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HISTORY, MANIFESTATION AND PREVENTIVE MEASURES FOR RUBELLA IN INDIA: A REVIEW

Deepak Chandra Sati and Rajeshwar Kamal Kant Arya *

Department of Pharmaceutical Sciences, Kumaun University, Nainital - 263136, Uttarakhand, India.

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Correspondence to Author:
Dr. Rajeshwar Kamal Kant Arya

Assistant Professor, Department of Pharmaceutical Sciences, Kumaun University, Nainital - 263136, Uttarakhand, India.

E-mail: rajeshwararya@gmail.com

ABSTRACT: Rubella is an eradicable illness on the grounds of immunization against it produces solid protection. The name rubella comes from the Latin language, and it means "little red". In olden times people thought that rubella was a variant of measles. German literature first described it as a separate disease, and hence it was also called "German Measles". People are the main reservoir of the infection. Before inoculation, rubella was endemic around the world, with plagues occurring every 6-9 years. Congenital rubella syndrome (CRS) acquires a very important place in rubella infection since it leads to a highly damaging effect on the health of newborns. It is transmitted to them by their mothers who have acquired this infection. Babies conceived every year with inborn rubella disorder is a disaster. Although, effective vaccination programs against rubella, especially in combination with immunization against measles has led to the eradication of this disease especially in developed countries like United States of America, still it is vital to recollect that having a powerful antibody does not ensure control of sickness – the immunization must be appropriated to all who require it. This review focused on the history, mechanism of rubella infection, manifestation and preventive measures for rubella in India. Indian government has launched MR vaccination campaign targeting the children of 9-12 year age group.

INTRODUCTION: Rubella is an infection that is spread through the air or by close contact in humans. Rubella virus (RV) belongs to the genus rubivirus. It belongs to the family Togaviridae. Rubella virus infection brings about various complications in a human-like maculopapular rash, second rate fever, lymphadenopathy, sore throat and general disquietude [1]. Its genetic material consists of positive-stranded sense RNA [2].

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Various agents like amantadine, trypsin, formalin, bright light, heat, lipid solvents, and low pH can inactivate rubella virus [3]. In olden times the only characteristic features of identifying congenital rubella were cataracts, deafness, and congenital heart disease. But around 1963, there was an outbreak of rubella infection in America and European countries, which effected many infants.

Now, it is well known that besides the above-mentioned characteristic features of identifying congenital rubella infection, many other manifestations of congenital rubella virus infection were present. Congenital rubella virus-infected various organs like endocrine glands, bones, bone marrow, liver, spleen, kidney and lungs. As the rubella virus infected these organs as a result there

various pathological effects are seen related to these organs like diabetes mellitus, thyroiditis, metaphyseal defects, thrombocytopenia, hepatitis, pneumonia, mental retardation, encephalitis, cataracts, cochlear athrophy, and patent ductus arteriosus. Other manifestations of congenital rubella are glaucoma, central auditory imperception, and peripheral pulmonic stenosis. Rubella contamination in a lady in the initial 8 to 10 weeks of pregnancy causes death or harm to the baby in up to 90% of cases [4]. Different imperfections can be produced in the baby like deafness, visual deficiency, cardiac, and mental disability [5]. The signs and indications of rubella are frequently so mellow that one hardly takes them into consideration, especially in youngsters [6].

Even, if signs and manifestations of rubella infection occur, they occur around two and three weeks after introduction to the infection [1]. They ordinarily last around a few days and may include mild fever of about 102 °F (38.9 °C) or lower. Headache, stuffy or runny nose, inflamed, red eyes, enlarged delicate lymph hubs at the base of the skull, the back of the neck and behind the ears [7]. The fine, pink rashes that start on the face and then rapidly spreads to the stomach and after that, to the arms and legs, before vanishing in a similar arrangement [4].

History of Rubella Virus: In 1814, George Maton, first perceived a specific disease that was mellow and had symptoms like rash, adenopathy and very low fever [8]. Henry Veale, in 1866, named the illness rubella [9]. The disease was in little consideration before 1942, when Norman Gregg saw the first-trimester maternal rubella caused genuine birth problems [10]. The full range and effect of rubella embryopathy remained unclarified until the point that rubella infection was segregated in tissue culture in 1962 by Parkman, Buescher, and Artenstein and also by Neva and Weller [11]. Utilizing the new devices of the infection research facility, numerous agents focused on the outcomes of an extreme rubella scourge in 1964, which influenced roughly 1% of pregnancies. Recently perceived transient signs of inborn rubella contamination (CRI) incorporate neonatal thrombocytopenic purpura, hepatitis, bone injuries, and meningoencephalitis and late-rising sequelae, for example, diabetes mellitus and dynamic rubella panencephalitis added to the disease. Coronary illness, mental hindrance, and deafness were described as beforehand characteristics of congenital rubella infection [8]. Sharp complexities were recorded between the examples of infection discharge and the insusceptible reaction of postnatal versus inherent rubella. The wide circulation of vaccine against rubella in 1969 caused a remarkable decrease in the incident of rubella [12]. Pockets of disease stay, even today in the United States. A sincere effort will be required to take out the rubella issue completely [13]. To start with, waterfalls, deafness, and intrinsic coronary illness were the main distinguishing qualities of inborn rubella, be that as it may, in the spring of 1963, a plague of rubella began in Europe and in same manner spread to the United States in 1964 and 1965, leaving a large number of newborn children affected by the disastrous effects of congenital rubella infection [14].

Investigations of these newborn children uncovered that congenital rubella disorder (CRS) has numerous appearances and influences basically covering all organ frameworks [10]. Rubella infection was first segregated from cell culture in 1962 and contained a solitary stranded, positive-sense RNA genome [15]. Rubella infection is the causative operator of rubella malady or purported German measles. Albeit most instances of contamination prompt a mellow, self-restricting measles-like illness, the genuine danger emerges when rubella infection taints the hatchling, especially amid the first trimester, when contamination can prompt unnatural birth cycle or inherent rubella disorder [5, 7]. The connection between maternal rubella contamination and inborn rubella disorder was first proposed by the Australian ophthalmologist Norman Gregg.

Gregg saw a generous increment in the quantity of innate waterfall cases found in his work on amid 1941 and could interface a background marked by maternal German measles in 78 of these cases [16]. In inherent rubella disorder, rubella infection can taint the placenta, spread to the embryo, and adjust the capacity of numerous fetal frameworks by interfering with organ development and causing foundational inflammation [17]. There is also an infection related with rubella which is known as intraocular diligent disease found in patient with

Fuchs' uveitis syndrome [18]. The sub-atomic structure of rubella infection was first noted with electron microscopy of antigen-immunizer edifices in 1967 and later verified by thin-segment techniques [8, 13]. Also, using electron microscopy rubella virus particles were found to be 50 and 85 nm in diameter. Rubella infection contains a pleomorphic nucleocapsid concealed in a host-inferred lipid membrane [19]. Two proteinaceous spikes, E1 and E2, are tied down to the outer layer of the film. The E1 protein realizes receptor-interceded endocytosis and is the immunodominant antigen. Antibodies against the killing space of E1 can be utilized as an associate of security against rubella virus [13]. The E2 protein is also film bound. To date, there is no definitively known cell receptor for rubella infection [20].

Nonetheless, the rubella E1 protein ties to myelin oligodendrocyte glycoprotein (MOG) and ectopic articulation of MOG on non-tolerant cells consider *in-vitro* infection. MOG is a cell receptor, particularly for maternal diseases that spread to the hatchling [21]. There is an abnormal state of homology between rubella E2 protein and MOG, which could clarify the capacity of antibodies against rubella to cause demyelination of rodent cerebrum cells. When diagnosis was made for rubella infection, tissue segments from human CNS, gastrointestinal tract, and placenta recolor very less to modestly for MOG, though all other solid tissues recolor negative [22]. The capacity of rubella to contaminate the placenta, and the neurological pathologies related to innate rubella disorder, combined with the nearness of MOG on both tissue sorts, support the speculation that MOG is a potential receptor for rubella [23]. The non-presence of MOG formation on some other tissue types like lymphocytes, respiratory tissue, or skin may be due to the fact that MOG isn't the receptor involved in essential procured rubella. Identification of host receptors for rubella infection will permit valuable understanding into viral pathogenesis and help to develop novel immunization competitors [24].

Although, much advances have taken place rubella remains a critical pathogen and a cause of concern around the world [25]. For instance, the rubella plague in Japan, in which more than 11,000 rubella cases were reported in the first half of the year 2013 and no less than 13 innate rubella disorder cases occurred, features the way that an incomplete inoculation methodology prompts significant flare-ups [26]. Seventy percent of the rubella cases in the Japanese flare-up happened in men aged 20-39 years, showing the shortcoming of an underlying procedure that gave rubella-containing immunization to immature young ladies [27]. In 2012 countries like Poland and Romania also witnessed rubella flare-ups that overwhelmingly affected men because of an inoculation technique that at first centered immunization around young ladies. Consequently, an overall sense of duty regarding rubella control ends, and possible destruction needs to be set up.

Congenital Rubella Syndrome: Rubella is a mellow, immunization preventable ailment, can show serious teratogenic impacts in the baby named as congenital rubella disorder (CRS) because of essential maternal rubella contamination [28]. It was found in 1941 by Australian Norman McAlister Gregg. It can happen in a developing fetus of a pregnant lady who has contracted rubella [29]. In the event that disease happens 0-28 days before origination, the baby has a 13% chances of being influenced. The disease happens, 0-12 weeks after origination, the hazard increments to 51%. On the off chance that the contamination happens 13-26 weeks after origination, the hazard is 23% of the newborn child being influenced by the malady. [23].

Newborn children are not, for the most part, influenced if rubella is contracted amid the third trimester or 26-40 weeks after origination [30]. Issues once in a while happen when rubella is shrunk by the mother following 20 weeks of incubation and keeps on spreading the infection after birth [31]. This disorder can cause following issues: Growth hindrance, Cataracts, Deafness, Congenital heart abandons, Defects in different organs, mental impediment [32]. Nagasawa *et al*. determined the changes in viral load and rubella specific antibody titer in CRS child patients. The boy has rubella infection at 10 weeks of gestation; there no any symptoms were observed at the time of birth, but rubella virus was found in pharynx, blood and urine sample, it was also observed that the physical and mental development was normal for one year, but he developed deafness at thirteen months and diagnosed with CRS. The infection in pharynx was

increased at the age of six months and found nil at the age of thirteen months. The antibody titer was found low at the age of nine-month which gradually decreased to nil. This case revealed that the antibody titer is declined after neonatal age, and this the most contagious age in patients with CRS [33].

Structure of Virus: The developing RV virion is a round or ovoid molecule around 60 nm in distance across. The virion contains an electron-lucent circular center made out of various duplicates of the RV capsid protein and a solitary duplicate of the viral RNA genome [34]. The RV center is encompassed by a host-determined lipid bilayer containing 5 to 6nm long spikes which venture from the virion surface; the spikes are made out of the E2 and E1 glycoproteins [35].

Capsid Protein: The capsid protein is a non-glycosylated, phosphorylated, disulfide-connected homodimer with a detailed atomic mass of 33 to 38 kDa. The capsid protein contains a bunch of proline and arginine deposits, which have been proposed to be associated with the RV genomic RNA to shape the viral nucleocapsids. Specifically, a 28-amino-corrosive space containing an expansive number of essential deposits has all the earmarks of being straight forwardly engaged to the RNA genome [31, 34].

The association of the capsid protein with the viral RNA may not be exclusively relied on the thickness of fundamental buildups in light of the fact that other essential locales inside the protein were found to tie inadequately [36]. It stays to be resolved whether different areas of the protein are associated with nucleocapsid development [37]. On the RV genome, a 29-nucleotide (nt) extend (nt 347 to 375) interfaces with the capsid protein, despite the fact that it isn't evident whether this is adequate for bundling of the genome [38].

E1 and E2 Glycoproteins: The virion envelope proteins, E1 and E2, are film glycoproteins. There are seen as spikes as E1-E2 heterodimers on the virion surface. The E1 and E2 proteins each contain a putative transmembrane (TM) area, which are 22 and 39 deposits long, separately [31]. For E2, the putative TM area is trailed by a decidedly charged 7-deposit arrangement, RRACRRR, and a 20-buildup locale which goes about like a flag succession for E1; the emphatically charged 7-buildup district is accepted to communicate with the contrarily charged phospholipid head gatherings of the lipid bilayer. For E1, the TM space is trailed by a 13-deposit cytoplasmic area [33]. The RV E1 glycoprotein relocates as a discrete band with an atomic mass of 58 kDa, while the E2 glycoprotein moves as wide heterogeneous band of 42 to 47 kDa [39]. Amino corrosive succession investigation of the E1 protein has since uncovered that it contains three N-connected glycosylation locales for all strains so far sequenced. Conversely, the quantity of N-connected glycosylation destinations of the E2 protein seems to differ contingent upon the strain [40].

The E2 protein of the M33 and HPV-77 strains has four N-connected glycosylation destinations, while the E2 protein of the Therien and RA27/3 strains has three. Studies utilizing RV-tainted cells and full-length cDNA clones of E1 and E2 have demonstrated that all the N-connected glycosylation locales are used, with N-connected sugars speaking to roughly 6 kDa and 15 to 20 kDa of the sub-atomic mass of the developed E1 and E2, individually [41, 42]. The part of N-connected glycosylation on the antigenicity and immunogenicity of E1 has been explored by a few studies. Concentrates in which recombinant E1 was communicated in *Escherichia coli* have demonstrated that glycosylation might be required for redress collapsing of E1 for the declaration of critical antigenic and immunogenic epitopes [43]. For E2, mutagenesis studies have demonstrated that evacuation of any of the N-connected locales brings about slower glycan handling and lower steadiness, with the seriousness of the deformity expanding with the quantity of N-connected glycosylation destinations expelled [44].

Notwithstanding N-connected sugars, the RV E2 protein contains O-connected starches. The nearness of these O-connected sugars most presumably adds to the heterogeneous idea of the virion type of E2 [45]. Heartbeat pursues naming of RV-contaminated cells has uncovered the nearness of intracellular types of E2 (39 kDa), which relocate more quickly than the virion type of E2 (42 to 47 kDa). The elements of the RV E1 and E2 glycoproteins have been examined widely.

Utilizing monoclonal antibodies, it has been demonstrated that the E1 protein contains no less than six non-overlapping epitopes, some of which are related to hemagglutination and balance [44]. E1 gives off an impression of being the primary surface protein, with areas engaged with the connection of the infection to the cell. Later investigations have uncovered that a 28-deposit inside hydrophobic space of E1 is in charge of the fusogenic movement of RV [46]. Moreover, this space is associated with the authoritative to E2 for heterodimer development. The capacity of E2 has been harder to decide. E2 is disulfide-connected to E1 in the developed virion and is inadequately uncovered. Along these lines, the antigenic destinations of E2 are less open to the portrayal of monoclonal antibodies. Be that as it may, E2 contains incomplete hemagglutination and killing epitopes and may likewise convey strain-particular epitopes [31].

Mechanism of Rubella Virus Infection: The viral genome includes positive-extremity; single-stranded RNA is encapsidated with different duplicates of capsid proteins, making an icosahedral center of virion [47]. The envelope proteins, E1 and E2, are known to have a profoundly immuno-predominant area and killing epitopes have been recognized on the two proteins. In this way, the envelopes proteins are involved to assume a part for viral disease however little is thought about the exact passage component of RV have into cells. For the most part, it is trusted that host cell segments effectively take an interest in viral section into cells. Layer lipids of host cells, for example, phospholipid and glycolipid give off an impression of being engaged with the cell restricting destinations for RV. This first pathway is by means of clathrin and another is through caveolae [48]. Clathrin-intervened viral disguise is interceded by arrangement of trademark film invagination, known as clathrin-covered pit [49].

Concealed or nonenveloped infections, for example, flu infection, Semliki Forest infection, vesicular stomatitis infection and human polyomavirus JC infection were known to utilize this clathrin-mediated pathway for their entrance to cells [47]. Another endocytic instrument, caveolae-mediated pathway, is directed by polymerization of caveolins and jar molded invagination of plasma film, which is a particular layer area made of primarily sphingolipid and cholesterol (lipid pontoon). Macropinocytosis is thought to be a non-particular and non-receptor subordinate instrument for viral disguise [48].

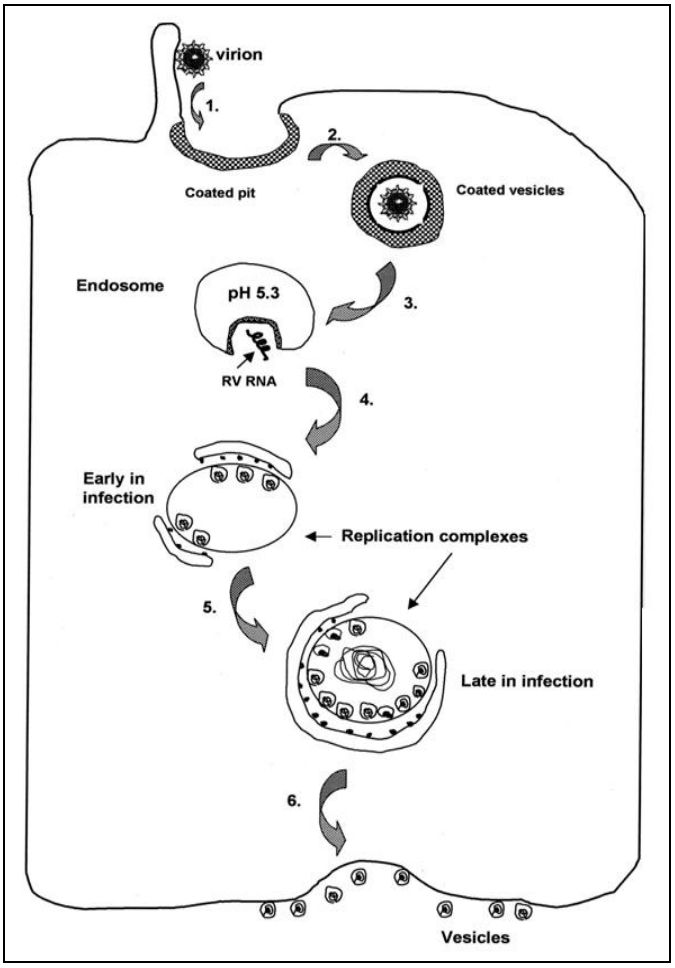

FIG. 1: SCHEMATIC PORTRAYAL OF THE BIOGENESIS OF RUBELLA VIRUS REPLICATION EDIFICE [32]

Stages Observed in Infection of Rubella Virus: [49, 50]

Stage 1: The RV virion joins to the cell surface and is translocated to the covered pit.

Stage 2: The covered pit at that point squeezes off to frame a covered vesicle that contains the virion.

Stage 3: The virion goes through a progression of endosomes with logically acidic pH until the point when it lands at an endosome where the ground is adequately acidic to trigger the uncoating procedure. The E1 and capsid proteins experience conformational changes that outcome in the arrival of the viral genomic RNA into the cytoplasm.

Stage 4: The release of the viral RNA triggers the change of the endosome, and vesicles are actuated to shape inside the endosome. This prompts the development of the replication complex.

Correspondingly, the rough endoplasmic reticulum (RER) relocates to the region of the infection altered endosome. At this starting point of the disease, the RER is related to the side of the vacuole where the vesicles are found.

Stage 5: As disease advances, the RER encompasses the whole vacuole, which is fixed inside with vesicles. While these occasions are happening, the infection changed endosome wires to a lysosome as a feature of its life cycle.

Stage 6: The replication complex proceeds in its life cycle as an infection adjusted lysosome and in the end removes its lysosomal substance, including the vesicles, after the combination of the lysosomal vacuole film to the plasma layer.

Transmission: People are the main characteristic host and store of rubella infection. The infection is transmitted from human to human by respiratory pressurized canned products [51]. Upon section into the upper respiratory tract, the infection duplicates in the mucosa and nearby lymph hubs [16]. Infection at that point enters the blood and spreads to local lymph hubs, where it reproduces, and a moment viremia follows [49]. The hatching time frame is roughly 14 days, after which infection is shed by respiratory discharges, enabling transmission to different hosts. The second viremia conveys infection to the skin, where a rash shows up following 14-21 days [52].

Pathogenesis: Following respiratory transmission of rubella infection, replication of the infection is thought to happen in the nasopharynx and territorial lymph hubs [53]. A viremia happens 5 to 7 days after the introduction with spread of the infection all through body [54]. Transplacental contamination of the embryo happens amid viremia. Fetal harm happens through demolition of cells and additionally mitotic capture [5, 12].

The hatching time of rubella is 14 days, with a scope of 12 to 23 days. Side effects are frequently gentle, and up to half of contaminations might be subclinical or in apparent [14].

Laboratory Diagnostic Approaches for Rubella: [20, 31]

1. Isolation of rubella infection (*e.g.* from nasopharynx, urine).
2. Serologic tests accessible fluctuate among research centers.
3. Positive serologic test for rubella IgM counteracting agent.
4. Significant ascent in rubella IgG by any standard serologic examine (*e.g.*, compound immunoassay).

Preventive Measures of Rubella in India: Indian Govt. has initiated the most ambitious campaign with WHO for the eradication and getting control on CRS by 2020 of measles and rubella (MR) [55]. India's National Technical Advisory Group on Immunization (IEAGMR) asserted to introduce that RCV in 2017 with two action plan i) The goal of Indian Govt. campaign is to cover the children of 9-15 years age group from all over India, ministry of health wants no children would be left behind either he/she previously missed the vaccination or the vaccination was failed and ii) the monovalent measles-containing vaccine (MCV) replaced with the bivalent MR vaccine within the routine childhood vaccination schedule (*i.e.* administered to all children aged 9-12 and 16-24 months old). The immunization is scheduled at 9 months and 18-24 months to follow up the immunization [55]. The vaccine has a safe and effective profile, on a 9-12 month immunization the sera conversion was found about 85-95% for measles and 95-99% for rubella respectively [55].

Previously the healing centers and private hospitals were giving the immunization. The teachers and health care workers are also spreading awareness among the students and parents. There is a vaccine hesitancy observed in all over the world, the vaccine hesitancy means the people are not accepting the vaccine or ignoring the importance of vaccination [56]. In India this hesitancy was due to unawareness, religious, and negative or misleading propaganda on social media [57]. Then, there is lack of awareness program among the parents regarding the risk and problem associated with the virus, the proper safety data, and benefits of vaccination are

not reaching to the parents. The success rate of vaccination is low because of the decreased prevalence of disease and parents are not vaccinating to healthy children [58]. The Govt. should make vaccination mandatory to all, the campaign should be promoted by the religious or famous personalities [59], whom peoples are following, Mr. Amitabh Bacchan is a great example promoting the polio vaccination campaign. There is an important task of targeting the families who refused to the vaccination; such resistant families should be persuaded and some influential personalities are to be searched who can change the mindset of those particular families. The vaccination hesitancy is not so simple; there are various factors that influence vaccination hesitancy such as complacency, convenience, and confidence. The Govt. introduced a solitary shot Measles-Rubella (MR) vaccine with an expected to cover about 3.6 crore youngsters against these two ailments and later will be reached to the whole nation [60].

The campaign was initiated in Karnataka, Tamil Nadu, Puducherry, Goa and Lakshadweep in the first phase. The whole country will be covered in four phases in eighteen months. All kids matured between nine months and under 15 years will be given a solitary shot of MR inoculation regardless of their past measles/rubella immunization status or measles/rubella illness status [61, 62, 63]. There is question can India achieve this goal by 2020? Dr Jacob John co-chairmen of IEAGMR said if the transmission of virus is blocked and about 90% of immunization occurs this is achievable [64].

DISCUSSION: Rubella is a mellow, immunization preventable ailment, can show with serious teratogenic impacts in the baby named as congenital rubella syndrome (CRS) because of essential maternal rubella contamination. This is one of the most dangerous viral infections, if unimmunized pregnant women get infected with this virus she can result in abortion or fetal death or baby with CRS [65]. For instance, the rubella plague in Japan, where more than 11,000 rubella cases were reported, in the first half of the year 2013. Also during this period, no less than 13 innate rubella disorder cases occurred. These incidences emphasize the fact that the way that an incomplete inoculation methodology prompts significant flare-ups is very dangerous.

Seventy percent of the rubella cases in the Japanese flare-up happened in men matured 20-39 years, showing the shortcoming of an underlying procedure that gave rubella-containing immunization only to immature young ladies and they were left unprotected.

In 2012, Poland and Romania also witnessed rubella flare-ups that overwhelmingly affected men because of an inoculation technique that at first centered on the immunization of young ladies. Consequently, an overall sense of duty regarding rubella control, end, and possible destruction sought to be set up. The rubella-containing vaccines (RCV) introduced in the Philippines in the year 2011, [66] it is not well established that what population is affected by rubella and congenital rubella syndrome in Philippines. For evaluating the effect and burden of rubella and congenital rubella syndrome in Philippines, various studies have been carried out; a report concludes that the CRS susceptible women have a high risk of giving birth to a CRS affected child [66]. The establishment of CRS surveillance and enhanced awareness on rubella case detection should be prioritized. For this purpose Indian government added the rubella antibody in the Universal Immunization Program along with the expectation to at first cover almost 3.6 crore youngsters against these two ailments. Later this program will reach the whole country. The goal of the immunization program in India is to prevent the current generation as well as upcoming generation from the rubella infection and also provide protection to the infants from its teratogenic effects.

CONCLUSION: In India and all over the world vaccination is the only method for the prevention of congenital rubella syndrome infection. It is expected that the implementation of MR vaccination campaign definitely would help in eliminating CRS from India. The vaccination hesitancy would be converted into acceptancy. Although, this is a time taking process but one day India will be able to eradicate it as we eradicated poliomyelitis and smallpox in the past.

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REFERENCES:

1. Gregg NM: Congenital cataract following german measles in the mother. Trans Ophthalmol Soc 1941; 3: 35-46.
2. Greenberg M, Pellitteri O and Barton J: Frequency of defects in infants whose mothers had rubella during pregnancy. Journal of the American Medical Association 1957; 165: 675-78.
3. Manson MM, Logan WPD and Loy RM: Rubella and Other Virus Infections During pregnancy Report On Public Health and Mechanical Subjects. London: Her Royal Majesty's Stationery Office 1960; 101.
4. Lundstrom R: Rubella during pregnancy: a follow-up study of children born after an epidemic of rubella in Sweden 1951, with additional investigations on proplylaxis and treatment of maternal rubella. Acta Pediatrica supplement 1962; 133: 101-10.
5. Witte JJ and Karchmer AW: Epidemiology of Rubella. American J of Diseases of Children 1969; 118: 107-12.
6. Plotkin SA, Oski FA and Hartnett EM: Some recently recognized manifestations of the rubella syndrome. Journal of Pediatrica 1965; 67: 182-91.
7. Lindquist JM, Plotkin SA, Shaw L, Gilden R and Williams ML: Congenital rubella syndrome as a systemic infection: studies of affected infants born in Philadelphia. USA. British Medical Journal 1965; 2: 1401-6.
8. Parkman PD, Buescher EL and Artenstein MS: Recovery of rubella virus from army recruits. Proceedings of the Society for Experimental Biology and Medicine 1962; 111: 225-30.
9. Leung AK, Hon KL and Leong KF: Rubella (German measles) revisited. Hong Kong Medical Journal 2019; 25: 134-41.
10. Stanley A: The History of Rubella and Rubella Vaccination Leading to Elimination. Clinical Infectious Diseases 2006; 43: 164-68.
11. Rager ZB, Bazarsky E and Skibin A: The effect of measles mumps-rubella (MMR) immunization on the immune responses of previously immunized primary school children. Vaccine 2003; 21: 2580-8.
12. Frey TK: Molecular biology of rubella virus. Advances in Virus Research 1994; 44: 69-75.
13. Frey TK and Abernathy ES: Identification of strain-specific nucleotide sequences in the RA 27/3 rubella virus vaccine. Journal of Infectious Diseases 1993; 168: 854.
14. Green RH, Balsamo MR and Giles JP: Studies of the natural history and prevention of rubella. American Journal of Diseases of Children 1965; 110: 348.
15. Horstmann D, Schluederberg A and Emmons JE: Persistence of vaccine-induced immune responses to rubella: comparison with natural infection. Reviews of Infectious Diseases 1985; 7: 80-87.
16. Parkman PD, Hopps HE and Meyer HM: Rubella virus: isolation, characterization and laboratory diagnosis. Am J Dis. Child 1969; 118: 68-75.
17. Plotkin SA and Orenstein WA: Vaccines, WB Saunders Company, Philadelphia, Edition 3, 1999: 409-40.
18. Winchester SA, Varga Z and Parmar D: Brown ke persistant intraocular rubella infection with fuchs' uveitis and congenital rubella syndrome. Journal of Clinical Microbiology 2013; 51(5): 1622-24.
19. Weibel RE, Stokes J, Buynak EB, Whitman JE and Hilleman MR: Live, attenuated mumps virus vaccine–clinical and serologic aspects in a field evaluation. The New England Journal of Medicine 1976; 276: 245-51.
20. Cutts FT, Henderson RH, Clements CJ, Chen RT and Patriarca PA: Principles of measles control. Bull WHO 1991; 69(1): 1-7.
21. Leibhaber H, Ingalls TH, LeBouvier GL and Hortsmann DM: Vaccination with RA 27/3 rubella vaccine. American Journal of Disease Child 1973; 123: 133-36.
22. Brown GC and O'Leary TP: Fluorescent-antibody marker for vaccine-induced rubella antibodies. Infection and Immunity 1972; 2: 360-63.
23. Buynak EB and Hilleman MR: live attenuated mumps virus vaccine. Vaccine development. Proceedings of the Society for Experimental Biology and Medicine 1966; 123: 768-75.
24. Weibel RE, Carlson AJ, Villarejos VM, Buynak EB, McLean AA and Hilleman MR: Clinical and laboratory studies of combined live measles, mumps, and rubella vaccines using the RA 27/3 rubella virus. Proceedings of the Society for Experimental Biology and Medicine 1980; 165: 323-26.
25. Stratton K, Ford A, Rusch E and Clayton EW: Adverse effects of vaccines: evidence and causality. Washington, DC: National Academy Press 2011; 5: 120-28.
26. Vestergaard M, Hviid A, Madsen KM, Wohlfahrt J, Thorsen P and Schendel D: MMR vaccination and febrile seizures: evaluation of susceptible subgroups and long-term prognosis. Journal of American Medical Association 2004; 292: 351-57.
27. Consolini DM: Thrombocytopenia in infants and children. Pediatrics Review 2011; 32(4): 135-40.
28. Dayan GH, Quinlisk MP, Parker AA, Barskey AE, Harris ML and Schwartz JM: Recent resurgence of mumps in the united states. The New England Journal of Medicine 2008; 358: 1580-89.
29. Dhiman N, Haralambieva IH, Vierkant RA, Pankratz VS, Ryan E and Jacobson RM: Predominant inflammatory cytokine secretion pattern in response to two doses of live rubella vaccine in health vaccines. Cytokine 2010; 50: 24-29.
30. Haralambieva H, Dhiman N, Ovsyannikova IG, Vierkant RA, Pankratz VS and Jacobson RM: 2'-5'-Oligoadenylate synthetase single-nucleotide polymorphisms and haplotypes are associated with variations in immune responses to rubella vaccine. Human Immunology 2010; 71(4): 383-91.
31. McNab FW, Rajsbaum R, Stoye JP and O'Garra A: Tripartite-motif proteins and innate immune regulation. Current Opinion Immunology 2011; 23: 46-56.
32. Schaid DJ, Rowland CM, Tines DE, Jacobson RM and Poland GA: Score tests for association between traits and haplotypes when linkage phase is ambiguous. American Journal of Human Genetics 2002; 70: 425-34.
33. Sydnor E and Peri TM: Healthcare providers as sources of vaccine preventable diseases. Vaccine 2014; 32: 4814-22.
34. Nagasawa K, Ishiwada N, Ogura A, Ogawa T, Takeuchi N, Hishiki H and Shimojo N: Congenital rubella syndrome: a case report on changes in viral load and rubella antibody titers. Pediatric 2016; 137(5): e20153333.
35. Thompson KM, Strebel PM, Dabbagh A, Cherian T and Cochi SL: Enabling implementation of the global vaccine action plan: Developing investment cases to achieve targets for measles and rubella prevention. Vaccine 2013; 31: 149-56.
36. Miller E, Watson JE and Pollock TM: Consequences of confirmed maternal rubella at successive stages of pregnancy. Lancet 1982; 83(02): 781-84.

37. Metcalf CJ, Lessler J, Klepac P, Cutts F and Grenfell BT: Impact of birth rate, seasonality and transmission rate on minimum levels of coverage needed for rubella vaccination. Epid and Infection 2014; 140(12): 2290-01.
38. World Population Prospects: The 2012 Revision, CD-ROM edition. New York: United Nations, Department of Economic and Social Affairs, Population Division 2013.
39. Kanchanalarp C, Cheewaruangroj W, Thawin C and Lertsukprasert K: Indication and surgical consideration of cochlear implantation at ramathibodi hospital. Journal of the Medical Association of Thailand 2006; 89(8): 1171-77.
40. Plotkin SA: Rubella Eradication. Vaccine 20011; 9(25): 3311-19.
41. Castillo SC, Marsigli C, Bravo AP, Flannery B, Ruiz MC, Tambini G, Gross S and Andrus JK. Elimination of rubella and congenital rubella syndrome in the Americas. Journal of Infectious Disease 2011; 204(2): 571-78.
42. Reef SE, Strebel P, Dabbagh A and Cochi S: Progress toward control of rubella and prevention of congenital rubella syndrome worldwide. Journal of Infectious Disease 2009; 1(204): 24-27.
43. World Health Organization: Rubella vaccines. WHO position paper. Weekly Epid Record 2000; 75: 161-72.
44. WHO, Rubella vaccines: WHO position paper–recommendations. Vaccine 2011; 29(48): 8767-68.
45. Marshall, WC, Hayes K and Chrispin AR: Unusual bone abnormality in congenital rubella. Br Me J 1967; 3: 47-50.
46. Waldorf KM and McAdams RM: Influence of infection during pregnancy on fetal development. Reproduction 2013; 146: 151-62.
47. Roche CJ, O'Keeffe DP, Lee WK, Duddalwar VA, Torreggiani WC and Curtis JM: Selections from the buffet of food signs in radiology. Radiograph 2002; 2: 1369-84.
48. Cutts FT and Vynnycky E: Modeling: The incidence of congenital rubella syndrome in developing countries. International J of Epidemiology 1999; 28(6): 1176-84.
49. Lee J and Bowden DS: Rubella Virus Replication and Links to Teratogenicity. Clinical Microbiology Reviews 2000; 13(4): 571-87
50. Lee JY, Marshall JA and Bowden DS: Characterization of rubella virus replication complexes using antibodies to double-stranded RNA. Virology 1994; 200: 307-12.
51. Dewan P and Gupta P: Burden of congenital rubella syndrome (CRS) In India: A Systematic Review. Indian Pediatrics 2012; 49: 377-99
52. Lee JY and Bowden DS: Rubella virus replication and links to teratogenicity. Clinical microbiology reviews 2000; 13(4): 571-87.
53. Case C, Funke B and Tortora G: Microbiology: An Introduction. Pearson Benjamin Cummings: San Francisco edition 8th, 2004: 604-05.
54. Winter AK, Pramanik S, Ferrari LM, Grenfell BT and Metcalf CJF: Rubella vaccination in India: identifying broad consequences of vaccine introduction and key knowledge gaps Epidemiology and Infection 2018; 146(1): 65-77.
55. Introduction of Measles- Rubella vaccine guidelines (campaign and routine immunisation). Operational guidelines. MoHFW, Govt. of India 2017. https://mohfw.gov.in/sites/default/files/Measles%20rubella%20vaccine%20operational%20guidelines.pdf.
56. MR Campaign: The state second in coverage. March 5, 2017. The Hindu. https://www.thehindu.com/todays-paper/tp-national/tp-karnataka/mr-campaign-state-second-in-coverage/article17411184.ece.
57. Noni EM: The SAGE working group on Vaccine hesitancy. Vaccine hesitancy: Definition, scope and determinants. Vaccine 2015; 33: 4161-64
58. Heidi L: Missing the signals: India's anti-vaccination social media campaign. The Vaccine Confidence Project. March 2017. [Homepage of the Vaccine Confidence Project: London School of Tropical Medicine on the Internet Available from: www.vaccineconfidence.org/missing-the-signals-indias-anti-vaccination-social-media.
59. Sachiko O, Ligia P and Mary Q: Exploring pathways for building trust in vaccination and strengthening health system resilience. BMC Health Service Research 2016; 16(7): 639-44.
60. Caitlin J, Rose W, Maureen O'L, Elisabeth E and Heidi JL: Strategies for addressing vaccine hesitancy – A systematic review. Vaccine 2015; 34: 4180-9.
61. Palanisamy B, Gopichandran V and Kosalram K: Social capital, trust in health information, and acceptance of Measles–Rubella vaccination campaign in Tamil Nadu: A case–control study. Journal of Postgraduate Medicine 2018; 64: 212-9.
62. Sreedevi A: Measles-Rubella vaccination campaign: A trust deficit. Journal of Postgraduate Medicine 2018; 64(4): 202-03.
63. Shrivastava SR, Shrivastava PS and Ramasamy J: Measles-Rubella Vaccination Campaign in India. International Journal of Preventive Medicine 2018; 9: 31.
64. https://www.thehindu.com/sci-tech/health/india-needs-the-rubellavaccine/article173698 30.ece
65. Kaushik A, Verma S and Kumar K: Congenital rubella syndrome A brief review of public health perspectives. Indian Journal of public health 2018; 62 : 152-54
66. Lopez AL and Francis PN: Raguindin, Maria Asuncion Silvestre, Xenia Cathrine J. Fabay, Ariel B. Vinarao and RicardoManalastas, Rubella and Congenital Rubella Syndrome in the Philippines: A Systematic Review, International Journal of Pediatrics 2016; 1-8.

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