

Congenital Rubella Syndrome – Is it Possible to Eliminate?

HASINA IQBAL¹, KAZI TAIB MAMUN², NABEELA MAHBOOB³,
SABRINA AFRIN⁴, HASNATUL JANNAT⁵

Abstract:

Congenital rubella syndrome (CRS) is one of the most devastating congenital infections and yet the only one which is vaccine preventable. Rubella remains an important pathogen globally with approximately 100,000 cases of congenital rubella syndrome estimated by World Health Organization (WHO) to occur each year. It is a public health challenge for clinicians and policymakers across the developing world including Bangladesh. The clinical manifestations of CRS in newborn are a spectrum of congenital defects such as growth retardation, cardiac defects, cataracts, and hearing impairment. The development of vaccines and implementation of vaccination strategies have substantially reduced the incidence of the disease and in turn of CRS in developed countries. In Bangladesh CRS is still an under-recognized public health problem. Therefore, routine vaccination and other preventive strategies should be taken maintained and surveillance studies should be conducted to eliminate CRS from our country.

Introduction:

Rubella, also known as German measles, is a viral illness characterized by maculopapular rash, lymphadenopathy, and fever. It is a highly contagious but generally mild disease, without consequences in most cases. However, maternal infection during the first trimester of pregnancy can cause a fetal malformation syndrome called congenital rubella syndrome¹. Therefore, it remains a public health problem in a significant number of countries. Global health experts encourage use of rubella vaccination, with the primary aim of preventing CRS. While large-scale rubella vaccination during the last decade has drastically reduced or eliminated both the virus and CRS in many developed and in some developing countries. But some countries have not yet incorporated rubella vaccine into their immunization schedule. As a result, through travel and migration, rubella has been imported into countries that had successfully eliminated the virus, leading to outbreaks and the reestablishment of transmission². WHO

recommends that all the countries that have not yet introduced rubella vaccine, and are providing two doses of measles vaccine using routine immunization and/or supplementary immunization activities should consider the inclusion of Rubella Containing Vaccine (RCV) in their immunization programme³.

Historical background of rubella

The clinical manifestations of the disease were described by two German physicians, De Bergan in 1752 and Orlov in 1758⁴. At that time, it was considered to be a derivative of measles and because of the strong German influence, the illness became popularly known as German measles. The disease was renamed rubella (from the Latin for reddish things) in 1866 by Henry Veale, a British Army surgeon; who found the original term “harsh and foreign to our ears”⁵. The notion that rubella was only a mild illness of children was dispelled in 1941, when Norman Gregg, an Australian ophthalmic surgeon, reported the devastating teratogenic effects of the virus⁶.

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1. Associate Professor, Department of Microbiology, Popular Medical College, Dhaka.
 2. Research Investigator, ICDDR, Dhaka.
 3. Assistant Professor Department of Microbiology, Popular Medical College, Dhaka.
 4. Lecturer, Department of Microbiology, Popular Medical College, Dhaka.
 5. Lecturer, Department of Microbiology, Popular Medical College, Dhaka.

Address of Correspondence: Dr. Hasina Iqbal, M. Phil (Microbiology), Associate Professor, Department of Microbiology, Popular Medical College, Dhaka. Email: dr.hasinaiqbal@gmail.com. Contact no.: 01711589374

Epidemiology of CRS

Before the introduction of rubella vaccine in 1969, the global incidence of Congenital Rubella Syndrome (CRS) ranged from 0.8-4/1000 live births during rubella epidemics to about 0.1-0.2/1000 live births during endemic periods⁷. During 1969-1976, reported rubella cases decreased from 57,600 to 12, 400⁸. The number of reported rubella and CRS cases decreased after these programs were implemented, from 20,395 rubella cases and 29 CRS cases in 1977 to 752 rubella cases and 2 CRS cases in 1984. In 1988, 225 cases of rubella were reported; the fewest since national reporting began⁹. According to the World Health Organization (WHO), an estimated 100,000 infants were affected each year worldwide. Annual number of reported rubella cases in Bangladesh was 13,464 in 2009 and 13,125 in 2010¹⁰.

About the Pathogen

Rubella virus was first isolated in 1962 by Parkman and colleagues and by Weller and Neva¹¹. It belongs to the *Togaviridae* family and is the sole member of the *Rubivirus* genus. It is the causative agent of rubella disease or so-called "German measles."¹² Rubella virus is an enveloped virus, circular or oval in shape and 60 nm in diameter. The virion is composed of a capsid core containing a single copy of genomic RNA. The outer membrane is a lipid bilayer containing specialized glycoproteins (E1 and E2)¹³. The E1 protein is responsible for receptor-mediated endocytosis and is the immunodominant antigen¹⁴. The measurement of antibodies against the neutralizing domain of E1 can be used as a correlate of protection against rubella virus¹⁵. The E2 protein is membrane bound and forms connections between rows of E1 proteins. The rubella E1 protein binds to myelin oligodendrocyte glycoprotein (MOG)¹⁶. The ability of rubella to infect the placenta and the neurological pathologies associated with CRS, coupled with the presence of MOG on both tissue types, supports the hypothesis that MOG is a potential receptor for rubella.

Pathophysiology of Rubella

Rubella commonly occurs in children and young adults. Transmission is by direct droplet contact from nasopharyngeal secretions, replicates in the lymphoid tissue of the upper respiratory tract and spreads hematogenously¹⁷. The first clinical manifestation of rubella is usually the appearance of a maculopapular

rash some 16 to 20 days after exposure. The rash first appears on the face and then spreads over the trunk and later over the extremities. Other symptoms typically include low-grade fever, lymphadenopathy, sore throat, and general malaise. Lymphadenopathy can be characteristic, involving the posterior cervical and occipital nodes, which can persist after the rash has resolved².

Possible complications of rubella are transient joint involvement such as arthritis and arthralgia being the most frequent especially in female¹⁸. More serious complications include thrombocytopenic purpura and postinfectious encephalopathy or encephalomyelitis which are very occasionally associated with postnatally acquired rubella¹⁹. A rare and usually fatal neurodegenerative disorder termed progressive rubella panencephalitis has also been reported as a late complication of childhood rubella²⁰.

Teratogenicity

Rubella can also be transmitted from infected pregnant women to their fetus. Maternal rubella infection can result in miscarriage, fetal death, stillbirth, or infants with a constellation of congenital malformations known as Congenital Rubella Syndrome (CRS)²¹. Manifestations of CRS encompass cardiac, cerebral, ophthalmic and auditory defects²². The risk of congenital defects varies from 10% to 90% depending on the gestational age of the fetus at the time of infection. Rubella infection when occurs just before conception or during the first 8–10 weeks of gestation, it may cause multiple fetal defects in up to 90% of cases, including fetal wastage or stillbirth²³. The risk of birth defects declines with infection later in gestation, and fetal defects are rarely associated with maternal rubella after the 16th week of pregnancy, although sensorineural hearing deficit may occur with infection as late as week 20²⁴. The defects associated with CRS most commonly affect the eyes e.g., cataracts, microphthalmia, glaucoma, pigmentary retinopathy, chorioretinitis. CRS can also affect hearing e.g., sensorineural deafness, the heart e.g., peripheral pulmonary artery stenosis, patent ductus arteriosus or ventricular septal defects, and the brain e.g., microcephaly. Those who survive the neonatal period may face serious developmental disabilities like visual and hearing impairments and have an increased risk for developmental delay, including autism. In fact, rubella is and should be considered a vaccine-

preventable cause of autism²⁵. Congenital rubella infection has also been associated with increased risk of endocrinopathies such as thyroiditis and insulin-dependent diabetes mellitus with associated long-term effects²⁶. Finally, a progressive encephalopathy resembling subacute sclerosing panencephalitis has also been observed in patients with CRS²⁷.

Global situation of Immunization

Rubella is a vaccine-preventable infection and considered to be potentially eradicable. Preventing the adverse pregnancy outcomes is the focus of rubella vaccination programs. The universal immunization of infants, adolescent girls and adult women is the most effective approach to eliminate rubella and CRS²⁸.

Rubella virus is a candidate for global eradication because human are the only known host and also for available safe and highly effective (> 95%) vaccines following a single dose²⁹. The recommended vaccine is a live attenuated viral rubella vaccine given by the intramuscular or subcutaneous route as monovalent, MR (measles-rubella) or MMR (mumps-measles-rubella)³⁰. The Advisory Committee on Immunization Practices (ACIP) recommends administration of the first dose of Rubella vaccines at 12–15 months of age but may be offered to children as young as 9 months, and administration of the second dose of MMR at 4–6 years of age. Revaccination is intended to sero convert those who do not respond to the first dose³¹.

Rubella incidence was greatest among preschool and elementary school children before rubella vaccine was licensed during 1969. Therefore, vaccination campaigns initially targeted children in kindergarten and the early grades of elementary school, with the aim of interrupting circulation of the virus and eliminating the risk for exposure among susceptible pregnant women. Rubella outbreaks continued to occur among older adolescents and young adults of military camps, high schools, colleges, and universities). During 1969-1976, reported rubella cases decreased from 57,600 to 12, 400⁸. In 1977, ACIP modified its recommendations to include the vaccination of susceptible post pubertal girls and women. During the same year, National Childhood Immunization Initiative was undertaken which sought to immunize greater than 90% of the nation's children against all vaccine-preventable diseases³².

Vaccinating susceptible post pubertal females confers individual protection against subsequently acquiring rubella infection during pregnancy, which in turn prevents infection of the fetus and consequent congenital rubella injury³³. Rubella vaccination of pregnant women should be avoided, and pregnancy should be avoided within 1 month of receiving the vaccine due to the risk of vaccine-induced CRS³⁴. Vaccination is also recommended for susceptible individuals in high-risk groups such as college students, health-care workers, and military personnel³⁵.

Despite the expected economic and medical benefits, only 116 (60%) of the 192 countries reported to the WHO in 2004 to have a rubella immunization program. Almost all of these countries offer the first dose of vaccine prior to age 24 months³⁶ and use live attenuated RA27/3 vaccine³⁷. This is an impressive improvement from 1996, when only 78 countries had such a program.

Estimates suggest that the burden of CRS in regions that had not yet introduced rubella-containing vaccination by 2010 may be very high. Very few countries in Africa, South East Asia and the Western Pacific regions had introduced rubella-containing vaccination by the year 2010 and therefore the current burden of CRS in these settings was likely to be similar to that estimated for 1996³⁸.

Three of the six WHO regions had set control or elimination targets for rubella³⁹. America targeted rubella and CRS elimination by 2010 and achieved it in 2009. The European Region had a target of rubella elimination by 2015 and the Western Pacific Region aimed to have significantly accelerated rubella control and CRS prevention to <1 CRS case per 100,000 live births by 2015. The African, Eastern Mediterranean and South-East Asian Regions did not establish rubella control or elimination goals³⁸.

Progress of Bangladesh on Rubella control

Bangladesh officially launched measles-rubella (MR) vaccine on 26th September, 2012 as part of its routine immunization programme to prevent rubella infection. The vaccine was introduced in place of only-measles vaccine to children aged 9 months⁴⁰. To reduce the measles and rubella disease burden, the Expanded Program on Immunization (EPI) in Bangladesh, managed by the Ministry of Health and Family Welfare (MoHFW), funded by the Global Alliance for

Vaccines and Immunisation (Gavi) conducted a Measles-Rubella campaigns (MRC) targeting more than 52 million children aged 9 months to 14 years from 25 January to 13 February 2014. Gavi also supported a Full Country Evaluation (FCE) in Bangladesh, from 2013 to 2016, to understand and measure vaccine coverage. MR vaccination coverage in high performing division was 4% before MRC and it increased to 95% after MRC. In the low-performing division, MR coverage increased from 11 to 85% after MRC⁴¹.

Conclusion:

Congenital rubella syndrome is a devastating condition that has multiple consequences for any society, both medical and financial. The primary objective of the rubella immunization program is the prevention of CRS. The major components of the rubella and CRS elimination strategy are achieving and maintaining high immunization levels for children and adults, especially women of childbearing age; conducting accurate surveillance for rubella and CRS; and undertaking control measures promptly when a rubella outbreak occurs.

Recommendation:

To eliminate CRS and to reduce CRS related morbidities, it is crucial to ensure mass immunization, monitor the magnitude of the disease and arrange rehabilitative services.

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