SYSTEMATIC REVIEW

Burden of Congenital Rubella Syndrome (CRS) in India: *A Systematic Review*

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Background: Rubella, though a mild, vaccine-preventable disease, can manifest with severe teratogenic effects in the fetus labeled as congenital rubella syndrome (CRS) due to primary maternal rubella infection. Despite a reduction in disease burden of several vaccine-preventable diseases through childhood immunization, CRS continues to account for preventable severe morbidity including childhood blindness, deafness, heart disease, and mental retardation.

Objective: To conduct a systematic review to describe the prevalence of CRS and its contribution to major long-term handicaps in Indian population. Another objective was to estimate the susceptibility to rubella infection in Indian adolescent girls and women of reproductive age-group. We also explored strategies to decrease CRS in India by identifying the immunogenicity of rubella containing vaccines (RCV) in Indian children and women, as well as their coverage in India.

Methods: Publications reporting 'CRS prevalence in general population as well as selected subgroups i.e., suspected intra-uterine infection, congenital ocular abnormalities, deafness, congenital heart disease, mental retardation, and congenital malformations', 'seroprevalence to rubella (IgG) amongst women and adolescents', and 'immunogenicity and coverage of RCVs' in Indian population were retrieved through a systematic search. Primary databases employed were Medline through PubMed and IndMed, websites of the WHO, and UNICEF. No restrictions were applied in terms of study designs. The primary outcome measure was 'congenital rubella syndrome' (CRS) which was further categorized as 'suspected CRS' and 'confirmed CRS' as defined by World Health Organization (WHO).

Results: Comprehensive evidence about the true burden of CRS in India is not available. Almost all studies have been done in institutional/hospital set-ups and community-based studies are grossly lacking. There are no studies assessing the prevalence of CRS in general population. All studies have evaluated the CRS burden in symptomatic cohorts of children. 1-15% of all infants suspected to have intra-uterine infection were found to have laboratory evidence of CRS. About 3-10% of suspected CRS cases are ultimately proven to have confirmed CRS with the aid of laboratory tests. CRS accounts for 10-15% of pediatric cataract. 10-50% of children with congenital anomalies have laboratory evidence of CRS. 10-30% of adolescent females and 12-30% of women in the reproductive age-group are susceptible to rubella infection in India. RCVs are highly immunogenic in Indian adolescents and women. The coverage data of RCVs in India is not available. However, the coverage of MMR vaccine has been reported as 42%, 30% and 5% from Delhi, Chandigarh and Goa, respectively.

Conclusion: This systematic review identifies and explores factors associated with the prevalence of CRS in India. There is a need for urgent action in terms of revamping the national immunization policy and introduction of RCVs in the national immunization program. Active surveillance of rubella and CRS is needed to redress the burden of CRS in India.

Keywords: *Congenital rubella syndrome, India, Prevalence, Rubella, Susceptibility, Vaccine.*

Rubella although a mild viral illness, is of high public health importance owing to the teratogenic effects that can result from congenital rubella infection (CRI), leading to miscarriage, fetal death, or birth of an infant with congenital rubella syndrome (CRS). The clinical spectrum of CRS includes ophthalmic, auditory, cardiac, and craniofacial defects. Worldwide, it is estimated that more than 100 000 infants are born with congenital rubella syndrome (CRS) each year [1]. According to the estimates based on a statistical model derived from the seroprevalence data from SEAR during 2000-2009, 46,621 infants with CRS are born annually in South East Asian Region (SEAR) alone [2].

Recognizing the fact that CRS is a cause of preventable morbidity including childhood blindness and deafness, which in turn has life-long special health and social needs, the World Health Organization (WHO) has advocated the use of rubella containing vaccines (RCV) in many countries (discussed later). To mitigate the CRS incidence, the United States strategized to vaccinate all infants against rubella [3], while the United Kingdom, targeted adolescent girls for vaccination [4]; however, both the strategies were only partially successful. The reason for partial failure of these strategies were that while in the United States pregnant women continued to be exposed to rubella in children and adults; in the United Kingdom unvaccinated girls who refused vaccination

were still exposed to rubella cases because of circulation of virus in the male population and children. It was soon realized that combining universal immunization of infants with vaccination of adolescent girls and adult women was the most effective approach to eliminate rubella and CRS. By 2009, 130 out of 193 member countries had incorporated rubella vaccine into their national routine childhood immunization programs. However, only 4 out of 11 countries in the WHO SEAR and 2 out of 46 member states in the WHO African region had incorporated the RCV into their immunization schedule till 2009 [2].

Before the introduction of rubella vaccine in 1969, the global incidence of CRS ranged from 0.8-4/1000 live births during rubella epidemics to about 0.1-0.2/1000 live births during endemic periods [5]. The World Health Organization established goals to eliminate rubella and CRS in the WHO Region of the Americas by 2010, and the WHO European Region by 2015, and in the WHO Western Pacific Region for accelerated rubella control and CRS elimination by 2015. Sustained vaccination strategy enabled America to decrease rubella cases by 98%, from 1,35,947 in 1998 to 2,998 in 2006. Consequently, the CRS incidence had also decreased. The last confirmed case of CRS was delivered in Brazil on 26 August, 2009 and no new cases of CRS were reported from America in 2010. The Pan American Health Organization (PAHO) is due to confirm rubella and CRS elimination from the American region by 2012 [6]. While the western hemisphere continues to make huge strides in its endeavor to control CRS, 52% of the developing countries, including India, which account for two-third of the global birth cohort, are yet to incorporate the MMR vaccine in their national schedule [1].

In addition to appropriate vaccination with good coverage, adequate surveillance of CRS is needed to ensure continued control. In 2009, out of 193 WHO member states, 123 states were reporting CRS and a total of 165 CRS cases were reported in 2009 [2]. While surveillance data on CRS from most developed countries is available, statistics from most developing countries including India is lacking. In India, no country-wide estimates of CRS burden and susceptibility to rubella infection are available as there is lack of a national surveillance and registry for rubella. In addition, diversity of laboratories and assay techniques makes comparison of data challenging [7]. In the absence of rubella surveillance data, understanding regional endemic-epidemic cycles of rubella virus is difficult and it is not possible to devise a national strategy to curtail the morbidity due to rubella infection. Therefore, there is a need to summarize and critically evaluate all available data related to the prevalence of congenital rubella syndrome and the susceptibility of Indian adolescent girls and women in reproductive age-group to rubella infection.

METHODS

Study Design

We aimed to review and describe the prevalence of CRS and its contribution to major long-term handicaps in Indian population. Another objective was to review the available literature to have an estimate of the susceptibility to rubella infection in adolescent girls and women of reproductive age-group, in India. We also looked at the studies documenting the immunogenicity of rubella containing vaccines (RCV) in children and women of reproductive age-group, and the population covered by the rubella containing vaccines, in India. For this, the standard methodology for conducting a narrative systematic review was adapted [8].

For the primary research question 'evaluation of prevalence of congenital rubella syndrome in India'; secondary research issues were framed to review the disease-specific burden of CRS in selected subgroups i.e., suspected intra-uterine infection, congenital ocular abnormalities, deafness, congenital heart disease, mental retardation, and congenital malformations. The second research question i.e., susceptibility of Indian adolescent girls and women of reproductive age-group to rubella infection, was addressed separately. Studies pertaining to either seroprevalence or susceptibility to rubella infection were searched. Seroprevalence (anti-rubella IgG positivity) was taken as surrogate marker for immunity to rubella infection.

To address the research questions, the primary databases employed were Medline through PubMed (*www.pubmed.com*) and IndMed (*http://indmed.nic.in/*). Specific sources including National Sample Survey, World Health Organization (WHO) reports available online (*www.who.int*), documents of the UNICEF available online (*www.unicef.org/india/*), National Family Health Survey (*http://www.nfhsindia.org/*), and documents of the Ministry of Health and Family Welfare, Government of India (*www.mohfw.nic.in*) available online were also accessed to address specific questions. Further, reference lists of included publications were searched to identify additional studies. No attempt was made to obtain unpublished data, or data unavailable in the public domain, or data available within specific institutions at the national, state or local level.

Inclusion and Exclusion Criteria

Types of publications: All types of publications available in scientific public domain and reporting on congenital rubella infection in India by direct data collection through

clinical examination, laboratory testing, or clinical history taking, were included. Publications based on indirect data sources or extrapolations were excluded.

Type of participants: Publications were included pertaining to rubella infection in neonates, infants, under-5 children, adolescents (10-19y), women of reproductive age-group (16-45y) and pregnant/parturient women. Studies on rubella infection in general population, general child population and special groups (children with suspected intra-uterine infection, congenital ocular abnormalities, cataract, blindness, hearing impairment, mental retardation, congenital heart defects, and congenital malformations) were also included.

Outcome variables

For this review, the primary outcome variable was 'congenital rubella syndrome' (CRS) which was further categorized as 'suspected CRS' and 'confirmed CRS' as specified by CDC [9] and accepted by World Health Organization (WHO), or as per author's definitions. WHO defines a *suspected CRS case* as an infant less than 1 year of age who does not meet the criteria for a probable or confirmed case but who has one of more of the following clinical findings: cataracts or congenital glaucoma, congenital heart disease (most commonly patent ductus arteriosus or peripheral pulmonary artery stenosis), hearing impairment, pigmentary retinopathy, purpura, hepatosplenomegaly, jaundice, microcephaly, developmental delay, meningoencephalitis, or radiolucent bone disease. WHO defines a *probable CRS case* as an infant without an alternative etiology that does not have laboratory confirmation of rubella infection but has at least 2 of the following: cataracts or congenital glaucoma, congenital heart disease (most commonly patent ductus arteriosus or peripheral pulmonary artery stenosis), hearing impairment, or pigmentary retinopathy; or an infant with one of the above findings and one of the following: purpura, splenomegaly, microcephaly, mental retardation, meningoencephalitis, radiolucent bone disease or neonatal jaundice. A *confirmed CRS case* is an infant with at least one symptom (listed above) that is clinically consistent with congenital rubella syndrome; and laboratory evidence of congenital rubella infection as demonstrated by isolation of rubella virus from appropriate sample, or detection of rubella-specific immunoglobulin M (IgM) antibody, or infant rubella antibody level that persists at a higher level and for a longer period than expected from passive transfer of maternal antibody (i.e., rubella titer that does not drop at the expected rate of a twofold dilution per month), or a specimen that is PCR positive for rubella virus. An infant with a positive blood test for rubella IgM who does not have clinically-confirmed CRS is classified as having *congenital rubella infection* (CRI).

Women with rubella specific antibodies (anti-rubella IgG) in titers deemed protective for rubella (as per manufacturer's protocol) detected using seroassays like hemagglutination-inhibition test (HAIT) or enzyme-linked immunosorbent assay (ELISA) were considered immune or *seropositive* for rubella. Women with equivocal results or those with absent antibodies or antibody titers below the protective level for rubella (as per the manufacturer's protocol), described variously as <10 U/mL, <11 U/mL, <12 U/mL, <15 U/mL using ELISA or <20 U/mL, in different studies were considered as *susceptible* to rubella.

Immunogenicity of rubella containing vaccine (RCV) was defined in terms of seroconversion atleast 4 weeks after vaccination with RCV. Pre-vaccination and post-vaccination serological status was determined by ELISA/HAIT. The change in the proportion of children having protective levels of anti-rubella antibodies, before and atleast 4 weeks after vaccination, were estimated to determine the immunogenicity of RCV.

Coverage of rubella containing vaccine (RCV) in a geographical area was defined in terms of percentage of children aged 12-60 months or adolescents and women in reproductive age-group who had received RCVs, as determined by the immunization history or by confirmation from the immunization records where available.

Searching the Literature

For searching the PubMed, a search string was devised by converting each research question into PICO format. Mesh headings were looked for the research theme in question and added to the PubMed search builder. Salient keywords were included during search. A search for MESH headings for 'congenital rubella syndrome', revealed 'Rubella Syndrome, congenital', which was relevant and yielded 27 subheadings. For assessing the prevalence of CRS in India, we searched PubMed using the search search string: "(Epidemiolog* OR Burden OR Morbidity OR Mortality OR Incidence OR Prevalence OR Profile) AND (Congenital rubella syndrome OR Rubella OR CRS OR German measles) AND India". An additional search was made for the secondary research questions by combining keywords/MESH terms for the secondary research question using the search string "(*) AND (rubella syndrome, congenital) AND India", where the asterisk represents the Mesh term/keywords for the secondary research question. Where no or limited search results were obtained by using the above search string,

search string was modified by deleting "India". To search the IndMed, the search string was kept simple using search keywords. The detailed search strings used are shown in ***Table* I**. The search date, search terms, search string and search output were recorded and saved.

The next step involved *screening all titles* and excluding the titles which were obviously not relevant; the remaining articles were processed further. The next step involved *examination of the abstract or the introduction* (where the abstract was not published) of the short-listed titles; the ones which were not found relevant were excluded and the remaining articles were processed further. The next step involved *examination of full-text articles*. Related *cross-references* in identified articles were also reviewed and similar steps were performed before short listing the cross-references. Only English language publications were sought and included.

Data Collection and Analysis

Each included publication was studied in detail and relevant data were extracted. All included studies were categorized according to the following categories:

1. *Study population*

- General population
- General child population
- Special groups: Children with (*i*) suspected intra-uterine infection; (*ii*) congenital ocular abnormalities; (*iii*) hearing impairment; (*iv*) mental retardation; (*v*) congenital heart defects; (*vi*) congenital malformations

TABLE I RESEARCH QUESTIONS AND SEARCH STRINGS USED

Q *No.*	*Research Question*	*Search string for searching PubMed*	*Search string for searching IndMed*
1	What is the prevalence of congenital rubella syndrome (CRS) in India? To determine the disease-specific prevalence of CRS in children with: Suspected intra-uterine infection+; Congenital ocular abnormalities*; deafness#; congenital heart disease£; mental retardation§; congenital malformations$	(epidemiolog* OR burden OR morbidity OR morbidity OR mortality or incidence OR prevalence OR profile) AND (cogenital rubella syndrome OR rubella OR crs OR German measles) AND India.	rubella AND India
2.	What is the proportion of women of reproductive age-group and adolescent girls susceptible to rubella infection in India?	(epidemiolog* OR serology OR susceptibility OR burden OR surveillance OR morbidity OR mortality OR incidence OR prevalence OR immunity) AND (women OR adolescents OR child-bearing OR pregnant) AND (rubella OR congenital rubella syndrome OR crs OR german measles) AND india	rubella AND India
3.	What is the immunogenicity of rubella containing vaccines in children and women of reproductive age-group in India?	(children OR adolescents OR adults OR females) AND (rubella vaccine OR mmr vaccine) AND (immunity OR serology OR safety OR immunogenicity OR seroprotection OR seroconversion) AND india	rubella AND vaccine AND india
4.	What is the coverage of the rubella containing vaccines in India?	(mmr coverage OR rubella vaccine coverage) AND india	rubella AND vaccine AND india

*PubMed search strings for: +(congenital infection OR intrauterine infection OR TORCH) AND (rubella syndrome, congenital) AND india; *(blindness OR cataract OR visual handicap OR eye defects OR retinopathy OR congenital malformation) AND (rubella syndrome, congenital) AND india; #(deafness OR hearing loss OR hearing defect OR sensorineural hearing loss OR congenital malformation) AND (rubella OR congenital rubella syndrome); £: (congenital heart defect OR patent ductus arteriosus OR heart disease OR congenital malformation) AND (rubella OR congenital rubella syndrome) AND india; §: (mental retardation OR intellectual disability OR mental handicap OR developmental delay OR neuromotor dysfunction OR congenital malformation) AND (rubella OR congenital rubella syndrome) AND india; $: (congenital abnormalities OR congenital malformation OR congenital defects) AND (rubella syndrome, congenital) AND india.*

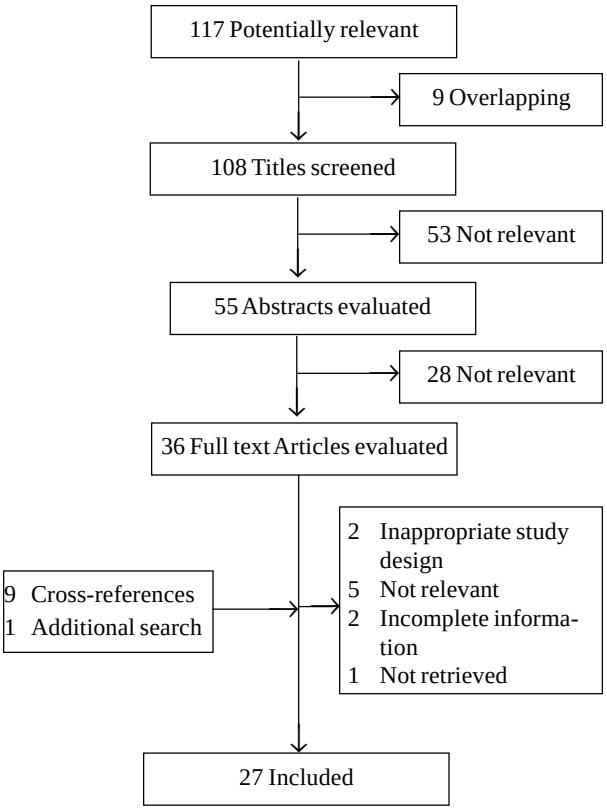

FIG. 1 *Search results for articles determining prevalence of congenital rubella syndrome in India.*

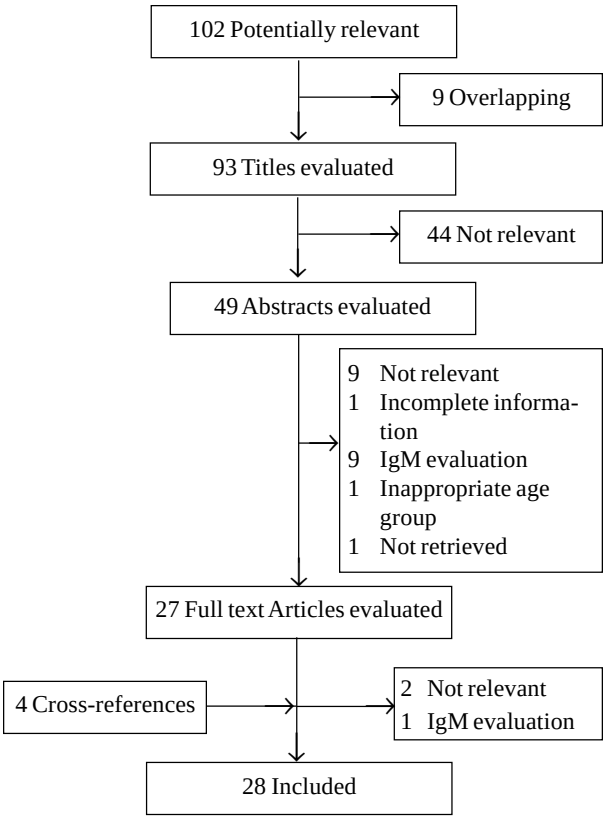

FIG. 2 *Search results for articles determining the susceptibility to rubella infection in Indian women and adolescent girls.*

2. Study-setting
   - Community-based
   - School-based
   - Hospital-based/Healthcare-based

The data were synthesized in a descriptive manner and no secondary data analysis was performed. Wherever possible, numerical data were tabulated.

RESULTS

The details of the search output in terms of citations identified, titles screened, abstracts short-listed and full-text examined are shown in ***Webtable* I** and ***Figures* 1** and **2**. Literature searches were carried out during December 2011; and updated on 6 February 2012.

1. Prevalence of Congenital Rubella Syndrome in India

No systematic review or nation-wide cohort study is available addressing the disease burden or prevalence of CRS in community settings. There are no studies evaluating the prevalence of CRS in general population or general child population. A total of 27 studies could be identified that had assessed the prevalence of CRS in certain specific populations. There are 11 studies which assess the burden of suspected intra-uterine infection due to CRS in children [10-20]. Out of 11 studies, 4 studies assess the prevalence of confirmed CRS in children with clinically suspected CRS [17-20]. There are 14 studies in children with congenital ocular abnormalities [14,19,20-31], 4 in children with hearing impairment [32-35], 5 in children with mental retardation [13-15,20,22], 2 in children with congenital heart disease [20,22],and 4 in children with congenital malformations [15,20,22,36]. Almost all of these studies have been done in hospital set-ups where cohorts of children with specific clinical features or symtoms have been evaluated. These are 4 laboratory-based studies [10,17,18,36]. There are 2 studies assessing the prevalence of CRS amongst school children attending schools for deaf and mute [33,35]. The study design was prospective in 11 studies [11-16,19,21,25,33,35], case-control in 5 studies [20,22,28,29,34] and retrospective in 11 studies [10,17,18,23,24,26,27,30-32,36].

Only one large community-based study has addressed the prevalence of CRS in India [21]. This study was

conducted in Tamil Nadu, over a period of 2 years (2002 to 2004), amongst 51,548 under-5 children with ocular abnormalities (cataract, corneal opacity, glaucoma, microphthalmos, optic atrophy, nystagmus, etc), mental retardation, or developmental delay. Probable CRS cases were recruited from hospital and outreach services of the Aravind Eye Care System. Clinical confirmation was based on the fulfilment of the World Health Organization (WHO) definition, and laboratory confirmation was based on a positive test for IgM antibody. 2.1% (*n*=1090) children had clinically suspected CRS (probable CRS) while 0.58% (*n*=299) were clinically confirmed CRS and 0.0009% (*n*=46) were laboratory confirmed CRS. Presence of cataract (*P* <0.0001), iris hypoplasia (*P* <0.0001) retinopathy (*P* <0.0001), microcornea (*P* =0.003) and glaucoma (*P* <0.0001) were significantly associated with clinical CRS. The presence of cataract (*P* <0.0001), microcornea (*P* <0.0001) and glaucoma (*P* =0.002) were significantly associated with laboratory confirmed CRS. Of all the eye signs evaluated for screening, cataracts were most sensitive (80.4%) for detecting CRS. Iris hypoplasia and pigmentary retinopathy were highly specific for CRS. Only 6 of the nearly 992 mothers of children with suspected CRS had been vaccinated against rubella.

Prevalence of CRS amongst children with suspected intra-uterine infection

There are 11 studies evaluating prevalence of CRS amongst children with suspected intra-uterine infection as shown in ***Table* II**; of these 8 are hospital-based [11-16,19,20] and 3 are laboratory-based [10,17,18]. Of these 7 studies have been conducted prospectively [11-16,18] while there is 1 case-control study [20] and 3 retrospective chart reviews [10,17,18]. There are 4 studies [17-20] assessing the laboratory evidence of rubella infection in clinically suspected CRS cases. ***Web Table* II** shows the detailed description of the studies evaluating the prevalence of CRS in children with suspected intra-uterine infection.

In a study from a tertiary hospital in Delhi [10], records of 200 infants and 360 older children with suspected intra-uterine infection, in whom IgM for rubella was done over a period of 13 years were reviewed. Only 2 infants showed evidence of acute rubella infection (IgM positive). Amongst the older children, 15 children (4%) showed anti-rubella IgM. The older children probably had acquired rubella infection with the common presenting complaints being maculopapular rash and lymphadenopathy. In contrast, in a prospective study from another tertiary care centre in Delhi [11], about 10% of babies suspected to have intra-uterine infection (15 out of 146) were found to be positive for anti-rubella IgM. Deorari, *et al.* [12] in a study from Delhi evaluated cord samples of 1302 consecutive babies for total IgM. If the total IgM was found to be more than 20mg/dL, intra-uterine infection was suspected and the samples were further processed for anti-rubella IgM. Out of 1302 cord samples, 270 had total IgM>20 mg/dL, out of which 8 samples tested positive for anti-rubella IgM.

In a study from Christian Medical College, Vellore [13], serum samples from 92 infants presenting with neonatal cholestasis, hematological, cardiac, neurological, ophthalmic, dysmorphic and/or other anomalies compatible with congenital infections, between January 1996 and December 1997, were tested for anti-rubella IgM. 9 infants (9.8%) tested positive for rubella infection.

Ballal, *et al.* [14] evaluated sera from 342 infants suspected of having congenital infection (bilateral congenital cataract, neonatal hepatitis, intrauterine growth retardation (IUGR), developmental delay with or without microcephaly, hepatosplenomegaly, cerebral palsy, pneumonitis and hydrocephalus) from January 1991-December 1993 for rubella specific IgM antibodies. Of the total 342 infants, 52 (15.2%) were found to be positive for IgM antibodies to rubella virus. The commonest clinical presentation in infants with lgM antibodies to rubella virus was bilateral congenital cataract (14/52) and developmental delay ± microcephaly (11/52).

Broor, *et al*. [15] in a study from a tertiary hospital in Delhi, evaluated 242 infants suspected of having intra-uterine infection for anti-rubella IgM. 12% infants (30/249) were positive for anti-rubella IgM. Manjunath *et al*. [16] in a multi-centric study from Delhi evaluated 272 infants with suspected intra-uterine infection, with clinical manifestations like congenital cataract, microphthalmia, congenital cardiac manifestations, deafness, low birth weight, microcephaly, neonatal hepatitis, or hepatosplenomegaly, and their mothers for rubella infection by hemagglutinatiobn test. Anti-rubella IgM estimation was done in only 16 infants. Overall, 90% of mothers (247/272) and 64.3% infants (175/272) were seropositive for rubella infection by hemagglutination test. The seropositivity was highest amongst neonates (73.6%), followed by infants between 1-3 months age (66.6%) and infants >3 months age (52.5%). 18.75% infants and 53.3% of mothers had antibody titers > 1:40. Evidence of congenital rubella was obtained in 18 babies; 16 babies had higher antibody titers than their mothers and an additional two babies were positive for anti-rubella IgM.

In a retrospective study from Chandigarh, from 1999 to 2006, Singh, *et al.* [17] evaluated the records of 947 children with suspected intra-uterine rubella infection. The

TABLE II. PREVALENCE OF CRS IN CHILDREN WITH CLINICALLY SUSPECTED INTRA-UTERINE INFECTION AND CHILDREN WITH OCULAR ABNORMALITIES

S. No	Study Group	Study Duration	Study Design	Place of Study	Age-group	Study Population (n)	Confirmed CRS (%)
Prevalence of CRS in Children with Clinically Suspected Intra-uterine Infection							
1.	Das, *et al.* [10]	1991-2003	LB, RCR	Delhi	0-12 months	200	1%
2.	Chakravarti, *et al.* [11]	2006*	HB, prospective	Delhi	0-12 months	146	10.27%
3.	Deorari, *et al.* [12]	1992-1994	HB, prospective	Delhi	0-1 month	270	2.9%
4.	Abraham, *et al.* [13]	1996-1997	HB, prospective,	Vellore	0-12 months	92	9.8%
5.	Ballal, *et al.* [14]	1991-1993	HB, prospective	Manipal	0-12 months	342	15.2%
6.	Broor, *et al.* [15]	1991*	HB, prospective	Delhi	0-12 months	249	12%
7.	Manjunath, *et al.* [16]	1979-1982	Multi-centric HB, prospective,	Delhi	0-12 months	272	6.6%
8.	Singh, *et al.* [17]	1999-2006	LB, RCR	Chandigarh	NA	947	2.8%
9.	Chandy, *et al.* [18]	2000-2008	LB, RCR	Vellore	0-12 months	646	9.4%
10.	Rajasundari, *et al.* [19]	2002-2005	HB, prospective	Madurai	0-60 months	65	26%
11.	Chakrabarty, *et al.* [20]	1975*	HB, CC	Calcutta	NA	66	48.5%
Prevalence of CRS in Children with Ocular Abnormalities							
1.	Vijayalakshmi, *et al.* [21]	2002-2004	CB and HB, prospective	Madurai	<5y	51,548	0.09%
2.	Rajasundari, *et al.* [19]	2002-2005	HB, prospective	Madurai	<5y	65	26%
3.	Chaturvedi, *et al.* [22]	1976*	HB, CC	Lucknow	NA	16	69%
4.	Mahalakshmi, *et al.* [23]	1998-2006	HB, RCR	Chennai	<1y	593	8.4%
5.	Khandekar, *et al.* [24]	2003-2005	HB, RCR	Chitrakoot	4months-18y	502	-
6.	Johar, *et al.* [25]	2001-2002	HB, prospective	Ahmedabad	10 days-15y	172	4.1%
7.	Malathi, *et al.* [26]	1990-1998	HB, RCR	Chennai	<12y	70	41% (IgM in serum) 10% (Viral culture)
8.	Madhavan [27]	1990-1998	HB, RCR	Chennai	NA	86	8.1% (Viral culture)
9.	Eckstein, *et al.* [28]	1993-1994	HB, CC	Madurai	<15y	514	10.5%
10.	Eckstein, *et al.* [29]	1993-1994	HB, CC	Madurai	<1y	95	26.3% (IgM in saliva) 27.9% (IgM in serum)
11.	Angra, *et al.* [30]	1987*	HB, RCR	Delhi	NA	200	21.5%
12.	Angra, *et al.* [31]	1982*	HB, RCR	Delhi	<1y	485	1.4% (serology) 0.6% (viral culture)
13.	Ballal, *et al.* [14]	1991-1993	HB, prospective	Manipal	<1y	50	28%
14.	Chakrabarty, *et al.* [20]	1975*	HB, CC	Calcutta	NA	18	66.6%

*CB: community-based, CC: case control, HB: hospital-based, LB: Laboratory-based, NA: Not available, RCR: retrospective chart review, * Year of Publication, where the study duration was not specified.*

children presenting with one or more of the following manifestations: fever, pneumonia, jaundice, encephalitis, cardiac anomalies, hearing defects, nephritic syndrome, growth retardation, or ascites, were screened for rubella infection by assay of anti-rubella IgM in blood. The age-wise distribution of suspected cases was 0-29 days: 279, 1 month-1 year: 484, and >1 year: 184. The seropositivity rates were 2.5%, 4.3%, and 2.3% amongst children in the age-group 0-29 days, 1 month-1 year, and > 1 year respectively. Overall 2.8% children were IgM positive for rubella infection.

Chandy, *et al.* [18] reviewed the laboratory results for 646 infants with clinically suspected CRS between the years 2000 to 2008. CRS was suspected in an infant if he/she had one or more of the following symptoms and signs: fever, pneumonia, bone lesions, lethargy, cataract, congenital heart disease, hearing deficiency, hepatosplenomegaly, jaundice, or developmental delay. The proportion of suspected CRS cases that were laboratory confirmed increased from 4% in 2000 to 11% in 2008. Overall 61 (9.4%) infants were positive for anti-rubella IgM. 7 of them also gave a history suggestive of rubella infection in mother during pregnancy. The most common clinical features seen in confirmed cases were developmental delay, deafness, hepatitis, cataract, hepatosplenomegaly and respiratory distress.

In another study from south India [19], 65 under-5 children with ocular abnormalities with/without systemic manifestations consistent with suspected CRS were evaluated in a prospective study for anti-rubella IgM and IgG [21]. 26% (17/65) children were laboratory confirmed CRS cases as per the WHO. 79% of children (48/65) were seropositive for rubella infection (IgM and/or IgG).

Chakrabarty, *et al*. [20] tested 140 children with congenital malformations (cases) and 151 healthy children (controls) for rubella antibodies. Cases were categorized into (*a*) Rubella Syndrome (diseases of heart, cataracts, mental retardation, deafness; *n*=66), and (*b*) Other malformed babies (urogenital malformations, anomalies of skull and brain, diseases of alimentary tract, miscellaneous defects; *n*= 74). Seropositivity in cases of rubella syndrome (48.5%) was significantly higher than that of other malformed group (17.5%) and controls (33.1%); also antibody titers in this group (GMT: 60.4) were significantly more than other malformed group (GMT: 36) and controls (GMT: 33.4).

Prevalence of CRS amongst children with congenital ocular abnormalities

There are 14 studies evaluating rubella as the etiology of ocular defects in children (***Table* II**). All except one study [21] were hospital-based. Of these, 6 studies are retrospective chart reviews [23,24,26,27,30,31], 4 are case-control studies [20,22,28,29] and 4 are prospective studies [14,19,21,25]. There are 3 studies in children with various ocular abnormalities suggestive of CRS (probable CRS) [19,21,22]; one of them is a large community-based study [21], which has been described previously.

Rajasundari, *et al.* [19] conducted a prospective study in 65 under-5 children with various ocular abnormalities consistent with a diagnosis of suspected CRS viz., congenital cataract, congenital glaucoma, pigmentary retinopathy, microcornea, cloudy cornea, corneal opacity, megalocornea and anophthalmia, with/without systemic features of CRS or maternal history suggestive of rubella infection. Multiple samples from blood, saliva, lens aspirates and throat swabs were tested for antibodies or viral RNA. 40% of under-5 children with ocular abnormalities were positive for anti-rubella IgM. 79% of children (48/65) were seropositive for rubella infection (IgM or IgG). Overall 26% children with ocular abnormalities (17/65) met the WHO case definition of CRS. Viral RNA was detected in 26 children; the isolation being highest from lens (92% of positives) followed by saliva (60% of positives).

In a study by Chaturvedi, *et al.* [22] in the 1970s, out of 197 children with congenital malformations, 16 had eye anomalies (cataract, optic atrophy, phthisis bulbi, ptosis, coloboma iris, cryptophthalmos, glaucoma, anophthalmos and micropthalmos). 151 healthy age-matched controls without congenital malformations were also evaluated. Out of 16 children with eye anomalies, 11 (69%) were seropositive for rubella by hemagglutination test. 28% of healthy controls (n=151) were found to be seropositive for rubella.

There are 11 studies evaluating CRS as an etiological factor for congenital cataract. In a study from south India over 9 years from a tertiary eye hospital, 8.4% of congenital cataract amongst infants was attributed to CRS based on detection of IgM rubella antibodies [23]. Khandekar, *et al.* [24] in a retrospective study evaluated the records of 502 children, aged 4 months to 18 years, with cataract. Of these, 88 children had congenital cataract. Of the 88 children with congenital cataract, 11 eyes had coloboma of iris, 6 had microcornea, 1 had marfan syndrome with subluxated lens, 3 cases had other signs of CRS. Thereby, attributing 4% of congenital cataract in under-18 children to be due to CRS in the absence of any laboratory diagnostic test (results based on clinical examination).

In a prospective, hospital-based study from western

India, out of 172 children < 15y age with cataract, 7 children (4.6%) had congenital rubella syndrome [25]. TORCH test for rubella in 63 patients out of 152 patients of non-traumatic cataracts and out of them 7 were found positive for the rubella. 5 children were less than one year of age at the time of presentation while 2 cases presented at the age of 7 and 8.5 years respectively. Eight mothers gave a history of skin rash during pregnancy, out of which one child was positive for rubella antigen. Rubella cataract was total lamellar type morphologically.

In a study from Tamil Nadu, the lens aspirates were collected during a 9-year period (1990 to 1998), from 70 children <12 years with congenital cataract [26]. The lens aspirates were processed for the isolation of rubella virus by conventional viral isolation culture method. Identification of the virus was confirmed by immunofluorescence using human anti-rubella virus specific hyperimmune serum. Out of these 70 children rubella antibodies were also assessed in 55 children by ELISA test. Rubella virus was isolated from lens aspirates in 7 out of 70 children with congenital cataract. Out of the 55 sera tested, 22 had both anti-rubella IgM and IgG antibodies, 13 had only anti-rubella IgG, 7 had only anti-rubella IgM; 13 samples did not have detectable rubella antibodies. Out of these 55 children, rubella virus could not be isolated in 49. Out of those 49 children, 12 (24.5%) were below the age of 6 months. Based on viral isolation, 10% congenital cataract was attributed to rubella infection. In another study from Tamil Nadu, Madhavan *et al.* [27] isolated rubella virus from 8.1% of lens aspirates from children with congenital cataract.

In a case-control study from Tamil Nadu [28], 514 consecutive children with cataract attending an eye hospital outpatient clinic were examined and their parents interviewed by a trained interviewer using a standardized questionnaire. Rubella serology was performed in infants to detect congenital rubella syndrome (CRS). Of the 366 children with non-traumatic cataract, 15% were due to congenital rubella syndrome. Amongst infants 25% congenital cataracts were due to rubella. Cataract of nuclear morphology was found to have a 75% positive predictive value for CRS. None of the controls (n=35) had serological evidence of rubella. In another study from the same centre [29], 95 consecutive infants with congenital cataract were assessed for rubella infection by detecting anti-rubella IgM in saliva. In 61 infants anti-rubella antibodies were also assessed in serum. 26.3% infants with congenital cataract (25/95) had anti-rubella IgM in saliva. 27.9% infants (17/61) had anti- rubella IgM in serum.

Angra [30] evaluated 200 children with congenital cataract for rubella antibodies and found 43 children were seropositive for rubella. They attributed 21.5% of congenital cataract to congenital rubella infection. Out of these 43 children, 17 children had clinical features suggestive of CRS. Previously, Angra [31] reported that amongst 485 infants with congenital cataract, 41 children had maternal history suggestive of intra-uterine rubella infection. Of these 41 children, 32 (78%) had clinical rubella syndrome. In 34 children (83%) the mother's serology was positive and in 7 children (17%) rubella antibodies were detected. Positive lens culture was obtained in 7.3% children (3/41).

In a study from Karnataka, out of 372 children with suspected intra-uterine infections; 50 had bilateral congenital cataract [14]. Serum samples of these infants were tested for rubella specific IgM antibodies by micro-ELISA. 28% (n=14) infants with bilateral congenital cataract were seropositive for rubella infection (IgM).

In a study by Chakrabarty, *et al.* [20] in the early 1970s, out of 140 children with congenital malformations, 18 had congenital cataract. 66.6% of the children with congenital cataract had rubella antibodies detected by hemagglutination test.

***Web Table* III** shows the detailed methods and results of various studies evaluating the prevalence of CRS amongst children with congenital ocular abnormalities. ***Table* II** shows the summarized results of ***Web Table* III** and hence should be interpreted with caution.

Prevalence of CRS amongst children with hearing impairment

There are 4 studies evaluating congenital rubella infection as an etiological factor for deafness in Indian populations (***Web Table* IV**). Of these, 2 studies have been conducted amongst children attending schools for deaf and dumb [33,35], while 3 of them are hospital-based [32-34]. There is 1 case-control study [34], 1 retrospective chart review [32] and 2 prospective studies [33,35]. Rout *et al.* [32] found perinatal rubella as a significant etiological factor for deafness amongst the 38 factors evaluated in a retrospective study reviewing records of 1000 children <15y with deafness. Other factors *viz.*, prenatal diseases, exposure to radiation during gestation, premature delivery, low birth weight, postnatal jaundice and neonatal seizures, were the significant predictors of hearing impairment in children. Reddy *et al.* [33] in a hospital and school-based study evaluated the cause of hearing loss in 1076 children < 14y and reported a history of intra-uterine rubella infection in 1.7% children with deafness. Out of the 17 children with hearing loss and suspected intra-uterine rubella infection, 88.24% (*n*=15) children had severe sensorineural hearing

impairment and 11.76% (*n*=2) of them had profound deafness. In another study from a tertiary hospital in Delhi [34], 140 neonates were tested by BERA to ascertain the incidence of congenital and early acquired sensory-neural hearing loss. The subjects included 70 normal born neonates and 70 high-risk neonates. The 70 neonates with various high risks included those with a family history of deafness, prematurity, asphyxia, perinatal infections, hyperbilirubinemia, neonatal sepsis, meningitis, ototoxicity, or fetal malformations. 44 out of 140 neonates showed abnormalities on initial BERA testing. Perinatal Rubella was observed in two cases, which showed hearing loss. In another study from south India [35], information was collected by questionnaire from parents and teachers of 928 deaf school children. 374 of these children were also examined. Streptomycin injections were responsible for 3.6% of cases and meningitis for 5.3%. 29% of children examined had ophthalmic signs of CRS.

Prevalence of CRS amongst children with mental retardation

There are no studies evaluating congenital rubella infection as a cause of mental retardation amongst Indian children. However, there are 5 studies evaluating rubella as an etiological factor in subsets of children with mental retardation/developmental delay with suspected intra-uterine infection/ congenital malformations (***Web Table* V)**.

In a study from Vellore [13], serum samples were collected from 92 infants presenting with features of intrauterine infections between 1996 and 1997. Rubella IgM antibodies were detected in 1 out of 13 children (7.6%) who had neurological abnormalities. Ballal, *et al.* [14] evaluated 342 infants with suspected intra-uterine infections. 83 of them had developmental delay ± microcephaly. 11 out of 83 infants (13%) with developmental delay were seropositive for rubella (IgM). In a prospective study from Delhi, out of 249 infants suspected with congenital infection, 39 infants had mental retardation ± microcephaly, none of whom had anti-rubella IgM in blood [15]. In a study by Chaturvedi *et al*., [22] out of 197 children with congenital malformations, 34 had congenital CNS anomalies (mental retardation ± microcephaly, mental retardation + cerebral palsy, meninogocele, hydrocephalus, cranial defects, spinal defects). There were 64 healthy age-matched controls. 45% (15/34) and 28% (18/64) of children with congenital CNS anomalies and controls, respectively, were seropositive for rubella by hemagglutination test. In another study, out of 140 children with congenital malformations, 10 children had mental retardation, 6 of them were seropositive for rubella infection [20].

Prevalence of CRS amongst children with congenital heart disease

In 2 hospital-based, case-control studies in children with congenital malformations, CRS was found to be present in about 30% of children with congenital heart diseases [20,22], as shown in ***Web Table* VI**. Chaturvedi, *et al*. [22] evaluated 197 children with congenital malformations; 30 of which had congenital heart defects (atrial septal defects, ventricular septal defects, patent ductus arteriosus, pulmonary stenosis, Fallot 's tetralogy, dextrocardia), and 151 healthy controls without congenital malformations. 33% of children with congenital heart defects (*n*=10) were seropositive for rubella. The rubella seropositivity in control group was 28%. Chakraborty, *et al.* [20] recruited 140 children with congenital malformations, out of which 35 children had congenital heart disease (ventricular septal defect, atrial septal defect, patent ductus arteriosus, pulmonary stenosis, Fallot's tetralogy, tricuspid atresia, and Eisenmenger complex). 32.1% (*n*=45) children with congenital malformations were seropositive for rubella while 34.3% (*n*=12) of children with congenital heart defects were seropositive for rubella. 50 out of 151 healthy controls without congenital malformations had rubella antibodies in blood.

Prevalence of CRS amongst children with congenital malformations

There are 4 studies amongst Indian children with congenital malformations where congenital rubella infection has been investigated as an etiological factor as shown in ***Web Table* VII**. Of these, 3 are hospital-based [15,20,22] and 1 study is laboratory-based [36]. There are 2 case-control studies [20,22], while there is 1 study each of prospective [15] and retrospective chart review [36] type. In a laboratory-based study from Delhi over 15 years (1988-2002), the overall prevalence of rubella infection (IgM) amongst infants with congenital malformations (cataract, deafness, septicemia, congestive heart failure, anemia, microcephaly, bronchopneumonia, anencephaly, etc) was 10.46% [36]. The prevalence showed a declining trend over the years, being as high as 34.5% in 1988 to 0% in 2002. The prevalence of rubella infection among children with congenital malformations was high in 1989 (21%), 1991 (18.7%), 1998 (19.5%), and 1999 (8.6%) which correlated with the increase in acute rubella infection in child-bearing age-group in the years 1988, 1991, and 1998.

Broor, *et al.* [15] showed that nearly one-fourth of infants with congenital malformations (23/90) had anti-rubella IgM in blood. Previously, Chaturvedi, *et al.* [22]

reported a prevalence of 46% amongst infants with congenital malformations compared to 41% amongst children with unspecified age-group with congenital malformations and 28% amongst controls. Seropositivity for rubella amongst cases aged below 3 years was found to be significantly higher than that in age-matched controls. In a study from Calcutta, [20] nearly one-third of children with congenital malformations (45/140) were seropositive for rubella, which was similar to that seen in controls (50/151, 33.4%). Children with congenital malformations were categorized into (a) Rubella Syndrome (diseases of heart, cataracts, mental retardation, deafness; n=66), and (b) Other malformed babies (urogenital malformations, anomalies of skull and brain, diseases of alimentary tract, miscellaneous defects; n= 74). Seropositivity in cases of rubella syndrome (48.5%) was significantly higher than that of other malformed group (17.5%) and controls (33.1%); also antibody titers in this group were significantly more than those of the other two groups.

2. Susceptibility of Adolescent Girls and Women of Reproductive Age-group to Rubella Infection

There are no systematic reviews or nation-wide studies assessing the susceptibility of Indian population to rubella infection in general or specific to children, adolescent girls or women in the reproductive age-groups. A total of 29 studies (***Table* III**) were included for the purpose of this review, as detailed earlier (***Fig*. 2**). For the purpose of this review we segregated these studies into 3 broad target groups: (*i*) adolescent girls in pre-fertility age-group, (*ii*) non-pregnant women of reproductive age-group, and (iii) pregnant women. There were 12 studies in adolescent females of pre-fertility age-group (10-15y) [37-48], 10 studies in non-pregnant women of reproductive age-group (16-45y) [21,22,36,40,42,45-49] , and 15 studies in pregnant women [23,30,43,44,51-61] . Of these, 3 studies were conducted in female health personnel of reproductive age-group (16-45y) [40,50,62].

A. *Susceptibility of adolescent girls in pre-fertility age-group to rubella infection*

Out of the 12 studies assessing seroprevalence to rubella among Indian adolescent girls in pre-fertility age-group, there is only 1 community-based study [39] while 2 studies are school-based [37,38]. The remaining 9 studies [40-48] were conducted in hospital-based settings. All studies have been carried out prospectively.

In a recent study, the serological status of 1,329 healthy adolescent school girls, aged 12-15y, from 12 districts of Maharashtra, namely, Ahmednagar, Beed, Dhule, Jalna, Kolhapur, Latur, Nasik, Nandurbar, Pune, Satara, Solapur, and Osmanabad, was assessed [37]. Overall rubella seropositivity was 76.4% in 1,329 girls (GMT: 36.08 IU/mLmL, 32.4-40.17). Solapur and Latur districts showed the lowest percent seroprotection (around 68%). The urban population had a comparatively better immune status than that of the rural population (80.2% versus 73.1%), the difference being statistically significant.

Sharma, *et al.* [38] reported a rubella susceptibility rate of 37.4% in a school-based study in Jammu, wherein 275 girls aged 11-18 years were evaluated for anti-rubella IgG levels [38]. Out of 275 girls, 90 were seronegative for rubella. The GMT of the population was 9.83 IU/mLmL, which was much below the deemed protective level for rubella of 25 IU/mL.

In a community-based study from Tamil Nadu [39], sera were collected from 148 girls aged 11-16 years residing in rural areas of Tamil Nadu. The sera were tested for IgG rubella antibodies by ELISA. 13.5% (20 out of 148) of adolescent girls were seronegative for rubella.

In a hospital-based study from Amritsar [40], out of 200 adolescent girls aged 11-16 years, 128 (64%) had anti-rubella IgG antibodies. The seroprevalence among women aged 16-25y (*n*=159), 26-35y (*n*=167), and 36-45y (*n*=54), was 69.2%, 77.2% and 59.3%, respectively. Overall 36% of adolescent girls in Amritsar were susceptible to rubella infection.

In a hospital-based study from Delhi, amongst 140 adolescent girls aged 9-12y, 10% were seronegative [41]. In contrast, in another study from Delhi, 45.4% of girls aged 10-14y were found to be susceptible to rubella infection [42].

In a study from Hyderabad [43], the prevalence of rubella was determined in different age-groupage-groups of the female population by estimating IgG antibodies to rubella virus using ELISA. 274 pairs of maternal-cord blood samples were collected. Samples were also obtained from 139 children aged 1-15 years and assayed for rubella antibodies. The sample was read as positive if the titers were >15 EU/mL. 94.9% of mothers and 94.1% of cord blood samples showed seropositivity. Children between 1 and 5 years showed the lowest seropositivity of 69.2% which gradually increased to reach near 95% levels by 15 years. There is continuous exposure to rubella infection in childhood through adolescence.

Pal, *et al.* [44] reported 20% susceptibility to rubella among 17 girls aged 10-15y in Chandigarh. About one-third of adolescent girls aged 10-15y were reported to be susceptible to rubella in Lucknow [45]. In 2 small studies from Calcutta in early 1970s, adolescent girls aged 12-14y

TABLE III SUSCEPTIBILITY TO RUBELLA INFECTION IN ADOLESCENT GIRLS AND WOMEN IN INDIA

S No.	*Authors*	*Place*	*Setting*	*Duration*	*Participants*	*Rubella susceptibility*
	Adolescent Girls of Pre-fertility Age-group					
1.	Sharma, *et al.* [37]	Maharashtra	SB	2008-2009	1329	23.6%
2.	Sharma, *et al.* [38]	Jammu	SB	2000	275	37.4%
3.	Ramamurty, *et al.* [39]	Tamil Nadu	CB	2003	148	13.5%
4.	Singla, *et al.* [40]	Amritsar	HB	2003-2004	200	36%
5.	Yadav, *et al.* [41]	Delhi	HB	2001 *	140	10%
6.	Yadav, *et al.* [42]	Delhi	HB	1995 *	11	45.4%
7.	Bhaskaram, *et al.* [43]	Hyderabad	HB	1991 *	139	7%
8.	Pal, *et al.* [44]	Chandigarh	HB	1974 *	17	20%
9.	Mathur, *et al.* [45]	Lucknow	HB	1974 *	31	35.5%
10.	Chakraborty, *et al.* [46]	Calcutta	HB	1973 *	30	66.6%
11.	Chakraborty, *et al.* [47]	Calcutta	HB	1971 *	21	66.6%
12.	Seth, *et al.* [48]	Delhi	HB	1971 *	43	29.5%
	Non-pregnant Women of Reproductive Age-group					
1.	Chandy, *et al.* [18]	Vellore	LB	2000-2008	770	12.5%
2.	Rajasundari, *et al.* [49]	Madurai	HP	2004-2005	500	11.8%
3.	Rustgi, *et al.* [50]	Delhi	CB	2005 *	230	17.8%
4.	Vijayalakshmi, *et al.* [51]	Madurai	HP	2002	1000	15%
5.	Singla, *et al.* [40]	Amritsar	HB & HP	2003-2004	147	23.1%
6.	Yadav, *et al.* [42]	Delhi	HB	1995 *	162	43.8%
7.	Mathur, *et al.* [45]	Lucknow	HB	1974 *	349	9.5%
8.	Chakraborty, *et al.* [46]	Calcutta	HB	1973 *	174	46.8%
9.	Chakraborty, *et al.* [47]	Calcutta	HB	1971 *	129	44.1%
10.	Seth, *et al.* [48]	Delhi	HB & CB	1971 *	261	21.8%
	Pregnant Women					
1.	Padmaja, *et al.* [52]	Kerala	HB	2003-2006	485	34.3%
2.	Gupta, *et al.* [53]	Delhi	HB	2003-2004	305	12.8%
3.	Gandhoke, *et al.* [36]	Delhi	LB, RCR	1988-2002	5022	14.6%
4.	Deka, *et al.* [54]	Delhi	HB	2001-2002	100	21%
5.	Thapliyal, *et al.* [55]	Haldwani	HB	2005 *	20	33.3%
6.	Singla, *et al.* [40]	Amritsar	HB & HP	2003-2004	233	32.8%
7.	Turbadkar, *et al.* [56]	Mumbai	HB	2003 *	BOH: 380	38.7%
8.	Bhaskaram, *et al.* [43]	Hyderabad	HB	1991 *	274	5.1%
9.	Khare, *et al.* [57]	Delhi	HB	1987 *	160	46%
10.	Black, *et al.* [58]	Vellore	HB	1984	237	5.5%
11.	Shanmugam, *et al.* [59]	Kerala	HB	1982 *	536	26%
12.	Mathur, *et al.* [60]	Lucknow	HB	1982 *	300	20.7%
13.	Chaturvedi, *et al.* [22]	Lucknow	HB, CC	1976 *	194	12%
					BOH: 144	
					N: 50	18%
14.	Chakravarty, *et al.* [61]	Calcutta	HB	1976 *	40	32.5%
15.	Pal, *et al.* [44]	Chandigarh	HB	1974 *	322	19%
16.	Seth, *et al.* [62]	Delhi	HB	1972 *	220	12.7%

*BOH: Bad obstetric history, CB: Community-based, CC: Case-control, HB: Hospital-based, HP: Health personnel-based, LB: Laboratory-based, RCR: Retrospective chart review, SB: School-based, *Year of Publication, where the study duration was not specified.*

showed very high susceptibility of nearly 67% [46,47]. The susceptibility rates among women aged 15-19y and 20-25y were about 41% and 46% respectively. A study from Delhi [48], between 1968 and 1969, evaluated 346 women aged 10-34y for rubella antibodies by hemagglutination test. About 30% of girls, aged 10-14y, were susceptible to rubella infection, while susceptibility among women aged 15-19y, 20-24y and 25-34y was 25.4%, 22.4% and 18.5% respectively.

A uniform finding from 4 studies [37,40,42,48] reveals that susceptibility to rubella infection in adolescent girls living in rural areas is higher than those living in urban areas. Also adolescent girls from upper socio-economic status were found more susceptibile to rubella infection [40,43].

B. *Susceptibility of non-pregnant females in reproductive age-group to rubella*

There are 10 studies assessing the seroprevalence to rubella amongst non-pregnant Indian females aged 16-45y [18,40,41,45-51]. Only 2 prospective studies have been done in the community-based set-up [48,50]. There is a single laboratory-based retrospective study [18], while the remaining 7 studies have been carried out in hospital-based settings [40,42,45-47,49,51]. Three studies assess the seroprevalence to rubella infection amongst female health personnel [40,49,51].

In a laboratory based study from Vellore [18], records of 770 women aged ≥18y attending the departments of obstetrics and gynecology and reproductive medicine unit, were examined to assess the susceptibility to rubella. 12.5% of women in the reproductive age-group were seronegative for rubella. Women in the 19–23 and ≥35 years age-groups showed better levels of immunity to rubella (91%) than those in the 24–34 years age-group (85.5%).

In a study from an eye hospital in Madurai [49], out of 581 health personnel (500 female and 81 male), 66 personnel (59 females and 7 males) were found to be seronegative for rubella. 493 health personnel were seropositive with good protective immunity and 22 had both IgM and IgG antibodies. Sixty six volunteers (59 females and 7 males) were found to be seronegative to rubella. 11.8% of female health personnel in the reproductive age-group were seronegative for rubella. Seronegativity was high among the laboratory/research staff and physicians and lowest among housekeepers/ caterers.

Rustgi, *et al.* [50] in a community-based study assessed rubella serology of 230 adolescent unmarried girls aged 15-18 y (115 girls of high socioeconomic status and 115 girls of low socio-economic status). Overall 17.8% girls were seronegative for rubella. Girls in the lower socio-economic status were less vulnerable to rubella (9.6% seronegative) compared to girls of higher socio-economic status (26.1% seronegative) (P <0.001).

In another study from three eye hospitals in Tamil Nadu [51], 1000 female health personnel were tested for IgG rubella antibodies. 15% of health personnel were seronegative for rubella. The susceptibility with respect to different age-groups was 18-19y: 13%, 20-24y: 15%, 25-29y: 16.4%, and 30-40y: 23.9%. With respect to the different eye centers, the proportions of seronegative female health personnel were: 11.7% (8.1-16.5) at Coimbatore, 15% (12.3-18.1) at Madurai, and 20.8% (14.7-28.6) at Tirunelveli. The proportion of seronegative personnel was significantly higher among married women (21.5%) than among single women (14.0%) (P = 0.02). Rates of seronegativity were highest amongst physicians and lowest among housekeepers.

In a rubella serosurvey from Amritsar [40], out of 580 subjects (including 80 health personnel), there were 380 women in the reproductive age-group. The seroprevalence in women in the age-groups 16-25y, 26-35y and 36-45y was 69.2%, 77.2% and 59.3%. Overall, 28.7% of women in the reproductive age-group were susceptible to rubella infection. Out of the 380 women, 233 were pregnant and had a seropositivity of 67.8%; the seropositivity in the 147 non-pregnant women was 76.9% the difference was not statistically significant. They also reported 20% seronegativity amongst 80 female hospital workers in Amritsar.

In a study from a tertiary hospital in Delhi [41], out of 162 females in the child-bearing age-group, 90 (56.2%) were seropositive for rubella. Nearly half of the females were susceptible to rubella infection.

In a study from Lucknow 500 sera were collected from females of different age-groups and 100 sera from pregnant women and tested for rubella antibodies by hemagglutination test [45]. Out of 500 sera tested 400 (80%) were positive. In the cord sera, 74.1% samples (43 out of 58) were positive and amongst infants 55.5% were positive, decreasing to 52.3% in age-group 2-3y. Six years onwards the seropositivity increased with increasing age, reaching peak at 26-30y (93.9%). A second peak was seen after 45y. Amongst the women in the reproductive age-group, 9.5% were seronegative.

In a survey from Calcutta among women aged 12-25y, rubella antibodies were tested in sera from 207 girls attending out-patient department. The seropositivity in age-groups 12-14y, 15-19y and 20-25y were 33.3%,

59.3% and 53.9% respectively [46]. In a similar study from Calcutta, seropositivity in age-groups 12-14y, 15-19y and 20-25y were 33.3%, 58.7% and 53.1% respectively [47].

In a hospital-based study from Delhi, 421 females aged 5-34y were tested for rubella antibodies [48]. Amongst the 220 women in reproductive age-group 12.7% were seronegative for rubella. The susceptibility in different age-groups was 5-9y: 52%, 10-14y: 29.5%, 15-19y: 7.1%, 20-24y: 11.6%, 25-29y: 15.5%, and 30-34y: 15.4%. The women from urban areas were more susceptible compared to women from rural areas. The mean antibody titer in urban females was highest in the 10-14y age-group and lowest in 25-34y age-group.

C. Susceptibility to rubella in pregnant females

Padmaja, *et al.* [52] in a hospital-based study, assessed the seroprevalence to rubella among pregnant women. Out of 485 pregnant women attending the antenatal clinics of 3 government maternity hospitals in Thiruvananthapuram, Kerala, between 2003 and 2006, 283 women (65.7%) were IgG-positive and 13 women (3%) were IgM positive, when tested in the first trimester. At the time of delivery only 37 women who were initially IgG-negative were tested again for rubella antibodies; among them, 28 (75.7%) were now IgG positive and 2 (5.4%) were IgM positive. Only, 3 seropositive women brought their babies for follow up and they were found to have normal hearing.

In a retrospective study from a tertiary care hospital in Delhi [53], case records of 305 pregnant women (73 of them had history of previous bad obstetric outcome: spontaneous abortion, premature labor or congenitally malformed or stillbirths) were assessed for immunity to rubella. 266 women (87.2%) had anti-rubella IgG. The age-wise prevalence of anti-rubella IgG was: 15-19y: 92.5%; 20-24y: 89.5%; 25-30y: 87%, and > 31y: 77.5%. The seropositivity rate among pregnant women aged 15-19y was significantly higher than those aged > 31y. Seropositivity in those with previous bad obstetric outcome was 91.7% against 85.7% in women with normal obstetric performance. Only 3 women (0.98%) were positive for anti-rubella IgM.

Gandhoke, *et al.* [36] reported that about 14.6% of pregnant women in Delhi were susceptible to rubella infection based on data collected between 1988 and 2002. Over 15 years, the susceptibility of pregnant women decreased from 51% in 1988 to 13% in 2002. In a prospective study from a tertiary hospital in Delhi, out of 100 pregnant women, 21 were seronegative for rubella [54].

In a small hospital-based study in Haldwani [55], 20 pregnant with bad obstetric history were tested for rubella antibodies. 4 women were positive for anti-rubella IgM and 10 women were positive for anti-rubella IgG.

Turbadkar, *et al.* [56] reported anti-rubella antibodies in 61.3% of pregnant women with bad obstetric history (BOH) in a prospective study in a tertiary hospital in Mumbai over 1 year. 26.8% of pregnant women with BOH had anti-rubella IgM antibodies. In a study from Hyderabad, nearly 95% of pregnant women were seropositive for rubella, demonstrating high levels of immunity [43]. While in a study from Delhi around the same time showed that only 54% of pregnant women had rubella antibodies [57]. A study from Vellore demonstrated that out of 237 pregnant women, 94.5% had rubella antibodies [58]. Shanumugam, *et al.* [59] assessed the serological status of 526 pregnant women for rubella by hemagglutination inhibition test (HAIT). 74.1% of women had antibodies for rubella; the prevalence rate was more during second trimester (77.5%). The geometrical mean titer (GMT) was 73 EU/mL for rubella antibody and rubella antibodies were found to be more prevalent in the age-group of 26-30 years (76.8%). In a hospital-based study from Lucknow, out of 300 pregnant women, nearly 21% were seronegative for rubella [60]. Chaturvedi *et al.* [22] undertook a case control study wherein there were 144 pregnant women with bad obstetric outcome as cases and 50 pregnant women with normal obstetric history as controls. 12% of cases and 18% of controls were seronegative for rubella. In a study from Calcutta, 32.5% of pregnant women were seronegative for rubella [61]. The susceptibility rates among pregnant women from Chandigarh [44] and Delhi [62] were much lower at 19% and 12.7% respectively. The rubella susceptibility among different age-groups of pregnant women from Delhi were reported as 15-19y: 7.1%, 20-24y: 11.6%, 25-29y: 15.5%, and 30-34y: 15.4%.

The seroprevalence amongst rural females was higher compared to urban females [37,40,48], as also in women from lower socio economic class [40,42,50]. The susceptibility rates to rubella infection amongst pregnant women vary from as low as 5.5% [58] to as high as 46% [57].

There are 6 studies evaluating rubella seroprevalence in pregnant women with bad obstetric history [22,36,43,55,56,60]. The seroprevalence amongst women with bad obstetric outcome was higher compared to women with normal pregnancy outcome. In a large laboratory-based study from Delhi over 15 years [36], 5022 samples from pregnant women were evaluated; the seroprevalence of rubella infection was higher in women

with bad obstetric history (87%) compared to those with normal pregnancy outcome (83%). Bhaskaram *et al.* [43] found the antibody titers to rubella in women with adverse pregnancy outcome (34.2 ± 4.2 EU/mL, n=8) or stillbirths (42.1 ± 3.9 EU/mL, n=23) was much lower than that seen in women with normal pregnancy outcome (51.8 ± 1.9 EU/mL, n=274).

3. Immunogenicity of Rubella Containing Vaccines in India

There are no systematic reviews or nation-wide studies assessing immunogenicity of rubella vaccine or MMR vaccine amongst children, adolescent girls, or women of reproductive age-group. We short-listed 9 articles for inclusion in our review; these included 4 studies evaluating the immunogenicity of rubella vaccine [37,38,41,63] and 5 studies evaluating the immunogenicity of MMR vaccine [64-68] (***Table* IV**). Three of the 4 studies on rubella vaccine were conducted in adolescent girls: 2 were school-based [37,38] and one was hospital-based [63]. Remaining one study [63] was conducted in female health personnel.

A. *Immunogenicity of rubella vaccines*

There are 4 studies assessing the immune response of rubella vaccine amongst Indian children (***Table* IV**). In a multi-centric study from 12 districts of Maharashtra [37], 1,329 female adolescent girls (12-15y) were assessed for their serological status in terms of rubella exposure. After enrolment, a pre-vaccination blood sample was collected from the participants followed by rubella vaccination (R-vac). Pre-vaccination rubella immunity was higher in the urban (80.2%) population compared to the rural (73.1%) population. Following R-vac vaccination, out of 1,159 participants who completed the study, all (100%) the urban and 99.5% of participants in the rural area developed antibodies against rubella. Overall, 99.7% of the participants developed antibodies to rubella. No significant adverse effects were reported by any participant.

Sharma, *et al.* [38] assessed the seroprevalence to rubella in 275 school-girls aged 11-18y from Jammu; the seronegative girls were administered rubella vaccine (R-vac, Serum Institute of India, Pune). The pre-vaccination rubella seroprevalence was 67% and 90 girls were seronegative. Eight weeks after immunization, the seroprevalence was 100%. The pre-vaccination rubella IgG GMT was 9.83 IU/mL which rose to 94.8 IU/mL after vaccination (P<0.01). No serious adverse effects were noted following vaccination.

Rajasundari, *et al.* [49] assessed the response to rubella vaccine amongst 60 health personnel; out of which there were 55 females aged 15-40y. The seroconversion was observed in all vaccinated individuals, as seen by the appearance of anti-rubella IgG antibodies by the fourth week, reaching the peak protective levels (>20 IU/mL) by the third month, remaining at the same level by the sixth month. There was also a progressive increase in the avidity after vaccination. A significant (P <0.001) difference in the mean avidity index (mean ± SD) was observed among the fourth week (9.2 ± 15.23), third month (36.9 ± 12.20) and sixth month (58.2 ± 9.25) post-vaccinated samples, indicating a progressive increase in the maturation of antibody from the first to the sixth month after vaccination.

Yadav, *et al.* [41] assessed 140 school girls aged 9-12y and found 10% were seronegative for rubella. The seronegative girls (n=14) were vaccinated with rubella vaccine and they observed 100% seroprevalence 4-6 weeks after vaccination.

B. *Immunogenicity of MMR vaccine*

There are 5 studies assessing the immune response of MMR vaccine amongst Indian children (***Table* IV**). Gomber, *et al.* [64] recruited 84 children at 4-6 years, all of whom had received one dose of MMR vaccine between 12-24 months, and found that only 81% were seropositive after 4-5y follow-up. They administered a second dose of MMR vaccine and showed 100% seroprevalence after 4-6 weeks. In contrast, Raut, *et al.* [65] recruited 99 children aged 1-10y (14.04 ± 1.80 y) who had received single dose of MMR vaccine and followed them up after 6 years to assess persistence of immunity. Only 41 children could be followed up. They reported 100% (95% CI: 91 to 100%) seroprevalence amongst children even after 6 years. Yadav, *et al.* [66] evaluated the rubella seroprevalence in 240 children, aged 9-18 months, who had not received MMR vaccine and found 24% seropositivity. After 4-6 weeks of MMR vaccination, the seropositivity rose to 96%. In another multi-centric study, 89 children aged 15-24 months who had previously received one dose of measles vaccine, were given MMR vaccine, and followed up to assess seroprevalence at 1 week and 4 weeks [67]. They reported a seroprevalence of 13% before vaccination which rose to 15% at 1 week after vaccination and 99% at 4 weeks after vaccination. Singh, *et al.* [68] also demonstrated that seroconversion rates to rubella antigen were high as well as comparable at 9, 12 and 15 months age, tested 4 weeks after immunization with MMR vaccine by ELISA.

4. Coverage of Rubella Containing Vaccines in India

No national estimates on the coverage of MMR vaccine are available [69]. We found 3 small regional surveys on

TABLE IV IMMUNOGENICITY OF RUBELLA CONTAINING VACCINES IN CHILDREN AND ADOLESCENTS IN INDIA

S No.	*Study Group; Setting; Duration*	*Place*	*Age-group (n)*	*Vaccine*	*Protective titer of Anti-Rubella IgG antibody*	*Duration of follow-up*	*Results*
Studies on Rubella Vaccine							
1.	Sharma, *et al.* [37]; SB	Maharashtra: 12 districts	12-15y (*n*=1159)	R-vac vaccine (Serum Institute of India), 1000TCID$_{50}$ of rubella virus (Wistar RA 27/3 strain)	≥11 EU/mL	6-8 weeks	Seroprevalence post-vaccination: Urban: 100% Rural: 99.5% Overall: 99.7%
2.	Sharma, *et al.* [38]; SB2000	Jammu	11-18y (n=275)	RA 27/3 rubella vaccine (Serum Institute of India)	≥25 IU/mL	8 weeks	Seroprevalence pre-vaccination: 67% (9.83 IU/mL) Seroprevalence post-vaccination: 100% (94.8 IU/mL)
3.	Yadav, *et al.* [41]; HB2001*	Delhi	9-12y (n=140); 14 seronegative girls administered vaccine	RA 27/3 rubella vaccine (Serum Institute of Pune), 1000 TCID50 of RA 27/3 strain	>10 EU/mL	6-8 weeks	Seroconversion: 100%Pre-vaccination titres: 306.1 EU/mLPost-vaccination titres: 569.1 EU/mL(P <0.001)
4.	Rajasundari, *et al.* [63]; HP2004-2005	Madurai	15-40y; 60 seronegative health personnel (55 females)	RA 27/3 rubella vaccine (Serum Institute of India)	>20 IU/mL	4 weeks	Seroprevalence post-vaccination at 4 weeks: 100%Levels of highly avid antibodies increased progressively after immunization. Avidity indexAt 4 weeks: 9.2 ± 15.23 At 6 months: 58.2 ± 9.25
Studies on MMR Vaccine							
5.	Gomber, *et al.* [64]; HB2007-2008	Delhi	4-6y old children who had received one dose of MMR vaccine between 12-24 months (n=84)	MMR Vaccine, Tisevac (Serum Institute of India), 1000 TCID$_{50}$ of Rubella (RA 27/3 strain)	>12U/mL	1st follow-up: 4-5y after first dose of MMR 2nd follow-up: 4-6 weeks after the second dose of MMR	Seroprevalence pre-vaccination: 81%Seroprevalence post-vaccination: 100%
6.	Raut, *et al.* [65]; CB1999 and 2005	Pune	1-10y (n=99)	MMR vaccine (Serum Institute of India) containing RA 27/3 rubella virus	Immune ratio ≥ 1.1	6y	Seroprevalence post-vaccination: 100% (n=41)

Contd.....

S No.	*Study Group; Setting; Duration*	*Place*	*Age-group (n)*	*Vaccine*	*Protective titer of Anti-Rubella IgG antibody*	*Duration of follow-up*	*Results*
7.	Yadav, *et al*. [66]; SB1997-1998	Delhi	9-18 (n=240)	MMR vaccine (Serum Institute of India) containing RA 27/3 strain	>10 EU/mL	6-8 weeks	Seroprevalence pre-vaccination (n=240): 24%Seroprevalence post-vaccination (n=202): 96%
8.	Bhargava, *et al.* [67]; HB1994*	Indore, Bombay, Pune	15-24 months (n=89)	MMR vaccine containing RA 27/3 strain	NA	1 and 4 weeks	Seroprevalence pre-vaccination: 13%Seroprevalence post-vaccination at 1 week: 15%Seroprevalence post-vaccination at 4 weeks: 99%
9.	Singh, *et al*. [68] HB, 1990-91	Vellore	9-15 months (n=111, HI test; n=121, ELISA)	MMR vaccine (Pluserix, Smith-Kline, and French, Rixensart, Belgium)	>15 EU/mL	4 weeks	**HI test:** Seroprevalence pre-vaccination: 35.1% Seroconversion rate after vaccination in seronegative children: 97% **ELISA test:** Seroprevalence pre-vaccination: 13.2% Seroconversion rate after vaccination in seronegative children: 95.2%

*CB: Community-based, HB: Hospital-based, HP: Health-personnel based; NA: Not available; SB: School-based; * Year of Publication, where the study duration was not specified.*

TABLE V IMMUNIZATION COVERAGE OF MMR VACCINE IN INDIA

Study Group	*Duration*	*Study*	*Age-group (n)*	*Study Design, Sampling technique*	Coverage
Chhabra, *et al.* [70]	2000-2003	Delhi	24-27 months (*n*=693)	CB, CS, systematic random sampling	41.6%
Dalal, *et al.* [71]	2000-2001	Goa	12-23 months (*n*=362)	CB, Cluster sampling	5%
Puri, *et al.* [72]	2004-2005	Chandigarh	Under-5 (*n*=1031)	CB, survey	27.6%

CB: Community-based, CS: Cross-sectional, NA: Not available.

coverage of MMR vaccine in Delhi, Chandigarh and Goa (***Table* V**). In a study from two urbanized villages of East Delhi, children aged 24-47 months were selected using systematic random sampling and coverage of 41.6% of MMR vaccine was reported during 2007 [70]. In a house to house survey conducted, between January 2004 and September 2005, from an urban sector of Chandigarh, MMR coverage of 27.6% in under-five children was reported [71]. In questionnaire-based survey, a mere 5% coverage was reported from Goa wherein 362 children aged 12-23 months were recruited from different parts of Goa using cluster sampling method from December 2000 to May 2001 [72].

DISCUSSION

This systematic review has examined the prevalence of congenital rubella syndrome in India with respect to general population as well as special population groups (ocular abnormalities including cataract, hearing loss, mental handicap, cardiac defects and congenital anomalies). Almost all studies have been done in institutional/hospital set-ups and community-based studies are grossly lacking. There are no studies assessing the prevalence of CRS in general population. All studies have evaluated the CRS burden in symptomatic cohorts of children. 1-15% of all infants suspected to have intra-uterine infection were found to have laboratory evidence of CRS. About 3-10% of clinically suspected CRS cases, ultimately get confirmed CRS with the aid of laboratory tests. CRS accounts for 10-15% of pediatric cataract. There are no studies estimating the prevalence of confirmed CRS in children with hearing loss, mentally retardation, or congenital heart disease. 10-50% of children with congenital anomalies have laboratory evidence of CRS. Almost all studies on seroprevalence of rubella amongst Indian females revealed that 10-30% of adolescent girls and 12-30% of women in the reproductive age-group are susceptible to rubella infection. Rubella vaccine was found to be highly immunogenic in Indian adolescents and women with 100% seroconversion documented 4-8 weeks after vaccination. MMR vaccine shows a 100% seroconversion when tested 4-6 weeks after vaccination, the immunogenic response 4-6 years after vaccination has been reported to vary from 81% to 100% [64,65]. The coverage data of RCVs in India is not available. However, the coverage of MMR vaccine has been reported as 42%, 30% and 5% from Delhi, Chandigarh and Goa, respectively.

There is only a single large community-based study in under-5 children with ocular abnormalities on this aspect [21]. 0.6% and 0.09% of under-5 children with ocular abnormalities have clinical CRS and confirmed CRS, respectively. Based on their findings, the prevalence of clinical CRS can be calculated as 6 per 1000 under-5 children with ocular abnormalities. Laboratory-confirmed CRS (anti-rubella IgM positive) prevalence can be calculated as 0.9 per 1000 under-5 children with ocular abnormalities. However, it is difficult to further extrapolate these results to the total population/ child population in India as there are no estimates of the burden of children with ocular abnormalities. Also, prevalence estimates based on this study would be confounded by the fact that children with CRS but without ocular abnormalities were probably missed out in this study. In addition, children with CRS who were too sick or physically handicapped were probably not brought to the hospital. In addition, the ones who were too sick had probably died before they could be brought to the hospital. Considering that only 41% of the deliveries in India are in institutional set-ups [73], the probability of institutional follow-up for children delivered at home is less and therefore the chances of detecting CRS in such children is remote. Consequently, the projected numbers of CRS in India based on such hospital-based studies would be an underestimate of the actual disease-burden.

Most of the studies we included in our review did not

use the standard case definitions for CRS [9]. Amongst the studies evaluating CRS prevalence amongst Indian children, only two studies have defined CRS as per the WHO [19, 21]. Most of the studies done in 1970s and 1980s have used hemagglutination test to detect rubella antibodies and have not distinguished between IgG and IgM antibodies. 12 studies have established rubella as an etiology of ocular abnormalities based on detection of anti-rubella antibodies in blood [14,19-23,25,26,28-31], and rubella antibodies in saliva [19,28,29]. Out of 14 studies only 4 studies have attempted viral isolation from lens aspirates [19,26,27,31]. While IgM antibodies decrease with time and may not be detectable after infancy, viral isolation from lens aspirates may be possible even upto 3 years age [13]. Therefore, tests using anti-rubella IgM estimation alone may under-diagnose CRS compared to combination of both the tests. In addition PCR is a highly sensitive and specific test which also helps to quantify viral load and it has been used only in 1 study [19]. The marked variation in the patient's ages and profiles, as well as the laboratory techniques used to confirm congenital rubella infection makes it difficult to compare the results of different studies and predict trends in CRS prevalence over time.

About 12-14% of childhood blindness in India is due to cataract [74, 75]. In India, CRS was found to be the second leading cause of non-traumatic childhood cataract, exceeded only by hereditary cataract [28]. Rubella cataract accounted for about 10% of pediatric cataract in India [28]. Therefore, by extrapolation about 1.5% of childhood blindness in India can be attributed to rubella cataract alone. The National prevalence of blindness/low vision is 0.8/1000 child population [76]. Therefore, the National prevalence of blindness/low vision due to rubella cataract is 0.012/1000 child population. In 2010, the under-15 Indian child population stood at about 370 million. Therefore, there were about 4440 children (<15y) in India in 2010 with rubella cataract. Since, CRS manifests with cataract in about 50-60% cases, therefore about 9000 children (<15y) in India had CRS in 2010. However, this is a very rough estimate. Rubella cataract also contributes to a significant financial burden. Approximately 70 million blind-person years are caused by childhood blindness of which about 10 million blind-person years (15%) is due to childhood cataract [75]. Since, rubella cataract contributes to 10% of pediatric cataract, as a corollary, about 2 million blind-person years are due to rubella cataract. Eventually, not all children with rubella cataract get operated and even those operated may have dismal outcomes. In a recent study from India, 50% of children with bilateral cataract remained legally blind following cataract surgery [77]. This may ultimately transcend into significant financial loss for the country.

There are no country-wide estimates on rubella seroprevalence in women of reproductive age-group. However, most studies from different regions in India indicate that rubella susceptibility in adolescents and women of childbearing age is more than 15%. There are 7 studies on rubella susceptibility among adolescents and women in childbearing age in Delhi between 1970 and 2006. While the time trends from Delhi indicate a lowered susceptibility to rubella infection over the years, high susceptibility rates of 34.3% and 38.7% were reported from Thirunavanthapuram and Mumbai respectively, in 2010 [52] and 2003 [56], respectively. Considering the WHO guidelines, which suggest that CRS can occur even when susceptibility levels in women are below 10% [78], the recent very high susceptibility rates are of concern. The findings of the present study indicate the need to plan strategies for rubella vaccination in the under-five children all over India and conduct mass scale vaccination with monovalent rubella vaccine for adolescent girls as has been done in the developed countries. Currently, MMR vaccine is given to children as a part of the State health policy only in Delhi, Goa, Puducherry and Sikkim [79-81]. Rubella vaccine is given to all adolescent girls since 2003 as a state policy in Goa [81]; all other states and union territories in India rely on private practitioners for rubella vaccination for adolescent girls. This may be the reason for the high susceptibility to rubella among Indian female population. WHO recommends that all member states that have first-dose measles-containing vaccine (MCV1) coverage >80%, should introduce RCV in their immunization program [5]. In 2009, the median MCV1 coverage was 96% (IQR: 92-99%) for the 130 states using RCV. However, 9 out of 130 member states have MCV1 coverage <80%; median MCV1 coverage being 76% (IQR: 74-91%) [5]. According to UNICEF-CES 2009 [68], the measles vaccination coverage in India is 74.1% for children aged 12-23 months. However, Andhra Pradesh, Assam, Delhi, Goa, Himachal Pradesh, Karnataka, Kerala, Maharashtra, Mizoram, Punjab, Tamil Nadu and all union territories have measles vaccination coverage > 80%. Given the evidence that both MMR and rubella vaccines are highly immunogenic amongst Indian population with protective titers persisting even after 4-6 years of immunization [64,65], we need to consider the introduction of MMR vaccine for all children aged 12-15 months and rubella vaccine for all adolescents in the pre-fertility age in a phased manner at least in these parts of India with high coverage of measles vaccine. However, this strategy needs to be propagated with caution, as this may be a double-edged weapon. It has been recognized by WHO that by introducing mumps and rubella vaccines into childhood vaccination programs that do not achieve high coverage (>80%), the median age at which rubella

infection occurs increases which in turn paradoxically increases the incidence of CRS [82,83].

No nation-wide data on coverage of MMR vaccine are available. However, the coverage of MMR vaccine in Delhi from two urban villages in east Delhi was reported as about 42% and that in Chandigarh was about 30%; the corresponding figures from Goa are a mere 5%. Though all the three regions have coverage estimates far below that aimed by the government (>80%), the relatively better coverage seen in Delhi compared to Goa, may be explained by the fact that while Delhi government adopted an extra Measles Mumps Rubella (MMR) vaccine since 1999 [79], Goa adopted MMR vaccine in the state immunization policy in 2003 [80]. Chandigarh showed comparable coverage figures to Delhi despite a lack of state immunization policy on MMR as this study was done in an affluent urban sector of Chandigarh.

The two WHO regions, American and European regions had set goals for rubella elimination by 2010. While the United States of America has managed to attain its set goal ahead of time through a 4 pronged strategy of national vaccination policy with high coverage among young children, ensuring high levels of immunity, adequate surveillance, and introduction of rubella vaccine in countries of western hemisphere to decrease risk of import of rubella cases [84,85], the European region is almost there [86,87]. The WHO has recommended 3 strategies to eliminate CRS from countries like India [7]. The first stage involves investigation of any rubella outbreak to assess CRS cases for at least 2 years and to determine susceptibility to rubella infection among women in childbearing age-group. The second stage is to begin a national rubella immunization program to actively report all rubella cases on a monthly basis and to report each CRS case. The third stage is investigation and reporting of each case of febrile rash within 48 hours. While India is still to grapple with the first stage of rubella elimination, the logistics of conducting a nationwide antenatal survey with stratified sampling to determine the risk for rubella in the community in India can be particularly daunting. Also the cost of Rubella IgG or IgM in a standard laboratory in India would be around 450 INR, which makes serosurveillance of rubella amongst Indian females of child-bearing age, a prohibitive option. In contrast, the cost of a single dose of indigenous MMR vaccine and rubella vaccine is 70 INR and 55 INR, respectively [88], making implementation of state immunization programs using RCV a more feasible option.

We could not estimate the true prevalence of CRS in India in the light of the limitations of the study designs and absence of national surveillance. Limitations of this review also include a lack of a meta-analysis and inability to access institutional or regional databases and the ERMED. However, our review process does have several strengths. The main highlights of our review process include a systematic approach, detailed literature search from multiple sources, inclusion of all publications that attempted to identify CRS cases in population directly through laboratory tests or indirectly by seeking detailed maternal history or clinical examination. We considered all types of study design. In the light of our findings we recommend a need to revise our national immunization policy to include rubella containing vaccines in the national immunization program and integrate the surveillance of rubella and CRS with measles surveillance.

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