# CONGENITAL RUBELLA SYNDROME IN MALAYSIA

DORA S.K. TAN

## SUMMARY

*Of the five diseases generally recognised as causing congenital defects,* viz., *toxoplasmosis, rubella, cytomegaloviral infection, herpes simplex and syphilis (TORCHES) studied in Malaysia, rubella was found to be the most important. A total of 574 children with features of congenital rubella syndrome (CRS) were examined for rubella-specific IgM (in infants four months and below), and for rubella HAI antibodies (in children six months to four-years-old), and compared with 374 normal Children of the same age groups. Whereas the prevalence rate of rubella in normal children was only 1.3%, in children with CRS (multiple defects) it was 87.3%; with congenital heart disease 71.0%; with congenital cataract 64.0%; with deafness 60.1%; with rash 30.8%; with hepatomegaly 17.1%; with mental retardation 4.1%. Congenital rubella was not important as a cause of neonatal jaundice (0.9%) and CNS defects (0%).*

## INTRODUCTION

A study of five generally recognised congenital diseases, *viz.*, toxoplasmosis, rubella, cytomegaloviral infection, herpes simplex and syphilis (TORCHES) in Malaysia has shown that of these diseases, rubella was by far the most important cause of congenital defects in the country.[1] In view of this, the investigation of rubella was further pursued and the findings are presented in this article.

Dora S.K. Tan, MBBS, DTM & H,
Institute for Medical Research
Jalan Pahang, Kuala Lumpur

## MATERIALS AND METHODS

Sera of three groups of children aged zero to four years were examined. A – 100 normal newly-born infants, from whom cord blood was obtained and found negative for IgA, to rule out placental leakage; these were received from the Chinese Maternity Hospital, Kuala Lumpur. B – 274 normal children aged one day to four years; the sera were received from paediatricians in hospitals throughout East and West Malaysia. C – 574 defective children, aged one day to four years, with cataract, congenital heart disease (mainly ventral septal defect), congenital rubella syndrome (with multiple deformities), deafness, rash (purpuric or petechial), hepatomegaly (with or without jaundice and splenomegaly), neonatal jaundice (from infants aged three weeks and under), mental retardation and defects of the central nervous system (microcephaly, hydrocephaly, cerebral palsy and convulsions).

Two serological techniques were employed in the diagnosis:

**Haemadsorption Immunosorbent Technique (HIT) for sera** of children aged four months and under. It detects the rubella-specific IgM and is based on the capture of specific IgM on to solid phase.[2] The advantages of this test includes simplicity, the unrestricted number of sera which can be

tested daily, the availability of results within 24 hours and lack of interference by rheumatoid factor and rubella-specific IgG.

**Haemagglutination-inhibition (HAI) test** for sera of children aged six months to four years. This conventional microtiter test detects mainly IgG antibodies. Goose red blood cells (RBCs) were used and the antigen was acquired commercially from Flow Laboratories Inc. Non-specific inhibitors in the sera were removed by the heparin-manganous chloride treatment method.[3]

## RESULTS

The results of the investigation are summarised in Table I. Rubella-specific IgM was not detected in the sera of 219 normal infants zero to four months old, and IgG was found in only five of 155 normal infants six months to four years. Therefore, out of the total number of 374 normal children, zero to four-years-old, only five (1.3%) were retrospectively diagnosed as having undergone intra-uterine infection with rubella.

The evidence of intra-uterine infection with rubella causing congenital rubella syndrome or CRS (87.3%), cataract (64.0%), congenital heart disease (71.0%) and deafness (60.6%) is unequivocal. Transient effects of congenital rubella were seen in 30.9% of children with rash, and 17.7% of those with hepatomegaly.

**TABLE I**
**RUBELLA IN CONGENITALLY-DEFECTIVE CHILDREN COMPARED WITH NORMAL CHILDREN (ZERO TO FOUR-YEARS-OLD) IN MALAYSIA**

| Defect | Age | Number examined | (+) ve | (%) | (GMT)* |
|---|---|---|---|---|---|
| Normal | Cord Sera | 100 | 0 | 1.3 | – |
| | 1 day – 4 mths | 119 | 0 | | – |
| | 6 mths – 4 yrs | 155 | 5 | | 24 |
| Congenital rubella syndrome ** | 1 day – 4 mths | 38 | 31 | 87.3 | – |
| | 6 mths – 4 yrs | 17 | 17 | | 120 |
| Congenital heart disease | 1 day – 4 mths | 35 | 28 | 71.0 | – |
| | 6 mths – 4 yrs | 27 | 16 | | 128 |
| Congenital cataract | 1 day – 4 mths | 34 | 27 | 64.0 | – |
| | 6 mths – 4 yrs | 41 | 21 | | 102 |
| Deafness | 6 mths – 4 yrs | 33 | 20 | 60.6 | 39 |
| Rash | 1 day – 4 mths | 17 | 7 | 30.8 | – |
| | 6 mths – 1 yr | 9 | 1 | | N.V.+ |
| Hepatomegaly (± jaundice, splenomegaly) | 1day – 4 mths | 91 | 14 | 17.1 | – |
| | 6 mths – 4 yrs | 50 | 11 | | 49 |
| Neonatal jaundice | 1 day – 3 wks | 113 | 1 | 0.9 | – |
| Mental abnormality | 1 yr – 4 yrs | 49 | 2 | 4.1 | 128 |
| Central nervous system defects †† | 1 day – 4 yrs | 91 | 0 | 0 | – |

* GMT – geometric mean titre.
** Two or more congenital deformities.
† N.V. = Not Valid.
†† Include microcephaly (32), convulsions (38), cerebral palsy (16), hydrocephaly (5).

On the other hand, congenital rubella was not found important as a cause of neonatal jaundice (NNJ) in infants three-weeks-old and under (0.9%) nor was it important in causing CNS defects, as results were negative in all the 91 infants with CNS defects examined. Of these, 32 had microcephaly. Only two or 4.1% of children above one year of age with mental retardation were retrospectively diagnosed as rubella cases, both of whom were not described as microcephalic.

Most of the infants with congenital heart disease (usually VSD) also had cataract (mainly bilateral). The CRS cases had two or more defects which sometimes included rash, hepatomegaly and cases described as 'small for gestational age' or 'failure to thrive'.

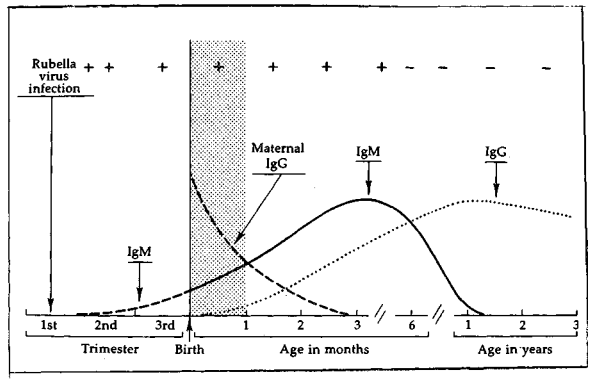


**Fig. 1 Schematic illustration of the pattern of viral excretion and antibody response in congenital rubella (from S. Krugman and R. Ward, *Infectious Diseases of Children and Adults* 5th ed., p. 245. Mosby, St. Louis, Missouri, 1973).**

The geometric mean titres (GMT) were calculated for the HAI test but not for the HIT because most of the titres of HIT-positive sera exceeded the maximum dilution used in the test, *viz.*, 1:1,280.

The GMTs were found to be very much higher in cases of CRS (120), congenital heart disease (128), cataract (102) and mental retardation (128) compared with the normal (24). In the children with hepatomegaly (49) and deafness (39), the GMT was also raised but not as markedly.

## DISCUSSION

The rationale for the scheme of testing is explained in the following. As rubella babies show no immunological tolerance they are capable of synthesizing rubella antibodies quite normally and begin to do so even before birth.[4] The specific IgM which they synthesize *in-utero* persists in their sera for about four to seven months after birth. Maternal IgG usually disappears totally by the sixth month of age. Dudgeon and co-workers[4] found that postnatal rubella is usually acquired at age five years and above and that normal children during the ages from six months to five years are largely sero-negative. Any IgG antibodies detected between six months to five years may thus be regarded as those having been synthesized by the infant soon after birth due to intra-uterine infection, especially in the absence of a history of post-natal rubella. (Fig. 1). Hence, their presence during this period serves as a means of retrospective diagnosis of congenital rubella.

Intra-uterine infection with the rubella virus may, therefore, be diagnosed by the detection of rubella-specific IgM in sera of infants aged four months and under, and IgG in sera of children six months to four years of age.

It is obvious from the foregoing results that a significantly high percentage of Malaysian children with CRS (87.3%), congenital heart disease (71.0%), congenital cataract (64.0%) and deafness (60.6%) have serological evidence of intra-uterine rubella infection. Gumpel *et al.*,[5] also found that more than 60% of deafness was due to congenital rubella. Rash (purpuric and petechial) due to rubella was encountered in 30.8% of 26 infants examined. Mental retardation of children with congenital rubella is not common although the rate (4.1%) is slightly higher than that in normal children (1.3%). It has been reported as uncommon in congenital rubella (0.7% to 1.6%) by other workers as well.[6]

Although only 60–64% of Malaysian women of childbearing age were considered immune, having detectable HAI antibody titres at eight or higher in their serum[1,7] outbreaks of rubella in Malaysia

have not reached the epidemic proportions as those encountered in the USA, Europe, United Kingdom, Australia and Canada before the rubella vaccination programmes were instituted. However, in recent years, the outbreaks of rubella in Malaysia have become more frequent and widespread especially in institutions, factories and military camps.[8,9] Congenital rubella, therefore, continues to take its toll of infants and toddlers and leaves its victims seriously handicapped throughout their lives, thus incurring high government expenditure in its attempts to treat and rehabilitate them. Pongpanich[10] in Bangkok reported a death rate of 46% of children born with congenital heart disease, and over 90% of these occurred in the first year of life.

The most vulnerable group is, of course, the susceptible pregnant women particularly those whose occupations bring them into contact with infected cases. An early vaccination programme aimed at reducing the risk in this group is thus highly recommended.

## ACKNOWLEDGEMENTS

The author is most grateful to all the paediatricians and ENT specialists throughout East and West Malaysia; the staff of the Chinese Maternity Hospital, Kuala Lumpur, for their invaluable and vital participation in this project. Thanks go also to the Director of the IMR for his kind permission to publish this paper. The technical assistance given by Puan Hazizah Abdul Hamid and Encik Zainal is much appreciated.

## REFERENCES

1 Tan Dora S K, Cheah W, Sukumaran K D, Stern H. The 'TORCHES' (Congenital diseases) Programme 1. In women of child-bearing age. *Singapore Med J* 1976; 17: 207-210.

2 Van der Logt J T M, Van Loon A M, Van der Veen J. Haemadsorption Immunosorbent Technique for determination of rubella immunoglobulin M antibody. *J Clin Microbiol* 1981; 13: 410-415.

3 Lennette E H, Schmidt N J, Magoffin R L. The hemagglutination-inhibition test for rubella. Comparison of its sensitivity to that of the neutralisation, complement fixation and fluorescent antibody tests for diagnosis of the infection and determination of immunity status. *J Immunol* 1976; 99: 785-793.

4 Dudgeon J A, Butler N R, Plotkin S A. Further serological studies on the rubella syndrome. *Brit Med J* 1964;2: 155-160.

5 Gumpel S M, Hayes K, Dudgeon J A. Congenital perceptive deafness: role of intrauterine rubella. *Brit Med J* 1971; 2: 300-304.

6 Editorial. The effects of German measles in pregnancy: an asssessment. *Med J Aust* 1965; 1: 864.

7 Lam S K. The seroepidemiology of rubella in Kuala Lumpur, West Malaysia. *Bull Wld Hlth Org* 1972; 47: 127-129.

8 Annual Report of the Institute for Medical Research, 1982, pp. 96.

9 Annual Report of the Institute for Medical Research, 1983, pp. 117.

10 Pongpanich B. Congenital heart disease in infants. Diagnosis and management. *J Paediat Obs Gynae* 1982; 1: 9-12.