant women, and surveillance for congenital rubella syndrome. *MMWR Recomm Rep* 2001;50(RR12):1-23.
29. Frey TK, Abernathy ES, Bosma TJ, Starkey WG, Corbett KM, Best JM, et al. Molecular analysis of rubella virus epidemiology across three continents, North America, Europe, and Asia, 1961-1997. *J Infect Dis* 1998;178:642-50.
30. Zheng DP, Frey TK, Icenogle J, Katow S, Abernathy ES, Soon KJ, et al. Global distribution of rubella virus genotypes. *Emerg Infect* Dis 2003:8:1523-36.
31. Zheng DP, Zhu H, Revello MG, Gerna G, Frey TK. Phylogenetic analysis of rubella virus isolated during a period of epidemic transmission in Italy, 1991-1997. *J Infect Dis* 2003;187:1587-97.
32. Kyaw-Zin-Thant, Myo-Myo-Min, Aung-Kyaw-Zaw, Kyawt-Tha-Sein, Htun-Naing-Oo. Rubella-specific immunoglobulin-G status among schoolgirls in Pyinmana, Central Myanmar. *Myanmar Health Sci Res* 2003;16:30-4.
33. World Health Organization. Rubella vaccines: WHO position paper. *Wkly Epidemiol Rec* 2000;75:161-9.