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REVIEW

Rubella and the devastating effects of congenital rubella syndrome

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Abstract
Rubella virus is a vaccine preventable disease that is endemic in many countries worldwide. We appraised the prevalence and risk factors for rubella and considered the effects of congenital rubella syndrome (CRS) in children. A systematic review of relevant literature was carried out according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA). Articles were searched for through PubMed, Medline, EMBASE, Scopus, Google Scholar, web of Science, and Index Medicus. Rubella and CRS are endemic in African as well as the South-East Asian region. The current global vaccination coverage of rubella was estimated to be 70%. However, many countries in African and South-East Asia are yet to include rubella vaccination in their national immunization schedules. Mauritius and Seychelles are exceptions in Africa, while Sri Lanka and Maldives in the South-East Asian region have implemented this regimen. Globally, only the Americas has successfully eradicated rubella. It is still endemic in many African countries with devastating effects among infants and pregnant women. Cases are unabated and several children continue to suffer the consequences of CRS. Concerted efforts are needed to create awareness and galvanize support to control the incidence of rubella and CRS

Introduction

Rubella is derived from a Latin word meaning "little red". It is a medical condition caused by the rubella virus, a member of the genus *rubivirus*, family Togaviridae.[1] It is an enveloped virus which is spherical, 50-60nm in diameter and contains a positive single-stranded RNA genome that is 9.8kb in length. Five proteins are encoded in the viral genome which includes two non-structural proteins (p90 and p150) and three structural proteins [glycoproteins E1, E2 and the Capsid protein (C)].[2] Only one serotype of rubella is known but many genotypes circulate globally. This implies that naturally acquired infection or vaccination confers immunity against recurrent acute infections. The wild-type and vaccine strains of rubella can be distinguished immunologically using assays that measure avidity of how serum produced against one strain can react with the other strain (Neutralization assays).[3] Twelve genotypes (1B, 1C, 1D, 1E, 1F, 1G, 1H, 1I, 1J, 2A, 2B and 2C) and one provisional genotype (1A) of rubella have been identified.[4]

Rubella was first described in the mid-eighteenth century and is also known as German measles or three-day measles.[5] The first clinical description of rubella was made by German physician and chemist, Friedrich Hoffman in 1740. This was confirmed by de Bergen in 1752 and later by Orlow in 1758.[6] The fact that three Germans were involved with the description of Rubella led to the common name "German measles".[7] Congenital rubella syndrome (CRS) is a series of manifestations that occur in a developing foetus. CRS can occur in a developing foetus of a pregnant woman who has contracted rubella, usually in the first trimester.[1] In 1941, Australian ophthalmologist Norman McAlister Gregg successfully described the relationship between CRS and cataracts.[8] The major complication of rubella is the teratogenic effects when pregnant women contract the disease, especially in the early stage of gestation. The virus can be transmitted to the foetus through the placenta, and is capable of causing congenital defects, abortions, and stillbirth.[9] Despite various vaccination campaigns, rubella has been reported to cause congenital defects and is a cause of prenatal disability in resource limited countries. However, large numbers of rubella cases and CRS remain undiscovered in developing countries.[10] This study reviewed the incidence and geographical distribution, risk factors, transmission, elimination strategies and vaccination campaigns for rubella and CRS.

Transmission of rubella virus

Rubella is globally spread with humans being the only reservoir of the virus, transmitted by respiratory droplets either directly or through contact with contaminated surfaces (close contact is required).[11] The virus can be transmitted to the foetus through the placenta and is capable of causing congenital defects, abortions, and stillbirths.[9] Virus shedding by infected persons is mostly through nasal and throat secretions.[12] An infected person remains contagious for one to two weeks before the onset of rash, until about one or two weeks after the rash disappears. Congenitally infected neonates can shed the virus for many months after birth.[13]

Congenital rubella syndrome

Rubella virus causes CRS in the newborn, this is the most severe complication of rubella. CRS follows intrauterine infection by the virus, and this comprises cardiac, cerebral, ophthalmic and auditory defects. CRS occurs when the virus in the pregnant woman affects the developing foetus in the first three months of pregnancy.[4] The foetal defects of CRS are teratogenic because of direct viral damage of infected cells. Regardless of the mechanism, any injury affecting the foetus during the phase of organogenesis in the first trimester results in congenital organ defects.[15] The risk of vertical transmission to the foetus, and likelihood of developing CRS is determined by the gestational age at the time of maternal infection.[16] The pathogenesis of CRS begins with maternal viraemia in which vertical transmission of the virus from mother to the foetus occurs following placental infection. All organs are infected by the virus however, the response of these organs to the virus depends on the stage of foetal maturation.[17] Chronic infection of CRS in infants can persist for months to years. Infants may shed the virus through urine, blood, eye, nasal or throat secretions, and cerebrospinal fluid thereby facilitating viral transmission to susceptible persons.[11] There are

two mechanisms of viral induced foetal damage. First, cell death through mitotic disruption and apoptosis. Second, endothelial damage of small blood vessels resulting in poor organ development.[18]

If infection occurs less than 28 days before conception, the infant has a 43% chance of being affected. If the infection occurs 0–12 weeks after conception, chances increase to 51%. If infection occurs 13–26 weeks after conception, the chance is 23% of the infant being affected by the disease. However, infants are not usually affected if the virus is contracted during the third trimester, or 26–40 weeks after conception.[19] Age of pregnancy and chances of developing organ defects are summarized in the Table 1.

In considering the outcome of CRS, focus is on period (weeks) of pregnancy when maternal exposure to rubella virus occurred. Risk is higher if exposure occurs during the first trimester, or if there is no history of maternal immunization or past infection. Also, evidence of intrauterine growth retardation during pregnancy may impact negatively on CRS.[14] A classic triad distinguishes CRS from other congenital conditions, namely (1) sensorineural deafness (58% of patients), (2) congenital heart disease especially pulmonary stenosis and patent ductus arteriosus (50% of patients) and (3) eye abnormalities especially pigmentary retinopathy, cataract and microphthalmia (43% of patients).[1] Other manifestations include spleen, liver, or bone marrow abnormalities some of which may disappear shortly after birth. In addition, intellectual disability, microcephaly, eye defects, low birth weight, and thrombocytopenic purpura can occur[19] Characteristic ‘‘blueberry muffin spots’’ (purple to dark-blue macules, papules, or nodules representing extramedullary haematopoiesis) are associated with CRS.[20]

Table 1. Age of pregnancy and chances of organ anomalies[1]

Age of pregnancy	Chances of Organ Anomalies
1-8 weeks	Cardiac defects and hearing impairment, other CRS anomalies (80%)
9-12 weeks	Hearing impairment and features of CRS (50%)
13-16 weeks	CRS anomalies (30%), hearing loss is more prominent than others
>20 weeks	Changes of foetal damage are minimal or none

In the laboratory, rubella can be diagnosed by virus isolation, detection of IgG antibodies at 3, 6 and 12 months of age, identification of rubella specific hemagglutination inhibition antibodies after 9 months of age, or demonstration of rubella specific IgM antibodies. IgM is produced by the foetus and does not cross the placenta hence this is indicative of rubella. False negative results for IgM were found in 20% of infected infants before 1 month of age. If they have clinically consistent signs but test negative after birth, infants should be retested at 1 month. In the case of a false-positive result, this may be a result of rheumatoid factor, other viral infections such as Epstein Barr virus and parvovirus, or heterophile antibodies.[14] Complete blood count may reveal leucopenia and thrombocytopenia used to monitor the course of thrombocytopenia, Liver function tests such as total and direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transpeptidase (GGT) levels may reveal hepatic injury in disseminated rubella infection, especially in neonates.[21]

Distribution and spread of rubella

The burden of rubella is global and in African countries children under the age of 15 years are

commonly affected. Susceptibility to rubella is known to occur in adults as well.[22] Rubella is a vaccine-preventable disease, yet still claims an estimate of 568 lives (mostly children) worldwide each day and it is a leading cause of preventable birth defects. In 2001, the CDC established the Measles and Rubella Initiative (MRI), a global partnership working towards a measles and rubella free world.[14] Since the isolation of the virus in 1962, it has become a global problem. The severity of rubella reduced markedly in 1969 after the discovery of the rubella vaccine but minor epidemics occur every 10 years while pandemics occur every 30 years.[23] During the 1962-1965 worldwide epidemic, an estimated 12.5 million rubella cases occurred in the United States, resulting in 20,000 cases of CRS.[24] A total of 100,000 cases of CRS occur yearly.[25] In the African region, it is estimated that 38,712 cases occurred in 2010, while the global estimate was 105,391, representing 36.7% of the global burden. In 2013, the incidence of CRS was estimated to be 69/100,000 live births in Democratic Republic of the Congo corresponding to 2,886 infants (95% CI 342, 6395) born with CRS per year.[26] The number of reported cases is high in countries where routine rubella immunization is unavailable or was recently introduced. In 1990, a total of 65,591 cases of rubella was reported in Mexico[27] China is the top on the list of countries with the highest rubella cases in the world.[27] As of 2020, there were 2,202 cases that accounts for 21.6% of the world's rubella cases. Among the top 5 countries are Mozambique, India, Democratic Republic of Congo, and Nigeria which account for 65.5% (Tables. 2). According to the Uganda Demographic and Health Survey key indicators report of 2017, 25% of adolescents between 15-19 years had begun childbearing and most of them were at risk of rubella and CRS.[27] One study in Abia State, Nigeria showed an incidence of new rubella infections of 6.81/1,000,000 population in 2007 which decreased to 2.28/1,000,000 in 2009, but soared to 6.34/1,000,000 in 2011.[28]

Table 2. Countries with the highest rates of rubella from 1999-2019

Year	Nigeria	SA	DRC	China	MOZ
1999	Nil	Nil	Nil	Nil	Nil
2000	Nil	541	Nil	Nil	Nil
2001	Nil	Nil	Nil	Nil	Nil
2002	Nil	208	Nil	Nil	Nil
2003	Nil	2089	Nil	Nil	Nil
2004	Nil	612	Nil	24015	Nil
2005	Nil	428	Nil	25446	Nil
2006	Nil	Nil	207	37137	Nil
2007	466	1072	Nil	74746	Nil
2008	422	Nil	969	120354	166
2009	234	2975	110	69860	69
2010	450	Nil	130	43117	70
2011	3691	3266	318	65549	143
2012	239	2298	1860	40156	428
2013	88	103	1704	17580	127
2014	102	10	864	11793	210
2015	419	54	464	81333	Nil
2016	503	819	204	4535	Nil
2017	543	1876	Nil	1605	102
2018	4772	1213	287	3930	117
2019	1644	1370	561	32539	74

SA = South Africa; DRC = Democratic Republic of Congo; MOZ = Mozambique

Several countries in Africa have conducted rubella seroprevalence surveys. However, none has established routine surveillance for CRS despite the fact that there is paucity of data on this in the

continent.[29] Serological studies done across Nigeria have shown that rubella is endemic in Nigeria.[30] Despite the devastating consequences of this condition and the high prevalence in many African countries, screening and vaccination of women and children is neither part of antenatal schedule nor among the diseases targeted for vaccination in routine immunization in many African countries.[31]

Vaccination coverage

Rubella among infants can be prevented by vaccination. In the USA, vaccination focuses on children between 12-15 months of age, and children 4-6 years old. Immunity of women childbearing age is determined and those of childbearing age are vaccinated to prevent vertical transmission.[32] Rubella vaccine is a live-attenuated, lyophilized and exists as monovalent (rubella only), bivalent (measles-rubella combination [MR]) or trivalent measles- mumps-rubella combination [MMR].[33] In the United States, the rubella vaccination programme targeted children to reduce the spread of the infection as well as to protect pregnant women. As a result, rates of CRS decreased by about half. However, disease incidence in individuals above the age of 15 years did not fall rapidly, and it became clear that much of the transmission was from adult to adult. Thus, in 1979 greater efforts were placed on vaccination of adolescent girls and adult women.[34] Emphasis was placed on CRS being the most severe complication of rubella infection, with the aim of eradicating CRS rather than eradicating rubella.[35] From 1996 to 2009, only two countries in Africa (Mauritius and Seychelles) had introduced rubella vaccine however, all countries in the Americas and European region had introduced the rubella vaccine in their national immunization schedule in 2009.[36]

The World Health Organization recommends that (1) countries considering the introduction of rubella vaccination should have achieved ≥80% coverage with the first dose of the measles vaccine, (2) MR vaccination strategy should commence with an MR vaccination campaign targeting both sexes and a wide age range (e.g. 9 months to 15 years), (3) the vaccination campaign should be immediately followed by the introduction of either the MR or MMR vaccine into routine immunisation programme in a 2-dose schedule, and (4) the first dose of the routine immunisation schedule can be delivered at 9 or 12 months of age.[37] Of the 46 countries in the WHO African Region, 17 (37%) had estimated first- dose measles-containing vaccine coverage of 80% in 2009.[33,38] More so, 15 additional countries carried out vaccination campaigns for rubella before its introduction in the routine vaccination schedule (Botswana, Burkina Faso, Cameroon, Cape Verde, Gambia and Ghana, Kenya, Namibia, Rwanda, São Tomé and Principe, Senegal, Swaziland, Tanzania, Zambia and Zimbabwe). At the end of 2017, the vaccine was used in 162 countries with a global coverage of 52%.[39] After 13 years, there was no significant change in the number of countries administering rubella vaccine in Africa and South-East Asia hence the high incidence of rubella and CRS. In 1996, only 2 countries commenced administration of rubella vaccine in Africa, 2 in South-East Asia, 10 in the Western Pacific, 21 in the Americas, 9 in Eastern Mediterranean and 39 in Europe. In 2009, the number of countries in Africa was unchanged, with 4 countries in South-East Asia, 35 in the Americas, 15 in Eastern Mediterranean, 37 in Western Pacific and 53 in Europe.[36]

In 2015, the WHO Region of the Americas became the first in the world to be declared free of endemic transmission of rubella. This reduced the incidence of rubella and CRS in the USA is shown in Table 3. The number of countries using rubella vaccines in their national programme continues to increase. In 2018, 168 out of 194 countries had introduced rubella vaccines and global coverage was estimated at 69%. Reported rubella cases declined by 97%, from 670 894 cases in 102 countries in 2000 to 14 621 cases in 151 countries in 2018. CRS rates are highest in the WHO African and South-East Asian regions where vaccination coverage is lowest (Table 4). By the end of 2020, the rubella vaccine was introduced in 172 member states of the WHO and the global coverage was estimated at 70%.[40] Few countries in the African and South-East Asian regions currently include rubella-containing vaccination in their national immunization schedule.[41] According to WHO, the Maldives and Sri Lanka remain the only countries in the South-East Asian region to have successfully eliminated rubella.[40]

Table 3. Cases of rubella and congenital rubella syndrome in USA, 1969- 2007

Year	Number of cases	Number of deaths	CRS incidence*
1969	57686	29	31
1970	56552	31	77
1971	45086	20	68
1972	25507	14	42
1973	27804	16	35
1974	11917	15	45
1975	16652	21	30
1976	12491	12	30
1977	20395	17	23
1978	18269	10	30
1979	11795	1	62
1980	3904	1	50
1981	2077	5	19
1982	2325	4	7
1983	970	3	22
1984	752	1	5
1985	630	1	0
1986	551	1	5
1987	306	0	5
1988	225	1	6
1989	396	4	3
1990	1125	8	11
1991	1401	1	47
1992	160	1	11
1993	192	0	5
1994	227	0	7
1995	128	1	6
1996	238	0	4
1997	181	0	5
1998	364	0	7
1999	267	0	9
2000	176	0	9
2001	23	2	3
2002	18	Nil	1
2003	7	Nil	1
2004	10	Nil	0
2005	11	Nil	1
2006	11	Nil	1
2007	12	Nil	0

*Per 10,000 live births

Table 4a*:* Burden of rubella cases in WHO-AFRO, -PAHO and -EMRO regions

Year	Africa (AFRO)	Americas (PAHO)	Eastern Mediterranean (EMRO)
1999	51	58755	5775
2000	865	39228	3122
2001	1572	24614	1328
2002	2265	14644	569
2003	4835	1203	510
2004	4452	3101	8368
2005	2868	5296	14967
2006	2457	2990	3685
2007	3993	13243	12071
2008	16297	4534	2363
2009	17422	18	2030
2010	2754	17	1398
2011	16190	8	2749
2012	10850	15	1681
2013	13739	11	3904
2014	7402	10	2945
2015	5302	5	1885
2016	4157	2	1981
2017	6166	7	931
2018	11787	2	1622
2019	6027	25	2603

Table 4b: Burden of cases of rubella cases in WHO-SEA, -EURO, and - Western Pacific regions

Year	South-East Asia (SEA)	Europe (EURO)	Western Pacific
1999	5093	804567	875
2000	1165	621039	5475
2001	983	800469	7366
2002	1187	617860	3222
2003	5093	304390	5002
2004	1231	263964	27097
2005	9834	206359	28659
2006	4135	193923	42912
2007	14073	67927	85194
2008	7436	23912	126487
2009	17208	11623	73077
2010	15275	10551	45966
2011	9810	9677	76022
2012	6877	30579	44275
2013	10434	39391	33677
2014	9690	653	12814
2015	6515	655	9398
2016	10361	1471	5446
2017	4386	842	4061
2018	4533	800	7262
2019	4537	671	35273

Eradication of rubella

In earlier times, rubella eradication would have seemed far- fetched, but several factors have now shown that rubella can be eradicated globally. Rubella affects humans only and is transmitted by only humans therefore controlling CRS cases automatically controls the reservoirs. There are effective vaccines and accurate diagnostic tests available.[35] Vaccination plays an important role in eradication and if vaccination coverage is less than 80%, an increase in CRS is possible.[42] In 2010, the WHO Strategic Advisory Group of Experts on Immunization concluded that rubella-measles vaccination and surveillance for fever and rash was effective in the control of rubella and the prevention of CRS.[40] To monitor the effects of rubella and CRS eradication, proper surveillance of rubella and CRS is key. If surveillance for CRS is present, rubella vaccination can be administered to infants with a booster dose administered at a later stage of childhood, however, vaccination of infants without associated vaccination of adults may not likely eradicate rubella.[35] WHO defines rubella elimination as "the absence of endemic rubella transmission in a defined geographical area for ≥12 months and the absence of CRS cases associated with endemic transmission in the presence of a well-performing surveillance system".[40] The Global Measles and Rubella Strategic Plan 2012-2020 period observed a significant reduction in the measles and rubella disease burden, an increase in the introduction of a second dose of rubella vaccines, and improvements in surveillance. However, despite the significant progress made, the regional measles and rubella elimination targets for 2020 were not met and emerging challenges are cause for growing concern. One of the major goals of any eradication campaign should involve closing the immunity gap between children and adults as well as reflect the fact that all six WHO regions have established or expressed a commitment to achieving regional elimination of measles and rubella.[40]

Conclusion

Rubella is preventable but many African countries have not included the rubella vaccine in their national immunization schedules, and this has hampered eradication strategies on the continent. Countries in Africa with high burden of rubella have paucity of prevalence and incidence data of the disease. In countries that experience winter and spring, rubella occurs most commonly during such periods. It is transmitted directly by respiratory droplets or by contact with contaminated surfaces. The virus can also be transmitted to the foetus through the placenta and may cause abortions, and stillbirths. Rubella can cause CRS in the newborn, this being the most severe complication of rubella. CRS follows intrauterine infection by the virus and causes cardiac, cerebral, ophthalmic, and auditory defects. Despite an effective control measure, vaccination is not entirely accepted, or generally deployed and this is worsened by poverty and population growth. Although, it has been eradicated in the United States, most parts of the world are still grappling with this childhood disease. Therefore, concerted efforts are needed by countries worldwide to eradicate rubella.

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