

# Rubella Virus

Dr. Ommar Swe Tin  
Consultant Microbiologist  
Measles/Rubella Section  
National Health Laboratory

# The regional goal

66<sup>th</sup> Meeting of the SEAR Regional Committee in September 2013 in New Delhi resolved to:

Adopt the goal of measles elimination and Rubella/Congenital Rubella Syndrome (CRS) control in the South-East Asia Region by 2020

# Rubella (German measles)

- Member of the genus Rubivirus of the family Togaviridae
- non-arthropod borne
- RNA Virus ( mean dia of 58nm with a 30nm core)
- Lipoprotein envelop with projections
- Icosahedral symmetry

# Clinical and Virological Features

- Infects susceptible individuals via respiratory route
- Nasopharyngeal secretions- principle source
- Primary replication---epi cells of nasopharynx
- IP-14-21 days
- Viremia-widespread dissemination of the virus (blood, nasopharynx, urine, stool, synovial fl, skin, cervix, & L/N)
- Joint symptoms-commonest complication, appear soon after the rash faded, lasts for 3-4 days

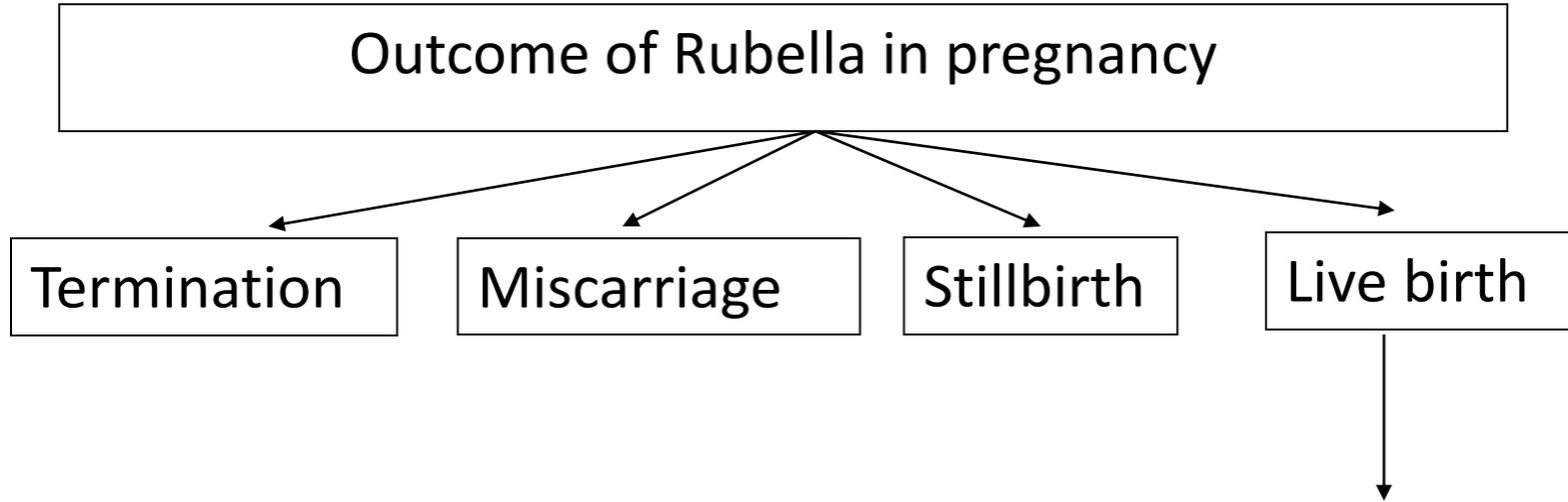
# Clinical and Virological Features contd

- Patients- infectious for 3 wks----nasopharyngeal excretion may occur up to a week before the onset of rash & for 7-10 days thereafter
- Viremia is present about a week before the onset of rash, and end as rubella Ab develop
- 25%- inapparent infection
- Typical rubelliform rashes may result from infection with enteroviruses, human parvovirus B19 & some arboviruses (Chikungunya)

# Rubella



# Why is rubella infection so concerning ?



1. Congenital Rubella Syndrome
2. Congenital Rubella Infection
3. Normal

# What is Congenital Rubella Syndrome (CRS)?

- A sequel of rubella infection in pregnancy
- Associated with Infection early in pregnancy
  - Weeks 1- 10 – 90% CRS\*
  - Weeks 11-12– 33%
  - Weeks 13-14– 11%
  - Weeks 15-16– 24%
  - Weeks  $\geq$  17– 0%

\* Miller E, Craddock-Watson JE, Pollock TM. Consequences of confirmed maternal rubella at successive stages of pregnancy. Lancet. 1982 Oct 9;2(8302):781-4. PubMed PMID:6126663.

The purpose of rubella vaccination program is thus prevention of congenital rubella infections which can lead to fetal deaths/loss, pre-mature delivery or CRS

# Congenitally Acquired Infection

- Rubella in pregnancy--fetal death and spontaneous abortion or delivery of a severely malformed infant, an infant with minimal damage or a healthy infant
- Outcomes depend on gestational age at which maternal infection occurs
- First 8 weeks of pregnancy- spontaneous abortion in 20% of cases
- 13<sup>th</sup>-16<sup>th</sup> weeks of gestation- 17% of infant may develop deafness & retinopathy

# Congenitally Acquired Infection contd

- Rubella virus can be recovered from most infants with severe congenitally acquired rubella at birth
- 3 months of age----50-60% of nasopharyngeal secretions
- 9-12 months of age---10%
- Delayed manifestation- diabetes mellitus & other endocrinopathies, sensory neural deafness, glaucoma and progressive panencephalitis

# How does CRS present clinically?

Organ specificity generally related to stage of gestational infection.

## **PERMANENT**

- Hearing Impairment
- Ophthalmologic
  - Cataract, Microphthalmia, Retinopathy, Glaucoma
- Heart defects
  - Patent Ductus Arteriosus
- Microcephaly
- Developmental Delay

## **TRANSIENT**

- Thrombocytopenia
- Jaundice
- "Blueberry muffin" appearance
- Hepatosplenomegaly
- Bone lucencies

## **DELAYED**

- Endocrinopathies
- Progressive auditory or ocular dysfunction

# Laboratory Diagnosis

- Virus Isolation

- confirmation of congenitally acquired rubella

- determining the duration of virus excretion in infant with congenital rubella

- Specimens– nasopharyngeal secretion, blood, urine, stool, cataract material, lens fluid, tears, CSF, amniotic fluid, placenta & fetal t/s , autopsy t/s

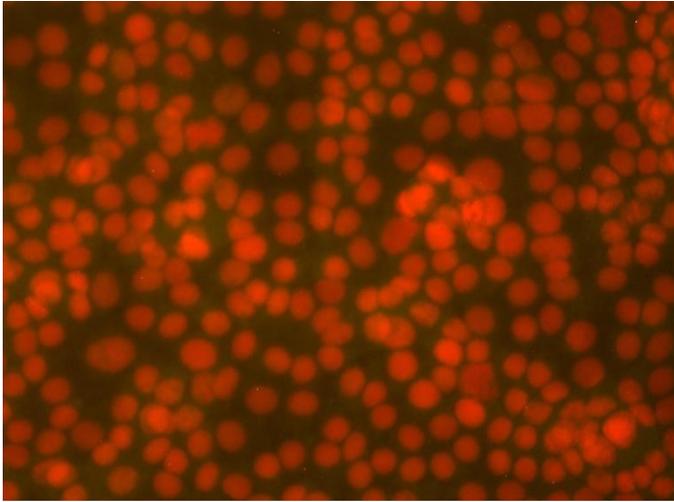
# Laboratory Diagnosis contd

- Inoculation of cell culture
  - RK13 (Rabbit Kidney cell line)
  - SIRC (Rabbit Cornea cell line)
  - Vero (Continuous Monkey cell line)
  - Characteristic CPE – a/f 2 weeks

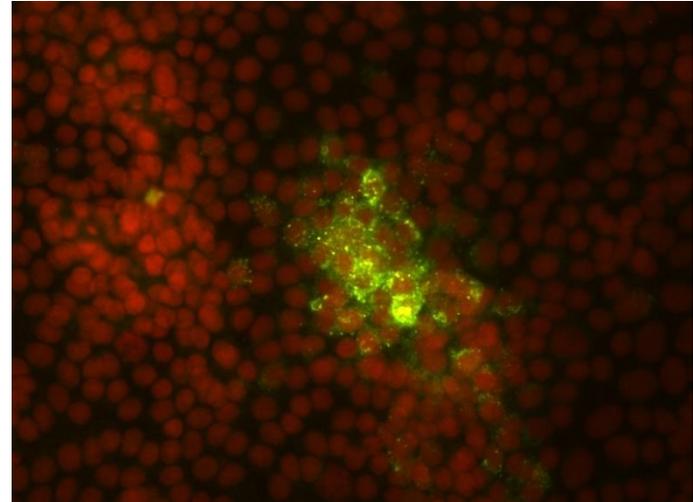
# Rubella virus: cytopathic effect (CPE) from clinical samples

- Unlike measles virus, CPE from clinical samples on the first cell culture passage is extremely rare.
- In fact, even after 3 passages, CPE cannot usually be detected.
- Therefore, alternate methods of virus detection are necessary in the case of rubella virus:
  - Immunofluorescence Assay (IFA)
  - Immunocolorimetric Assay (ICA)
  - RT-PCR

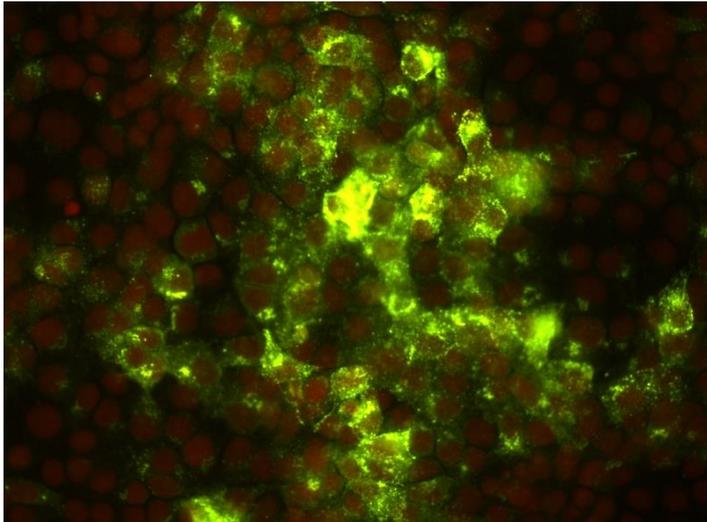
# Rubella Virus IFA Detection Results



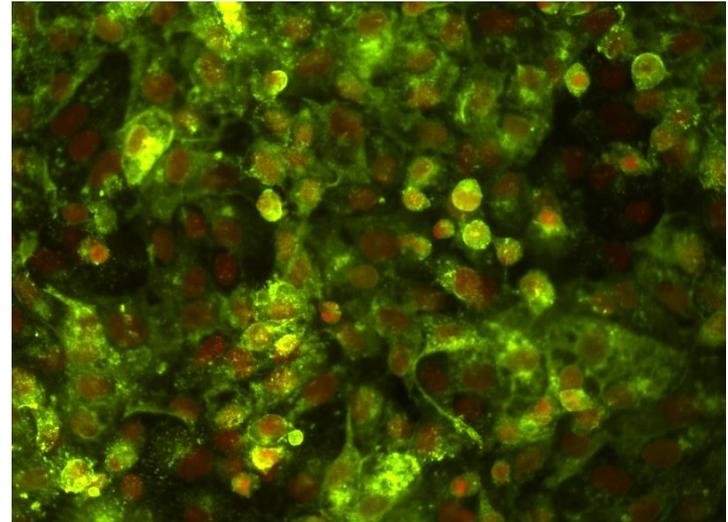
**Negative Control**



**Clinical sample – acute case**



**Clinical sample – CRS case**



**Positive Control – RA27 vaccine**

# Laboratory Diagnosis contd

- Detection of Viral Antigens and Nucleic Acid
  - IIF
  - PCR

# Laboratory Diagnosis contd

- Serological Test- detection of rubella Ab (IgM & IgG)
  - Single Radial Haemolysis (SRH)
  - Enzyme Immunoassay
  - Latex agglutination

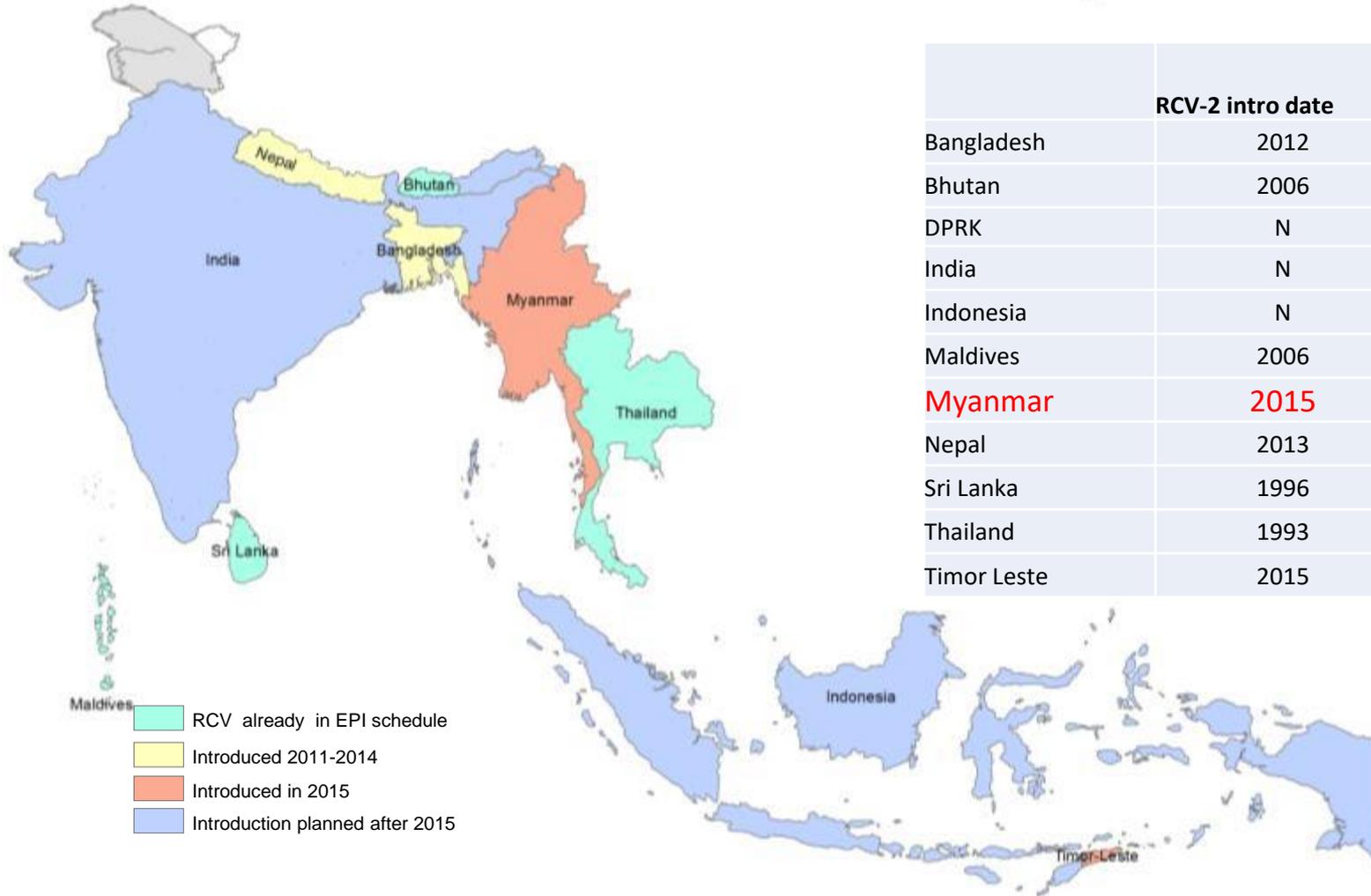
# Epidemiology

- world wide
- endemic in temperate climates
- seasonal peaks during spring and early summer
- 80-85% of women of child bearing age were immune

# Prevention

- MMR Vaccination

# Rubella-containing vaccine introduction in SEAR, 2015

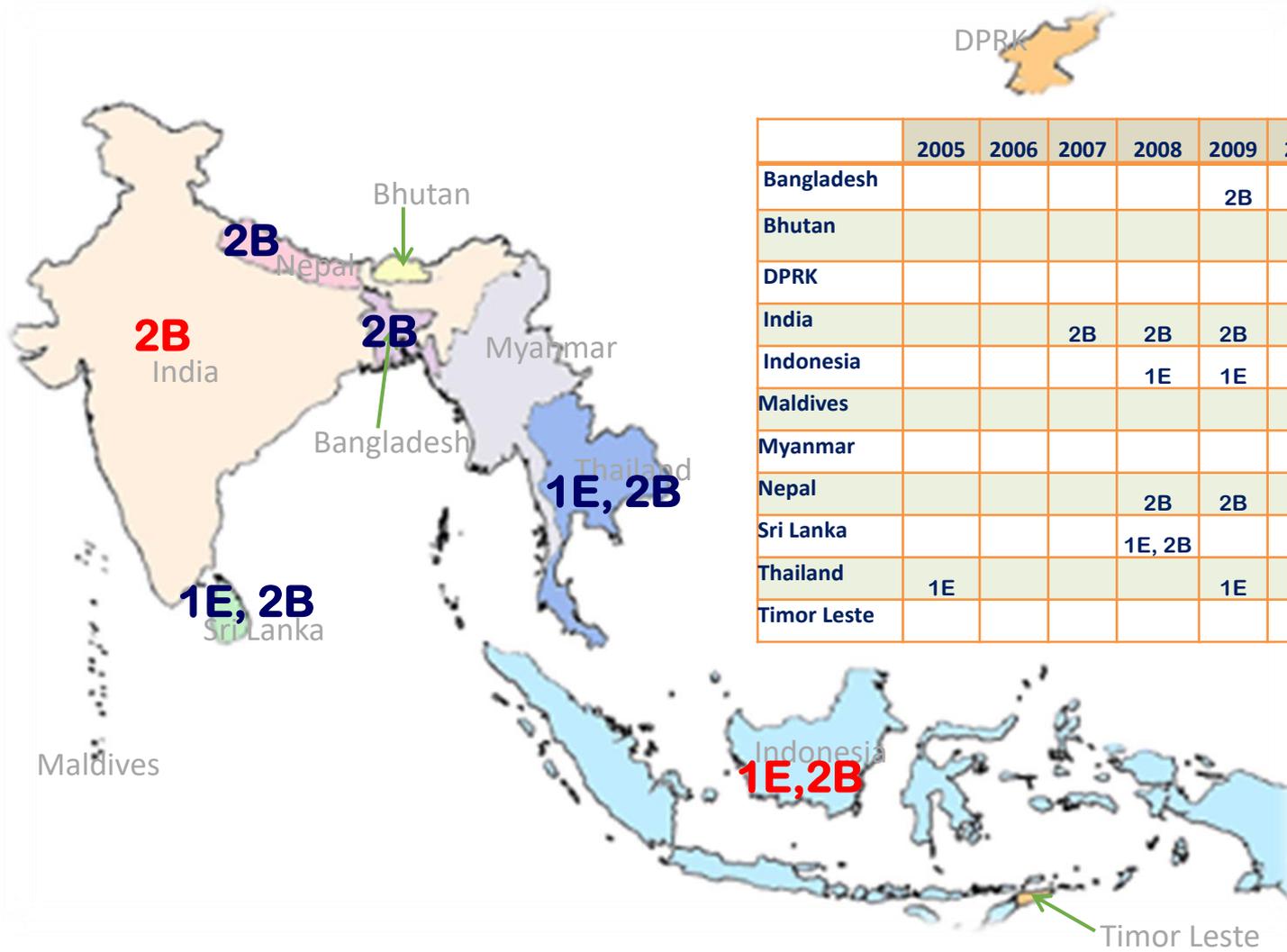


	RCV-2 intro date	Remarks
Bangladesh	2012	
Bhutan	2006	
DPRK	N	
India	N	2018
Indonesia	N	2018
Maldives	2006	
<b>Myanmar</b>	<b>2015</b>	
Nepal	2013	Sept-15
Sri Lanka	1996	
Thailand	1993	
Timor Leste	2015	Nov-15

 RCV already in EPI schedule  
 Introduced 2011-2014  
 Introduced in 2015  
 Introduction planned after 2015

- All countries are expected to introduce RCV by end 2018.

# Rubella genotype distribution in SEAR between 2005 - 2015

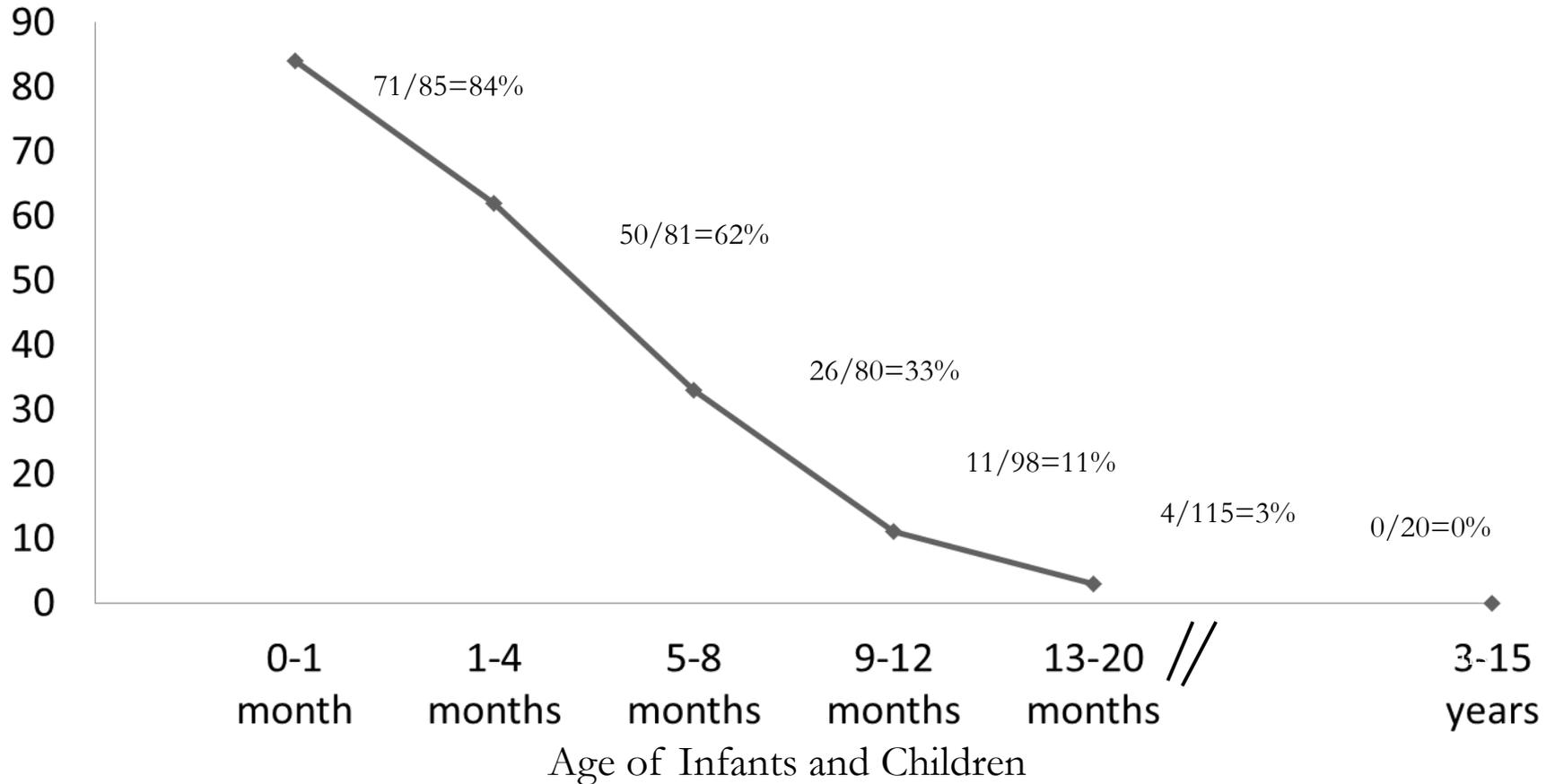


	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Bangladesh					2B						
Bhutan											
DPRK											
India			2B	2B	2B						
Indonesia				1E	1E	1E	1E	1E, 2B	1E, 2B		
Maldives											
Myanmar											
Nepal				2B	2B	2B		2B			
Sri Lanka				1E, 2B			2B	2B			
Thailand	1E				1E	2B	2B	2B	2B		2B
Timor Leste											

\*data until 31 March 2015.

# Infection Control Measures is a challenge

Incidence of Virus Excretion by Age in Infants and Children with CRS



# Infection Control Measures- Whose role is it ?

- Clinicians Vs Surveillance program
- Child shedding virus for at least 12-15 months of age can be a source of another outbreak
- Health care workers not immune to rubella could be susceptible
  - More worry of the pregnant nursing and other female staff
- Many EPI program do not offer RCV to health care workers and adults
- Viral culture methods not readily available so can't measure infectivity of infant, so infection control measures must remain in place

# What could be Key indicators for CRS surveillance ?

Criteria	Indicator	Threshold
Reporting rate	Annual rate of suspected CRS cases by country	≥1 per 10 000 live births
Adequate investigation	% suspected CRS cases with the following 8 data points completed: name and/or identifier, place of residence, sex, date of birth, date of reporting, date of investigation, date of specimen collection, and vaccination history of mother; also clinical examinations for deafness, blindness, and congenital cardiopathy.	≥80%
Lab Confirmation	% suspected cases with adequate blood specimen	≥80%
Viral detection	% confirmed cases with adequate specimen analyzed for virus detection/isolation	≥80%
Monitoring viral excretion	% confirmed cases with at least 2 negative tests for virus detection/isolation, after 3 months of age, with 1-month lapse between tests	≥80%

# WHO CRS related definitions

**Suspected CRS case:** Any infant less than one year of age in whom a health worker suspects CRS.

A health worker suspects CRS for infant aged 0-11 months with heart disease and/or suspicion of hearing impairment and/or one or more of the following eye signs: white pupil (cataract), or larger eye ball (congenital glaucoma) or pigmentary retinopathy.

Or when an infant's mother has a history of suspected or confirmed rubella during pregnancy, even when the infant shows no signs of CRS.

# WHO CRS related definitions

## Clinically-confirmed CRS:

An infant in whom a qualified physician detects at least two of the complications listed in (a) below or one in (a) and one in (b):

- (a) cataract(s), congenital glaucoma, congenital heart disease, loss of hearing, pigmentary retinopathy
- (b) purpura, splenomegaly, microcephaly, mental retardation, meningoencephalitis, radiolucent bone disease, jaundice with onset within 24 hours after birth

# WHO CRS related definitions

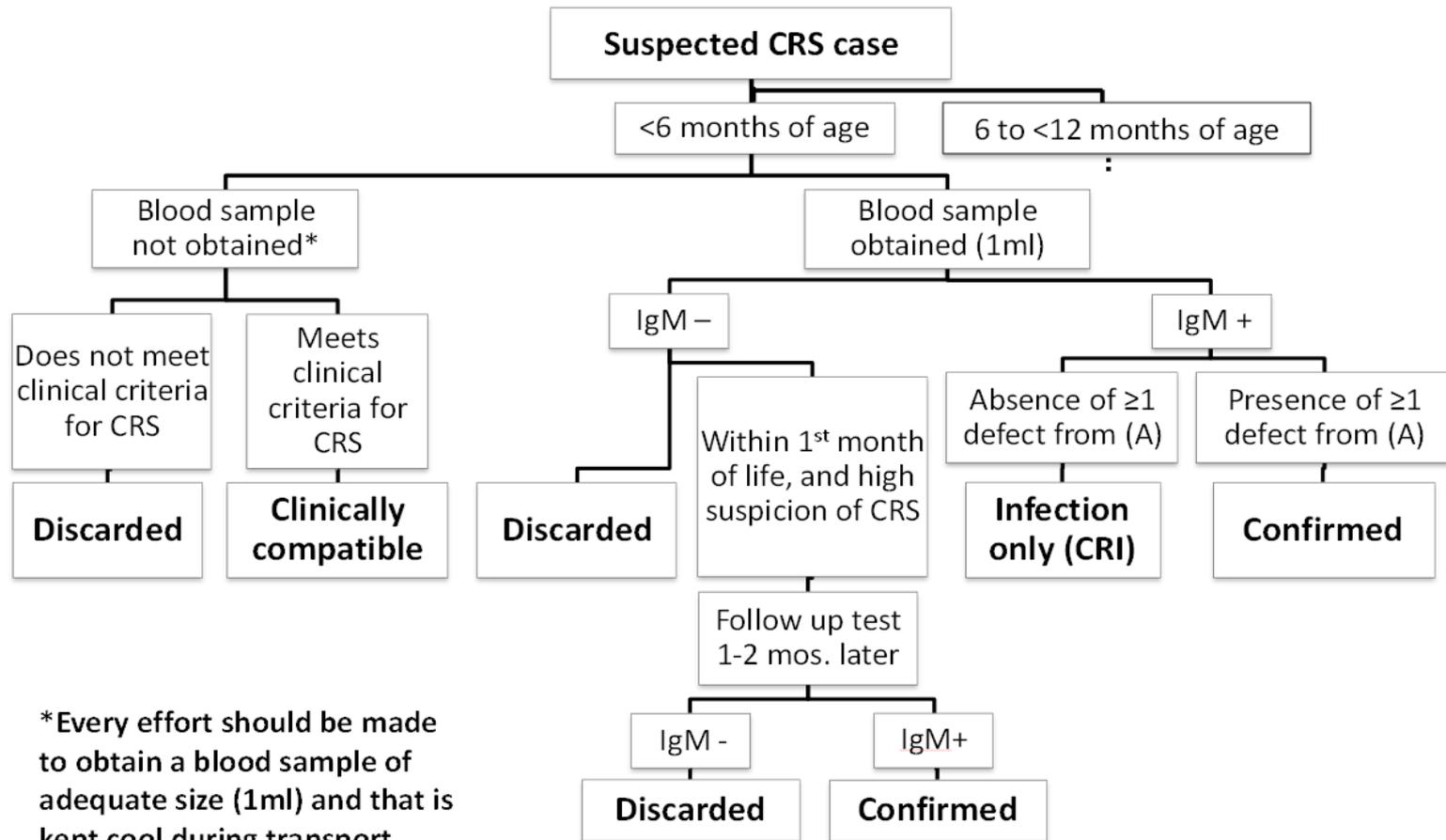
## Laboratory-confirmed CRS:

- An infant who is a suspected case (who has 1 condition from group A) who meets the laboratory criteria for CRS case confirmation.
- An infant with clinically compatible CRS who has:
  - Positive blood test for rubella-specific IgM
    - 100% positive at 0-5 months and 60% positive 6-11 months
  - Persistent rubella-specific IgG beyond 3-6 months
  - Virus detection by culture or RT-PCR

# Criteria for Laboratory Confirmation of CRS

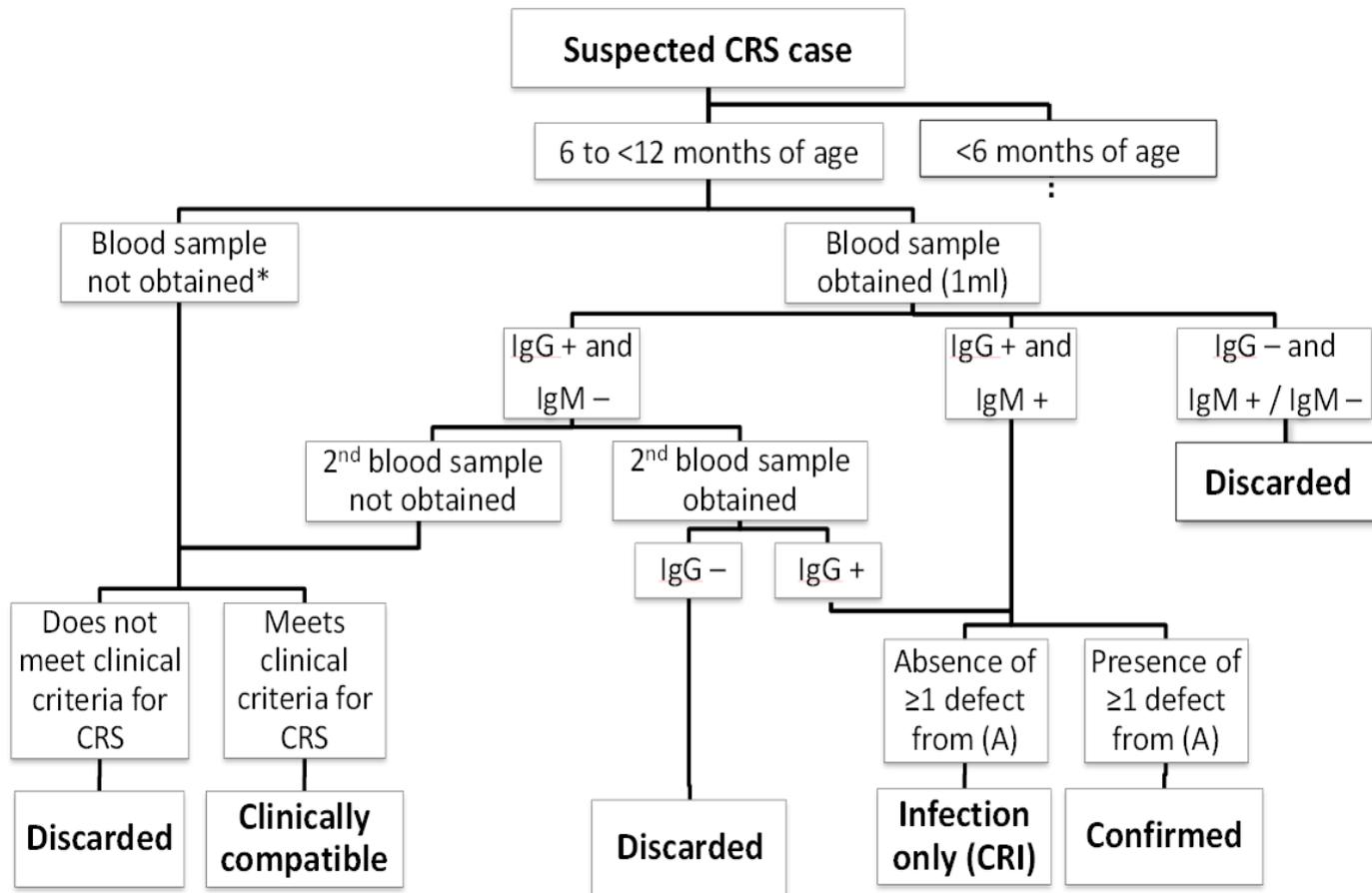
- Rubella **IgM antibody** detected, or
- Sustained rubella **IgG antibody** level as determined on at least two occasions between 6 and 12 months of age in the absence of receipt of rubella vaccine; or
- Rubella **virus detection** (e.g. nucleic acid detection by RT-PCR or rubella virus isolation) in an appropriate clinical sample (best results come from throat swabs, but nasal swabs, blood, urine, or cerebrospinal fluid specimens are also acceptable).

# Flow chart of classification of CRS cases depending on age group (< 6 months)

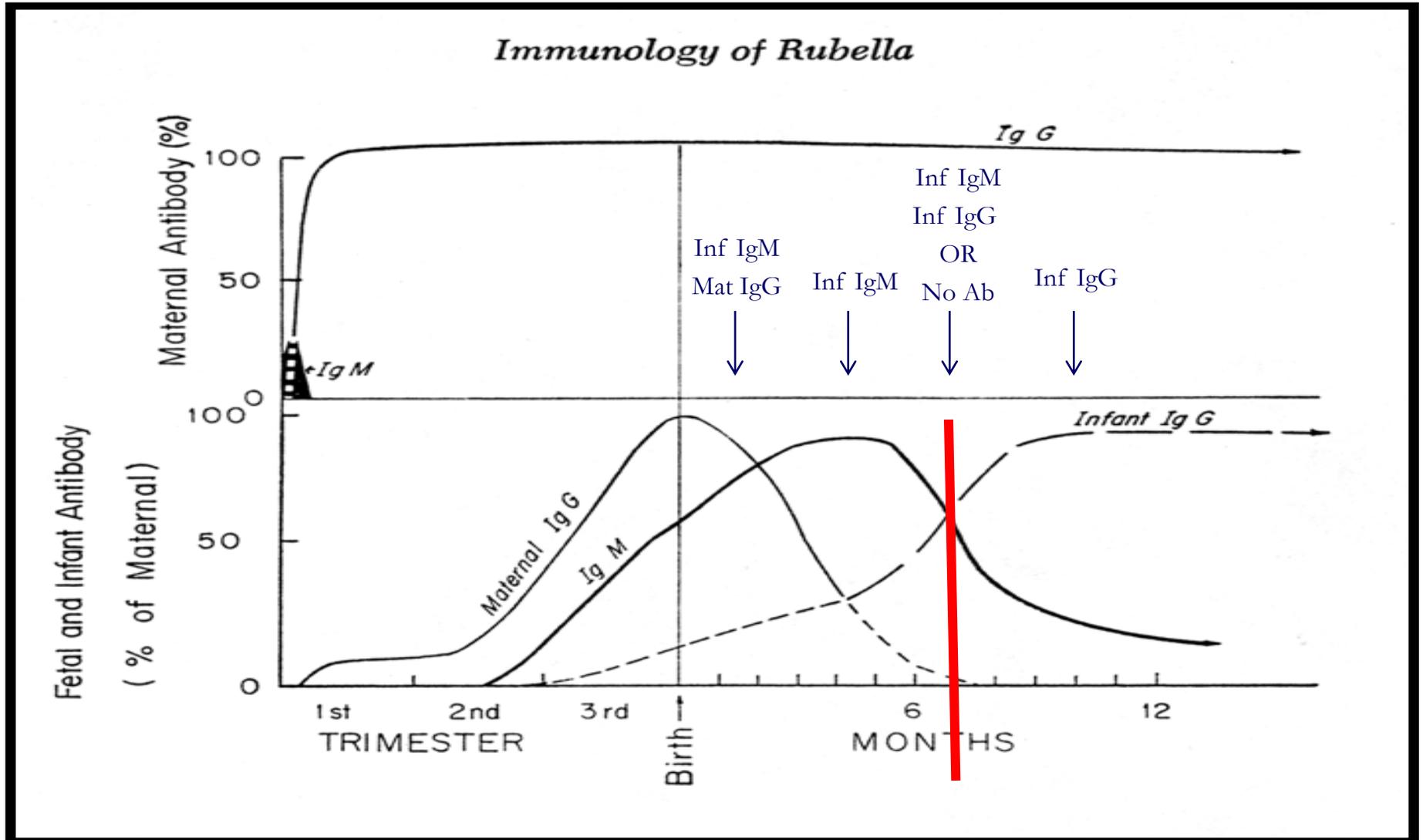


\*Every effort should be made to obtain a blood sample of adequate size (1ml) and that is kept cool during transport

# Flow chart of classification of CRS cases depending on age group (6 to < 12 months)



# Immune Response to Rubella Infection in Mother and Child



# Infection Control Issues

- Infants with CRS may shed Rubella virus for up to one year and have been the cause of Rubella outbreaks
- Only persons immune to Rubella should have contact with these infants
- It is important to continue testing the infant for virus throughout the first year of life so that infection control measures can continue until virus shedding stops
- This has to be confirmed by two negative results of viral testing of specimens obtained one month apart from infants at least three months of age

# Hospital Guidelines for Infants with CRS

- Guidelines for Isolation Precautions in Hospitals\*
  - CRS - Contact Isolation
    - precautions during any admission until 1 year of age, unless nasopharyngeal and urine cultures are negative for virus after age 3 months two times.
- Health Care Worker persons taking care of the infant are rubella - immune, vaccinate those that are not immune

# Guidelines for Caring for Infants Outside the Hospital

- Make sure persons taking care of the infant are rubella - immune, vaccinate those that are not immune
  - All pregnant women who have contact with the infant should be rubella immune

# Challenges to Infection Control Measures

- Health workers not immune to rubella or don't know status
  - IgG testing not available to check immunity
  - Rubella vaccine not available
  - No emphasis made on ensuring immunity in HW
  - recommendation (November 2013) – health workers must be immune to both measles and rubella (when rubella vaccine introduced)
- Viral culture methods not readily available so can't measure infectivity of infant so infection control measures must remain in place for 12 months

*Thank you*