Original article

Progress in rubella control initiated through measles elimination strategies: the Malaysian experience

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Abstract

Objective: To analyse the laboratory surveillance data from 2004 till 2008 to examine the changing trend of rubella cases in Malaysia. **Methods**: Samples for this study were either received through the measles case based surveillance program or were hospital cases received for sero-diagnosis of congenital rubella syndrome (CRS). Specific rubella IgM antibody test was carried out on all samples that were negative for measles IgM antibody and for sero-diagnosis of CRS. **Results**: Through the surveillance program for measles, the samples received for rubella had increased five fold from 365 in 2004 to 1 522 in 2007. Positive rubella cases detected had also increased from 4.1 % in 2004 to 33.2 % in 2007. The age group 11 to 20 years accounted for 73.6 % of rubella cases confirmed in 2008, with a higher incidence among males than females. Positive rubella IgM was detected in 25 CRS cases during the 6 year period between January 2003 and December 2008. **Conclusion**: The measles elimination program had contributed to significant progress in the control of rubella, with the majority of rubella cases detected through this strategy. Since rubella is not notifiable in Malaysia, this integrated measles and rubella surveillance should be continued. However, to enhance the progress, specific targets should also be established in the national program to eliminate rubella and CRS.

Keywords: Rubella; Congenital rubella syndrome; Mump-measles-rubella (MMR) vaccination; Surveillance

INTRODUCTION

Rubella or German measles is a common childhood infection, characterized by non-specific signs and symptoms including transient erythematous rash on the face and neck that may be accompanied by adenopathy and slight fever. In most cases, the infection is usually mild but adult cases frequently present with polyarthralgia or polyarthritis. The most important consequences of rubella are fetal anomalies, known as congenital rubella syndrome (CRS) that occurs as rubella infection during early pregnancy, especially during the first trimester. The anomalies most commonly associated with CRS are severe impairments in growth and development, microcephaly, hepato-splenomegaly, cataracts, congenital heart disease, sensorineural deafness and meningitis[1].

It has been estimated that over 100 000 cases of CRS occur in developing countries each year[2]. CRS can be prevented by ensuring women of childbearing age are protected both through vaccination and by preventing their exposure to indigenously circulating rubella virus. A single dose of rubella vaccine confers immunity in 95 % or more of recipi-

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ents, hence many countries have established the target of eliminating rubella. In Malaysia, the monovalent rubella vaccine was introduced in 1987 to target populations, specifically, female schoolchildren at the age of 12 years old and women in the reproductive age group. Due to the selective strategy in vaccination, many older people were susceptible to rubella infection. Only in 2002, rubella vaccine was given in combination with mumps-measles-rubella (MMR), and targeted to both boys and girls at 1 year and 7 years age.

In 2003, the WHO Western Pacific Region Member States resolved to eliminate measles, another vaccine preventable disease with rash and fever illness and committed the Region to achieve measles elimination by 2012[3]. Effective strategies included establishing an integrated case-based surveillance for measles and rubella with laboratory testing of all suspected cases. National laboratories were encouraged to test specimens for rubella specific IgM antibody on specimens that were measles IgM antibody negative.

We have reviewed national laboratory data from 2004 till 2007 to study the trend of rubella and CRS incidence in Malaysia. Most of the specimens tested for rubella antibody, except specimens received for sero-diagnosis of CRS were measles IgM negative samples from measles suspected cases. The source of the laboratory data for this study was from the National Public Health Laboratory (NPHL) and the Institute for Medical Research (IMR) in Kuala Lumpur. Hospital samples received at the IMR in 2008 for measles and rubella laboratory investigation were also tested for rubella specific IgG to evaluate the prevalence of rubella susceptibility.

MATERIALS AND METHODS

Case definition and patient samples

Blood samples were collected by attending physicians from measles and rubella suspected cases at the acute stage of their rash illness. They included:

(1) all cases from health facilities where attending physicians suspected measles or rubella infection;

(2) cases for laboratory investigations from hospitals where clinical presentation reported fever and maculopapular rash and / or conjunctivitis or cough or coryza;

(3) measles or rubella suspected outbreaks;

(4) suspected cases of CRS from government hospitals sent for serodiagnosis to the IMR

All the samples were accompanied with a request form complete with patient details and clinical history and sent to NPHL or IMR for laboratory investigations.

Measles and rubella serological assay protocol

At NPHL and IMR, all serum specimens were tested using the Enzygnost Anti-Measles-Virus / IgM enzyme immunoassay (Dade Behring, Marburg, Germany). At IMR, all serum specimens for specific IgG were tested using the Enzygnost Anti-Measles-Virus IgG enzyme immunoassay (Dade Behring, Marburg, Germany). The test procedure, interpretation and validation of test results followed manufacturer's instructions. Equivocal samples were retested and reclassified as positive or negative, where indicated.

At NPHL all serum samples that were negative for measles IgM were tested for rubella specific IgM using the Enzygnost Anti-Rubella-Virus / IgM enzyme immunoassay (Dade Behring, Marburg, Germany). At IMR, rubella antibody was tested using Axsym, automated analyzer (Abbott Laboratories)

Validation of test results

The national data for MMR vaccine coverage were obtained from the Surveillance Unit, Disease Control Division, Ministry of Health Malaysia.

RESULTS

From January 2004 till May 2008, a total of 4 703 sera were tested for Rubella IgM antibody(Table1). Three thousand one hundred and eighty-one (67.6%) of these samples were received from measles surveillance cases that were negative for measles IgM antibody. Figure 1 shows the changing trends of suspected measles and rubella cases reported to the national laboratories for laboratory confirmation. There is a general decreasing trend for measles incidence as seen from laboratory data but an increasing trend in laboratory confirmed rubella cases. In 2007,1 340 serum specimens were received by the two government laboratories for measles and rubella testing but measles IgM antibody was detected in only 3.8 % of the sera, whereas rubella IgM antibody was detected in 33.2 % of these specimens.

Between January 2003 and December 2008, a to-

tal of 1 696 sera was received at IMR from infants below 6 months age for laboratory investigation of various fetal anomalies and routine investigation of low birth weight babies including babies with jaundice or anaemia. Specific rubella IgM was detected in 25 samples during this 6 year period. Positive IgG, in the absence of IgM was detected in another 32 infants aged 6 months to 12 months who had varying spectrum of anomalies in their development.

In 2008, the IMR tested 1 004 serum samples received from government hospitals for rubella specific IgM and IgG antibodies. Rubella specific IgM was detected in 197 out of the 1 004 sera tested, while specific IgG was detected in 744 of the sera (74.1%). In 243 of these sera, rubella IgG levels were below cut-off point for positive detection (24.2 %). Equivocal samples were not included in the data analysis. The age distribution of these samples are shown in Table 2 and Figure 2. As seen from Figure 2, rubella cases were higher in the age group, between 11 and 20 years with a higher incidence among males (76.6 %) compared to females (23.4 %). The susceptible age groups who tested rubella IgG negative were between 11 to 20 years of age and also infants below 12 months of age.

Table 1 Measles and rubella laboratory data from 2004 till May 2008.

Year	Measles		Rubella	
	Total samples received	Total positive IgM (%)	Total samples received	Total positive IgM (%)
2004	2 791	1 014(36.3%)	365	15(4.1%)
2005	1 393	185(13.3%)	901	128(14.2%)
2006	616	27(4.3%)	602	41(6.6%)
2007	1 340	52(3.8%)	1 522	506 (33.2%)
Till May 2008	1 524	29(1.9%)	1313	424(32.3%)

Table 2 Rubella serodiagnosis of hospital cases received at the Institute for Medical Research in 2008

Age Groups (Years)	Rubella IgM positive $N=197$ *	Rubella IgG negative $N=243$ *
<12 months	4	50
1 – 5	1	8
6 – 10	8	8
11 – 15	108	83
16 – 20	37	57
21 – 25	12	10
25 – 30	8	12
>30	15	13
Total	193	241

Note * Age was not available for 4 samples tested for Rubella IgM and for 2 of the samples tested for IgG antibody

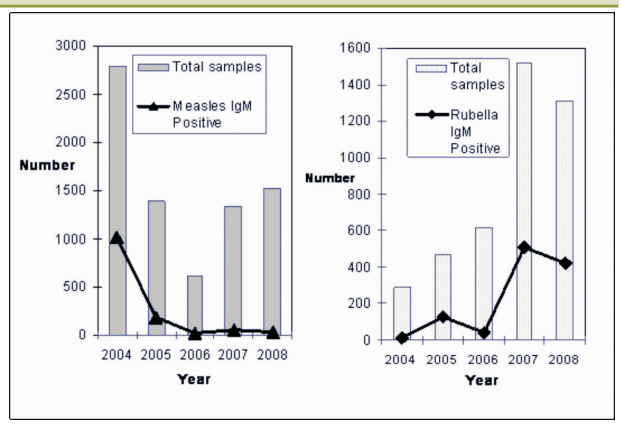

Figure 1 Measles and rubella laboratory confirmed cases from 2004 to May 2008.

DISCUSSION

Rubella is not a notifiable disease in Malaysia and the actual burden due to rubella has not been estimated. Local reports had obtained data for burden of disease from hospital records, disease outbreak reports, serological surveys and laboratory reports. Since most cases of acquired rubella are mild and do not require hospital admissions, these figures have been under estimates. Moreover, the common symptoms of rubella (maculopapular rash, low-grade fever, posterior cervical and suboccipital adenopathy, and arthralgia / arthritis, especially in adult females) can easily be mistaken for other rash diseases and a definitive diagnosis of rubella can only be made by specific laboratory methods.

Our study showed that with integrated measles and rubella testing, established by the WHO measles

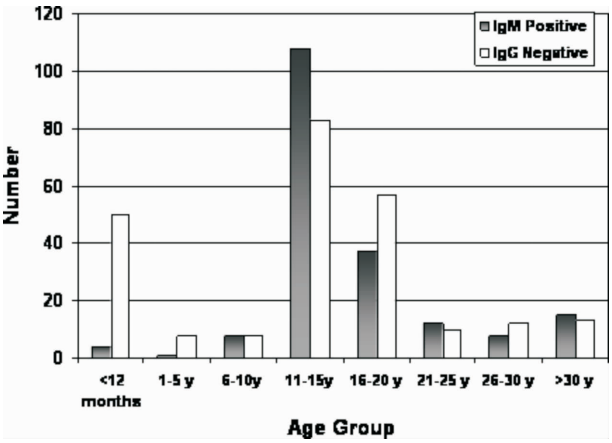

Figure 2 Age distribution of hospital cases tested for Rubella IgM and Rubella IgG received at the Institute for Medical Research in 2008.

elimination strategies, more samples were received for laboratory confirmation of rubella since 2004. An average of 1 525 samples were received annually for laboratory investigation through an ongoing sensitive surveillance for measles cases, but the number of positive measles cases however had decreased from 36.3 % in 2004 to 3.8 % in 2007. Through this surveillance for measles, the samples received for rubella had increased five fold from 365 in 2004 to 1 522 in 2007. Positive rubella cases detected through this strategy has also increased from 4.1 % in 2004 to 33.2 % in 2007. It must be cautioned that the figures do not represent actual rubella incidence since samples were investigated through the measles case based surveillance. Many measles cases were clinically diagnosed by physicians and reported through the notifiable infectious disease surveillance but not confirmed by the laboratory. The increasing trend of rubella positive cases by laboratory confirmation is still a definite progress in the control of this disease, since public health managers are alerted about rubella outbreaks early enough to implement control measures.

The impetus for the control of rubella is prevention of CRS. Experiences of developed countries have shown that immunization against rubella is the only effective way for the elimination of CRS cases. The monovalent rubella vaccine was introduced in Malaysia in 1987 and given selectively to female school children and young women of child bearing age. Although high vaccine coverage rates were reported, CRS cases were still encountered in hospitals. From previous reports, it was seen that government hospitals admitted between 50 to 230 cases of CRS annually and serological surveys indicated about 40 % of the female population in the child bearing age were susceptible[4,5]. Obviously, unimmunized younger children who were not the target group of the monovalent rubella vaccine were potential sources of infection for susceptible adult women. In our study involving 1 696 hospitalized infants aged below 6 months, from 2003 till 2008, positive rubella IgM was detected in 25 CRS cases during this 6 year period. In a cross-sectional study among pregnant women in an antenatal clinic in 2002, the rubella immunity status was 92.3 % [6]. In another study, in 2008, the prevalence of rubella susceptibility among pregnant mothers was reported to be 11.4%[7]. Based on these data, the selective rubella vaccination program in Malaysia has been partially successful despite the presence of some CRS cases.

During the period of study, suspected measles outbreaks had occurred among adolescents in closed institutions, which were later confirmed as rubella[8]. These outbreaks reported a higher incidence among males compared to females. Based on our study, the age group of 11 to 20 years accounted for 73.6% of rubella cases confirmed in 2008, with a higher incidence among males than females. These individuals may have had low levels of rubella immunity as they were not the target group for the rubella immunization with monovalent vaccine and too old to have been part of the 2-dose (MMR) vaccination program, introduced in 2002. Immunoglobulin G seropositivity was 74.1 %.

In 2002, when the MMR was introduced in the EPI, Malaysia adopted the universal strategy of immunizing all children irrespective of gender. MMR coverage rates has been above 85 %. High immunization rates among children can reduce the rubella risk for seronegative women but they do not eliminate the risk. The circulation of rubella virus in the community, in the family or professional settings of susceptible fertile women can produce a case of CRS. It is encouraging to note that, through the enhanced measles surveillance with suspected case reporting and laboratory confirmation, the rubella susceptible population can be identified and secondary immunization or catch-up vaccinations initiated using monovalent rubella vaccine. Surveillance is very important for the control of rubella and CRS, since most rubella cases are subclinical and may otherwise be undetected.

Since case based surveillance for measles has improved in the Western Pacific Region, along with decrease in transmission of the measles virus, other countries have also reported an increasing number of suspected measles cases that were confirmed as rubella [9] The regional office has recommended that all suspected measles cases that are IgM negative should be tested for rubella. Using a simplified case surveillance case definition such as acute fever and rash to identify potential measles and rubella cases can further increase sensitivity for both diseases.

The measles elimination program has contributed to significant progress in control of rubella with the majority of rubella cases detected through this strategy. This strongly suggests that the measles and rubella control programs should continue to be integrated. However to enhance the progress achieved, specific targets should also be established in national programs to eliminate CRS. The occurance of rubella outbreaks among young adults indicate that much still needs to be done since susceptible women of child bearing age remain at possible risk of exposure to rubella during pregnancy. Elimination of CRS will require all women of child bearing age to be immune. The greatest challenge in this direction will be to strive to achieve higher MMR vaccination coverage rates in children and continue vaccination of susceptible women with monovalent rubella vaccine. Since rubella is not notifiable, surveillance, monitoring and detection of rubella and CRS are also important to achieve our goal of rubella and CRS elimination.

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REFERENCES

1 **Cutts FT**, Robertson JL, Diaz O, Samuel R. Control of rubella and congenital rubella syndrome (CRS) in developing countries, part 1: Burden of disease from CRS. *Bull WHO* 1997;75(1): 55 – 68.

2 **Robertson SE**, Featherstone DA, Marta GD, Bradley S. Rubella, congenital rubella syndrome: Global update. *Am J Pub Hlth* 2003; 14(5):306 – 315.

3 WHO. Regional EPI targets: eliminate measles and control hepatitis B by 2012. The World Health Organization Regional Committee for the Western Pacific, 2003 Resolution no. WPR/RC54. R3.

4 **Narimah A**. Rubella Immunization in Malaysia – 20 years on, and the challenges ahead. *Med J Malaysia* 2005;60 (3): 1 – 3.

5 **Chua KB**, Lam SK, Hooi PS, Chua BH, Lim CT. Retrospective review of serologic rubella activity in University Hospital Kuala Lumpur. *Med J Malaysia* 2000;55:299 – 303.

6 **Sekawi Z**, Muizatul WMN, Marlyn M, Jamil MAY, Ilina I. Rubella vaccination programme in Malaysia: analysis of a seroprevalence study in an antenatal clinic. *Med J Malaysia* 2005;60:345 – 348.

7 **Theng CA** , Ming KE. Prevalence of Rubella Susceptibility Among pregnant mothers in a community – based antenatal clinic in Malaysia: A cross-sectional study. *Asia Pac J Publ Health* 2008; 20 (4):340 – 346.

8 **Muhd Yusof AB**, Selvanesan S, Norizah I, et al. Rubella Outbreak Amongst Residential Students in a military vocational school of Malaysia. *Med J Malaysia* 2006; 61 (3): 296 – 301.

9 WHO. Measles Bulletin. The World Health Organization Regional Office for the Western Pacific, 2008 WPR/2008/DCC/04/EPI/(2)/2008/INF.

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