Developing Rubella Vaccination Policy in Nepal—Results From Rubella Surveillance and Seroprevalence and Congenital Rubella Syndrome Studies

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Background. The Government of Nepal is interested in preventing congenital rubella syndrome (CRS). Surveillance data were analyzed and studies conducted to assess the burden of rubella and CRS and aid in developing a rubella vaccination strategy.

Methods. (1) Analysis of rubella cases reported through measles surveillance, 2004 - 2009; (2) in 2008, rubella seroprevalence among women 15 to 39 years of age was evaluated; and (3) in 2009, children attending a school for the deaf were examined for ocular defects associated with CRS.

Results. From 2004-2009, there were 3,710 confirmed rubella cases and more than 95% of these cases were less than 15 years of age. Of 2,224 women of childbearing age (WCBA) tested for anti-rubella IgG, 2,020 (90.8%) were seropositive. Using a catalytic infection model, approximately 1,426 infants were born with CRS (192/100,000 live births) in 2008. Among 243 students attending a school for the deaf, 18 (7.4%) met the clinical criteria for CRS.

Conclusions. Rubella and CRS were documented as significant public health problems in Nepal. A comprehensive approach is necessary, including introducing rubella vaccine in the routine program, assuring immunity among WCBA, strengthening routine immunization, integrating rubella surveillance with measles case-based surveillance, and establishing CRS surveillance.

Rubella is usually a mild febrile rash illness in adults and children. Clinical manifestations frequently include diffuse punctate and maculopapular rash with fever, although up to half of rubella cases may present without a rash or be subclinical. Serious consequences may occur if a pregnant woman becomes infected, particularly if infection occurs during the first trimester. These could include a constellation of birth defects known as congenital rubella syndrome (CRS) or even fetal death. Common manifestations of CRS include cardiac, ophthalmic, and auditory defects and developmental delay. Worldwide, rubella remains the most common cause of vaccine-preventable birth defects, with estimates indicating that ~110,000 cases of CRS occur in developing countries annually [1].

Nepal has not yet introduced a rubella-containing vaccine into their national immunization program, but introduction of the combination measles-rubella vaccine has been tentatively planned for introduction before 2011 [2]. There are no published studies that have

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profiled susceptibility to rubella infection among women of childbearing age or documented the burden of CRS in Nepal. To develop an appropriate strategy for introduction of a rubella-containing vaccine in Nepal, the epidemiology of rubella disease from January 2004 through December 2009 was examined, and a cross-sectional rubella IgG seroprevalence study among women of childbearing age was conducted from October through December 2008. To document presence of CRS, children attending a school for the deaf were examined for ocular defects associated with CRS in August 2009. This report summarizes results from these investigations and suggests possible methods for introducing a rubella-containing vaccine in the National Immunization Program.

METHODS

Surveillance

In 2003, measles sentinel surveillance was established in Nepal with use of the platform of the existing Acute Flaccid Paralysis surveillance system, and since March 2003, blood specimens have been collected from 5–10 cases of febrile rash illness in suspected measles outbreaks as per the national measles outbreak investigation protocol. Specimens are tested for measles IgM antibodies at the National Public Health Laboratory (NPHL), which is a WHO-accredited national measles reference laboratory in Kathmandu, Nepal. From January 2004 through December 2006, specimens determined to be measles IgM negative were tested for rubella IgM antibodies. In January 2007, Nepal introduced measles case-based surveillance in a phase-wise manner, whereby all febrile rash illnesses in suspected measles outbreaks and suspected measles cases that presented to participating sentinel sites were investigated with a standardized case investigation form and serum samples were collected for both measles and rubella IgM testing by enzyme-linked immunosorbent assay (ELISA). By the end of 2007, there were 31 sentinel case-based surveillance sites: 58 by December 2008 and 109 by December 2009. Genotyping of outbreak specimens is conducted at the Measles Regional Reference Laboratory in Bangkok, Thailand.

Seroprevalence

A cross-sectional study was conducted at 10 hospitals that were selected on the basis of geographic location to represent all 5 developmental regions of Nepal and after having adequate outpatient attendance to meet sample size requirements by age group. Any woman of childbearing age who attended the outpatient department of one of these hospitals from October through December 2008 was eligible for enrollment. Age range and categories were based on fertility data reported in the 2006 Nepal Demographic and Health Survey (NDHS), which included data on women 15–49 years of age in 5-year age strata [3]. Because the NDHS showed a sharp decrease in fertility after 39 years of age, childbearing age for this study was defined as 15–39 years in 5 age strata (15–19 years, 20–24 years, 25–29 years, 30–34 years, and 35–39 years).

Participants completed a standardized questionnaire that included questions on demographic characteristics and pregnancy and immunization histories. A 3–5-mL blood sample was collected by venipuncture from each participant. Serum samples were separated and stored at 2–8°C until tested at NPHL in Kathmandu. Rubella-specific IgG antibodies were detected by enzyme immunoassay (Enzygnost; Behring) [4]. Participants with an IgG titer of $\geq$10 IU were considered to be rubella seropositive, whereas $<$10 IU were considered to be negative. Ten percent of specimens were sent to the WHO-accredited Regional Measles Reference Laboratory in Bangkok, Thailand, for quality control and were 97% concordant.

CRS Among Hearing Impaired Children

To estimate the proportion of children with hearing impairment who also had ocular manifestations associated with CRS, a cross-sectional study was conducted in a population of hearing-impaired children at Bal Mandir School for the Deaf, Kathmandu, in August 2009. Participating children were examined by an ophthalmologist to assess ocular morbidity in the context of CRS and underwent audiometric testing by an audiologist to determine the extent of hearing impairment. Sociodemographic and medical histories were collected using a standardized instrument.

Data Management and Analysis

For sample size determination for the seroprevalence study, it was necessary to estimate the proportion of rubella-seropositive women in the study population. Because of the lack of rubella seropositivity data from Nepal and the wide range in rubella seropositivity reported from various studies across Asian countries [5], we assumed that 50% of women of childbearing age would be seropositive because this assumption is associated with the maximum sample size. Under this assumption and with an acceptable 95% confidence interval (CI) of 45%–55%, the sample size required was at least 384 persons in each age strata, which was rounded up to 400 persons per strata. This was divided uniformly across each of the 10 study sites and 5 age strata. Seropositivity was defined as having a positive IgG antibody test result. The percentage of seropositive women was estimated with 95% CIs for each age group, by region.

To estimate the incidence of CRS in age groups, age-specific seroprevalence data from this survey were used to estimate age-specific proportions of women susceptible to rubella based on a simple catalytic infection model [1] with a constant force of infection. Estimated incidences were calculated by first obtaining the maximum likelihood estimate of the force of infection and then using that estimate in the simple catalytic model to estimate the age-specific susceptibility proportions. Rubella infection incidences for an age interval were calculated as the

difference between estimated seroprevalences at the upper and lower limits of the age interval. These incidences were then combined with Nepal's age-specific fertility rates, the number of women in each age band, and gestation-stage-specific risk of congenital rubella infection [6] to estimate the number of CRS cases expected annually.

For the CRS study, students with hearing impairment who also had cataracts, congenital glaucoma, or pigmentary retinopathy as described in the case definition were classified as clinically confirmed CRS using the WHO case classification scheme [7].

Human Subjects Consideration

Signed consent was obtained from participants in the seroprevalence and CRS studies with use of informed consent forms translated into Nepali. Consent was obtained from caretakers for children <18 years of age. If a participant or caretaker of a minor child was illiterate, the informed consent form was read aloud and signed by a witness and the participant or caretaker was asked to make a mark where signatures were otherwise required. In addition, each child provided verbal assent for participation. Children ≥7 years of age were also asked to sign an assent form noting their agreement to participate. For children who were unable to read, the form was read aloud and then the children were asked to give verbal assent in front of a witness. The witness signed the form noting the child's verbal assent. Participants were free to withdraw from participating at any point. Confidential information was protected to the full extent permissible by law.

Participants in the seroprevalence study were provided a fixed compensation to cover costs associated with transportation to and from the study site. Eye glasses were provided free of charge to children in the CRS study who had visual acuity of 6/18 or worse that could be improved with eye glasses. Medical treatment for nonsurgical ophthalmic problems was provided at no cost at the time of examination. Children requiring hospitalization or surgical treatment for cataracts or hearing loss were provided with an explanation and referred for further medical care.

RESULTS

Surveillance

From January 2004 through December 2009, a total of 15,535 cases of febrile rash illness (suspected measles) were identified either during outbreak investigations (n = 10,116) or from sentinel surveillance reporting sites (n = 5419). Of the 2615 samples collected and tested for rubella-specific IgM antibodies, 1187 (45%) were laboratory confirmed as rubella (Table 1). An additional 2523 (16%) of the 15,535 reported cases were confirmed as rubella through epidemiological links to laboratory-confirmed rubella cases. In total, 3710 (24%) of the febrile rash illness cases identified through surveillance were confirmed as rubella. More than 95% of confirmed cases occurred among persons <15 years of age, with roughly equal distribution between male and female participants (Table 2). Confirmed rubella cases were widely distributed throughout the country, with seasonal distribution peaking during the late winter and early spring. To date, the Regional Measles Reference Laboratory has isolated only the 2B genotype of rubella virus from urine samples collected from patients associated with rubella outbreaks.

Table 1. Number of Febrile Rash (Suspected Measles) Cases Identified, Number of Serum Samples Collected, and Percentage of Serum Samples Testing Positive for Rubella IgM, Nepal, 2004–2009

Year	No. of cases identified	No. of samples collected	No. (%) rubella IgM positive
2004	8672	175	71 (40.6)
2005	1698	241	161 (66.8)
2006	1042	204	103 (50.5)
2007	658	313	85 (27.2)
2008	1494	656	266 (40.5)
2009	1971	1026	501 (48.8)
Total	15,535	2615	1187 (45.4%)

Seroprevalence

In all, 2248 women 15–39 years of age were enrolled in the seroprevalence study. Adequate specimens were obtained and anti-rubella IgG testing was completed for 2224 enrolled women (99%). Of these, 2020 (90.8%) were rubella IgG seropositive. Nationally, the percentage of women who were seropositive ranged from 88.3% for women 15–19 years of age to 92.7% for women 35–39 years of age. Seropositivity was slightly lower among women 30–34 years of age (88.7%) than among women 20–24 (92.4%; P = .053) or 25–29 (91.5%; P = .151) years of age (Table 3).

Table 2. Distribution of Rubella Cases by Age Group and Sex, Nepal, 2004–2009

Age group, years	Total no. (%) of cases	No. (%) females
<1	106 (2.9)	54 (50.9)
1–4	1,173 (31.6)	551 (47.0)
5–9	1,696 (45.7)	850 (50.1)
10–14	557 (15.0)	296 (53.1)
15–19	100 (2.7)	64 (64.0)
20–24	29 (0.8)	17 (58.6)
25–29	28 (0.8)	20 (71.4)
30–34	12 (0.3)	7 (58.3)
35–39	5 (0.1)	3 (60.0)
≥40	4 (0.1)	3 (75.0)
Total	3710	1865 (50.3)

Table 3. Total Number of Women Tested (Percent Rubella IgG Seropositive) and 95% Confidence Intervals for Seropositivity, by Age Group and Region, Nepal, October–December 2008

		Age Group, years				
Region		15–19	20–24	25–29	30–34	35–39
Central	No.	95	153	158	115	105
	% [95% CI]	89.5 [83.2–95.7]	93.5 [89.5–97.4]	93.0 [89.0–97.0]	90.4 [85.0–95.9]	97.1 [93.9–100.0]
Eastern	No.	92	95	91	91	90
	% [95% CI]	91.3 [85.5–97.1]	88.4 [81.9–94.9]	89.0 [82.5–95.5]	91.2 [85.3–97.1]	87.8 [80.9–94.6]
Far Western	No.	44	47	46	42	46
	% [95% CI]	86.4 [75.9–96.8]	89.4 [80.3–98.4]	87.0 [77.0–97.0]	81.0 [68.7–93.2]	89.1 [79.9–98.4]
Mid Western	No.	33	61	50	46	44
	% [95% CI]	87.9 [76.3–99.4]	98.4 [95.1–100.0]	94.0 [87.3–100.0]	84.8 [74.1–95.4]	93.2 [85.5–100.0]
Western	No.	139	168	139	121	113
	% [95% CI]	86.3 [80.6–92.1]	92.3 [88.2–96.3]	92.1 [87.6–96.6]	89.3 [83.7–94.8]	93.8 [89.3–98.3]
All	No.	403	524	484	415	398
	% [95% CI]	88.3 [85.2–91.5]	92.4 [90.1–94.6]	91.5 [89.0–94.0]	88.7 [85.6–91.7]	92.7 [90.2–95.3]

In 2008, 742,505 births were expected from the estimated population of 5,769,491 women in Nepal [8]. Of these, 66,751 (9.0%) would have been to rubella-susceptible women. On the basis of a constant force of infection of .093, we estimate that in 2008, 6091 pregnant women would have been infected. We estimate further that ~1426 infants were born with CRS (192 cases/100,000 live births) (Table 4).

CRS in Hearing Impaired

Auditory and ophthalmic testing was completed for 243 (93%) of the 262 children enrolled at Bal Mandir School for the Deaf. Overall, 18 (7.4%) met clinical criteria for CRS. All 18 children had pigmentary retinopathy. One child with pigmentary retinopathy also had a history of cataract surgery. Among the 18 students with CRS, 2 had moderate (41–65 db) hearing impairment, 8 had severe (66–80 db), and 8 had profound (81–120 db). Other ophthalmic criteria to confirm CRS were not found among the remaining 225 examined children. Eight (44.4%) of the 18 children with CRS were female. The median age of children with CRS was slightly younger (13 years) than that of the study population of students enrolled in the school (16 years; range, 9–25 years).

DISCUSSION

Findings from separate investigations document the public health significance of acute rubella infection and CRS in Nepal. Our investigations have demonstrated that the majority of reported rubella cases (>95%) in Nepal are among persons <15 years of age, and ~91% of women 15–39 years of age have acquired rubella in the past. We estimate an annual CRS disease burden of ~1400 cases. Therefore, it appears that rubella is an endemic disease in Nepal and primarily a disease of children and adolescents. However, a substantial annual burden of CRS exists in Nepal, because ~10% of women of childbearing age are rubella susceptible and at risk. Furthermore, our investigations have also demonstrated the presence of cases consistent with the

Table 4. Estimated Number of Women, Number Infected With Rubella, Fertility Rate, Annual Expected Number of Births, Percent of Women Who Are Rubella Susceptible, Number of Births to Rubella Susceptible Women, and Estimated Number of Pregnant Women Infected With Rubella Per Year By Age Group, Nepal, 2008

Age group, years	Estimated no. of women*	Estimated no. of women Infected with rubella per year	Fertility rate per 1000 women**	Annual expected births	Percentage of women who are rubella susceptible	No. of births to rubella-susceptible women	Estimated no. of pregnant women infected with rubella per year
15–19	1,454,382	26,807	98	142,529	11.7	16,676	2021
20–24	1,321,585	15,301	234	309,251	7.6	23,503	2754
25–29	1,157,877	8421	144	166,734	8.5	14,172	933
30–34	996,652	4553	84	83,719	11.3	9460	294
35–39	838,995	2407	48	40,272	7.3	2940	89
Total	5,769,491	57,489		742,505		66,751	6091

NOTE.

* Health Management Information System, Government of Nepal, 2008; **Nepal Demographic and Health Survey, 2006.

CRS case definition in children enrolled in a school for deaf in Kathmandu, Nepal.

The seroprevalence study findings documented overall seroprevalence of 90.8%; however, females aged 15–19 years had a lower seroprevalence of 88.3%. There was a moderate risk of rubella seronegativity among females aged 15–19 years, compared with women aged 20–24 and 25–29 years with seroprevalence of 92.4% and 91.5%, respectively. These findings are compatible with cumulative ongoing risk of exposure to rubella and are consistent with a previous review of seroprevalence studies among women of childbearing age [5]. Seroprevalence rates were lower among women aged 30–34 years than among women aged 25–29 or 35–40 years. The reason for the relatively lower seroprevalence in this age group is unknown but may be related to cyclical rubella epidemic transmission patterns in the country.

In the deaf school study, children with clinically compatible CRS case definition were identified. Pigmentary retinopathy, usually asymptomatic, is the most common eye defect of congenital rubella syndrome. Although there are other causes of pigmentary retinopathy, detection of pigmentary retinopathy in children with congenital hearing impairment is an indicator of congenital rubella syndrome. The true burden of CRS reported is likely underestimated, because the school-based survey would not have captured children with severe cardiac abnormalities, mental retardation, or severe visual impairment.

There were several limitations to the studies reported. The surveillance data presented were collected through a surveillance system that was primarily designed to identify measles cases rather than rubella cases. Coupled with the fact that up to half of rubella cases may be present without a rash or are subclinical, it is likely that many cases of rubella infection were not captured by the surveillance system. The seroprevalence study was completed on a convenience sample of women attending selected hospitals and, therefore, may not be representative of women of childbearing age in the general population of Nepal. However, despite these limitations that underestimate the burden of rubella in Nepal our results demonstrate that rubella disease primarily infects children less than 15 years of age, that there is moderate susceptibility among women of childbearing age, and that this disease susceptibility results in the occurrence of CRS.

The Technical Advisory Group on Immunization for South East Asia has recommended that countries that have not yet introduced a rubella-containing vaccine should strengthen surveillance for rubella and CRS, review the significance of rubella and CRS disease on public health, and build the necessary political and financial commitments for vaccine introduction [9]. Experts attending the Vaccine Prioritization Workshop for South East Asia identified rubella vaccination as an immediate priority for prevention of rubella infection and CRS [10].

Rubella vaccine introduction has been included in the Government of Nepal's comprehensive multiyear plan for 2007–2011 [2]. Adding rubella vaccine to the routine immunization program is cost-effective, cost-beneficial [11], and programmatically feasible, because measles vaccination is ongoing and combination vaccines obviate the need for an additional injection.

Because of the Government of Nepal's interest in preventing CRS, the considerable annual burden of CRS, and moderate susceptibility among women of childbearing age (9% overall, but >11% for women 15–19 years of age), 2 general policy approaches for vaccine introduction should be considered by the Government of Nepal: (1) prevent CRS through vaccination of adolescent girls and/or women of childbearing age or (2) control and eventually eliminate rubella and CRS through universal vaccination of infants and young children (with or without mass campaigns) and assure immunity in women of childbearing age [11].

Prevention of CRS Through Vaccination of Adolescent Girls and/or Women of Childbearing Age

We estimated 66,751 births to rubella-susceptible women per year in Nepal. With the intense rubella transmission documented in Nepal, children born to these women are at risk of acquiring CRS. Therefore, targeting women of childbearing age, including adolescent girls, should be considered as part of a comprehensive strategy. Some of the possible options include offering of rubella vaccination to girls at the time of school completion, premarital vaccination for women, postpartum vaccination, or vaccination of adolescent girls and women in institutions, such as training institutions, universities, or places of employment. If supplemental immunization activities (SIAs) are to be considered, a plan will need to be in place to guarantee that the new cohorts of women of childbearing age are also provided vaccine either through SIAs or a routine program targeting women of childbearing age. A policy of rubella vaccination targeting only women of childbearing age essentially assures immunity in the key group that needs to be protected to reduce the burden of CRS [11]. However, such a policy does not reduce rubella transmission among children, who are the main reservoir for rubella transmission, or in adult men and, therefore, will have minimal impact in reducing the risk of exposure to rubella virus among susceptible pregnant women. Therefore, if this policy is not implemented well, women of childbearing age will continue to remain susceptible and pregnant women will be at risk of rubella infection and its consequences.

Control and Eventual Elimination of Rubella and CRS Through Universal Vaccination of Infants and Young Children, With Assurance of Immunity in Women of Childbearing Age

Nepal has identified a goal of measles elimination by 2015 [12]. Countries undertaking measles elimination should consider taking the opportunity to also eliminate rubella through the use of combination measles-rubella vaccine in both routine

childhood immunization programs and in periodic mass vaccination campaigns [11]. Because rubella is almost always given with a measles-containing vaccine, the additional cost of the rubella containing-vaccine would be ~$0.30 per dose.

For a country to introduce rubella-containing vaccine into their national childhood immunization program, the recommendation in the 2000 WHO rubella position paper is that the first dose of measles-containing vaccine (MCV1) coverage should be >80%. However, this 80% threshold applies to a policy designed to eliminate rubella virus transmission completely rather than a program of rubella control and CRS prevention that has sufficiently high vaccination coverage to avoid a potential paradoxical increase in the risk of CRS [13]. The latter policy would have a lower coverage threshold that varies depending on the R0 (mean number of secondary cases a typical single infected case will cause in a population with no immunity to the disease in the absence of interventions to control the infection). In addition, since the WHO position paper was published in 2000, follow-up campaigns for measles have become the standard for countries to reach measles mortality reduction and elimination goals. In many countries, SIAs have been able to achieve higher levels of measles vaccination coverage than the routine vaccination program by better accessing hard-to-reach children. By including rubella-containing vaccine in the SIAs, high levels of immunity for rubella can be ensured.

In Nepal, national routine measles vaccination coverage rates during 2000–2008 ranged from a low of 71% (2000) to a high of 85% (2006). Although measles vaccination coverage for 2009 is estimated at 75.3%, district level coverage for measles vaccine at 9 months of age ranges from 45.4% to 98.1% [8]. In contrast, supplementary immunization campaigns against measles have achieved >90% coverage nationally and in most districts [14]. Because of the interest of the Government of Nepal to prevent CRS, a comprehensive approach will be needed. Nepal should consider ways of integrating rubella into the measles elimination framework, such as including the use of measles-rubella vaccine for periodic measles vaccination campaigns (rather than single antigen measles vaccine) and introducing a rubella-containing vaccine into the routine immunization program. Targeting women of childbearing age should be considered as an integral part of the vaccination strategy either through SIAs, the routine program, or both. Other components of the comprehensive strategy include strengthening routine vaccination, integration of rubella surveillance with measles case-based surveillance, and integrating CRS surveillance into the vaccine preventable diseases surveillance system.

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