The cost-effectiveness of rubella vaccination among women in Maharashtra

Revised- Outcome Report

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Study title and investigators details

Title: The cost-effectiveness of rubella vaccination among women in Maharashtra

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Content

List of Abbreviations

Immunoglobulin	Ig
Reverse Transcriptase Polymerase Chain Reaction	RT-PCR
Congenital Rubella Syndrome	CRS
Enzyme-Linked Immunosorbent Assay	ELISA
World Health Organisation	WHO
United State Dollar	US$
Global Alliance for Vaccines and Immunizations	GAVI
Quality-Adjusted: Life-Year	QALY
Disability Adjusted Life Years	DALY
Human papillomavirus	HPV
Plaque-Forming Units	PFU
Measles Mumps Rubella	MMR
Measles Rubella	MR
Measles Mumps Rubella Varicella	MMRV
Hemagglutination Inhibition	HI
Rubella containing virus	RCV
Region of the Americas	AMR
European Region	EUR
Western Pacific Region	WPR
Eastern Mediterranean Region	EMR
South-East Asian Region	SEAR
African Region	AFR
Supplementary Immunization Assay	SIA
Incremental Cost-Effectiveness Ratio	ICER
Health Management Information System	HMIS
Neutralization test	NT
focus reduction neutralization test	FRNT
Rubella Virus	RuV
Enzyme Immuno Assays	EIA

International Unit	IU
Intra muscular	IM
Confidence Interval	CI
Headquarter	HQ
Lower Middle Income	LMI
Upper Middle Income	UMI

Executive Summary

Title: The cost-effectiveness of rubella vaccination among women in Maharashtra

Background: Rubella virus is a leading cause of vaccine-preventable birth defects and can cause epidemics. India has set a goal to eliminate measles and rubella/Congenital Rubella Syndrome (CRS) by 2023. Towards this goal, Union Ministry of Health and Family Welfare has launched the Measles and Rubella Vaccination Campaign in 2017 with a view to providing measles-rubella (MR) vaccines to children between the ages of nine months and under 15 years. Although rubella virus infection usually produces a mild febrile rash illness in children and adults, it is one of the major threats to women of childbearing age group because of its major adverse outcome in the new borne, i. e. congenital rubella syndrome (CRS). Congenital rubella syndrome, a devastating constellation of birth defects, is caused by rubella infection during pregnancy. Despite being vaccine preventable, CRS continues to account for preventable severe morbidity including childhood blindness, deafness, heart disease, and mental retardation. In order to reduce the disease burden of CRS, the women of reproductive group should be immunized

Aim: This study aims to conduct cost-effectiveness analysis of rubella vaccination among women of reproductive age group (20-39 years) in Maharashtra.

Methodology

Study population: The study population is a cohort of women with high fertility rate (i. e. age group 20-39 years) in Maharashtra.

Exclusion criteria:

- The women who have undergone female sterilization or hysterectomy
- The women whose husbands have undergone male sterilization

Intervention: MR vaccine was the study intervention, which was compared with current status (no vaccination) in the study population. Outcome of vaccination was measured in CRS cases averted due to vaccination. The decision tree analysis was conducted in order to perform cost effectiveness study.

Results: The total number of women in age group 20-30 years was estimated to be 2,03,76,000 (Government report population projection of India and States 2020). The target population for rubella vaccination among the women of the above-mentioned age group was calculated by subtracting the total number of persons who have undergone female or male sterilization or hysterectomy. The estimated target population based on the exclusion criteria was found to be

1,34,31,859. Considering the susceptible population, force of rubella infection, and vaccine effectiveness, if the cohort gets vaccinated, total number of rubella infections and CRS cases among the cohort will be 2,508 and 17respectively. While, if vaccine will not be given to the cohort, 83,593 women can have natural infection and will lead to 580 CRS cases. Considering all the parameters available from secondary literature, 563 CRS cases can be prevented due to vaccination in women of reproductive age with high fertility rate (age group 20-39 years) in Maharashtra. Due to vaccination of the study cohort, INR 39,01,601/- can be saved per CRS case averted. The total QALY gained by vaccination cohort will be 1,44,374 and ICER is -15,213.18 cost per QALY gained. The results obtained from deterministic decision analytical model were most sensitive to lifetime cost of CRS treatment, life expectancy at birth and the quality-of-life weight of CRS. Even if we vary most important parameters (force of infection of rubella, mother to child transmission rate, general fertility rate, vaccination cost) in sensitivity analysis, the vaccination strategy remains cost effective. The cost effectiveness was also assessed considering lower coverage of vaccination. The results of the assessment show that as the vaccination coverage reduces, the number of CRS cases increases and the cost saved per CRS cases decreases, even with lower vaccination coverage, the intervention "Rubella vaccination" remains to be cost saving.

Recommendation:

The MR vaccination of women of age group 20-39 years in Maharashtra would be a cost-effective strategy considering huge lifetime CRS management cost. Availability of MR vaccine at health facility for women, increasing the awareness regarding CRS among women will encourage them to take the MR vaccination in the health facilitates which would help to reduce the CRS burden among children and rubella infection among women.

1. Introduction:

1.1 Background: Rubella is a highly contagious disease caused by Rubella virus. The Rubella virus is a cubical, medium sized (50 to 85 nm) lipid-enveloped virus with an RNA genome belonging to the Togaviridae family and the genus Rubiviruses (Lambert, Strebel, Orenstein, Icenogle, & Poland, 2015). The infection is spread by airborne droplets from infected person. The symptoms of Rubella infection are similar to symptoms of Measles, which include, red rash, low fever and nausea (Mayoclinic, 2020). Human-to-human transmission of Rubella virus occurs via droplets generated while coughing or sneezing. Most of the infected persons develop rash after 14 to 17 days although the incubation period of Rubella virus have been seen up to 14 to 23 days (Heggie & Robbins, 1969). The period of 1-5 days after appearance of rash are the most infectious period (WHO, 2019a).

Rubella virus can be a major threat to foetus if infection occurs in pregnant women (Mayoclinic, 2020). If Rubella virus infects a pregnant woman during foetus organ development, it can cause organ abnormalities, hearing impairments, eye and heart defects, thyroid dysfunction, diabetes, autism etc. (WHO, 2019a). There is 90% probability of transfer of Rubella virus from mother to foetus in her early pregnancy (WHO, 2019a).

1.2 Rubella history: Most of the symptoms of rubella have been found similar to Measles; however German Physicians distinguished Rubella from other exanthemas, naming it as German Measles. In 1841, A British physician coined the term Rubella in a report of an outbreak in an Indian school (Veale, 1866). The Rubella Virus was isolated by two groups independently in Boston and Washington, DC in 1962 (Weller & Neva, 1962), (Parkman, Buescher, & Artenstein, 1962). Rubella virus infection became pandemic in Europe in 1962-1963 and it spared in US to become pandemic there in 1964 to 1965. As an effect of this pandemic, many pregnancies resulted into wave of abortions and abnormal infants (Parkman et al., 1962; Tatiana Lanzieri). The pandemic gave a reason to many scientist groups to work on need of time, a Rubella vaccine.

The Rubella virus replicates in the nasopharynx which can be site of effect for immune intervention at first point. The nasopharyngeal replication of virus can be blocked by a secretory Immunoglobulin A antibody (IgA), induced by the past infection of Rubella or by Rubella vaccination. Another site for prosperous immune intervention is local lymph nodes where virus spreads after replication in nasopharyngeal cavity. After a week's incubation period, viremia in lymph node can be cleared either by passive antibodies or induced antibodies from prior

infection/vaccination (Reef & Plotkin, 2018). As a result of efforts from scientific community, several attenuated stains of Rubella virus were developed for vaccination and sequentially reached to clinical trials during 1965 to 1967 (Meyer et al., 1969; Stanley A. Plotkin, John D. Farquhar, Michael Katz, & Fritz Buser, 1969; Abel Prinzie, Constant Huygelen, Jerome Gold, John Farquhar, & James McKee, 1969). Commercial use of Rubella vaccine in Europe and America was started from 1969 and had major effect on Rubella and Congenital Rubella Syndrome (CRS) epidemiology.

Diagnosis of Rubella virus can be done by detection of RNA by RT-PCR as well as detecting antibodies by ELISA (Reef & Plotkin, 2018). Among Infants with CRS, IgM antibodies persists for a year, however IgM titres decline in six months after birth; whereas low avidity IgG antibodies may remain for longer period among infants with CRS. However, among 95% of infants with CRS, persistence of IgG antibodies can be detected beyond six months (Stanley A. Plotkin et al., 1967).

1.3 Rubella Epidemiology: Rubella virus has a potential to spread across the world and grow into epidemic disease as demonstrated previously in United States during 1964-1965 (WHO, 2011; Witte et al., 1969). This epidemic led to 12.5 million cases of rubella which included more than 20000 cases of CRS, >11250 of miscarriage, >12000 cases of congenital abnormalities like deafness, blindness, and developmental delay, and also >2000 cases of encephalitis (Reef & Plotkin, 2018). An Australian physician Norman McAlister showed relation between congenital cataracts and maternal rubella (Gregg, 1991). Outbreaks of Rubella were also noted across the world and basic reproductive rate has been found within 6 to 7 in developed and most developing countries, but extends in crowded developing countries (Reef & Plotkin, 2018). A rubella epidemic usually arises in every 5–9 years as seasonal pattern. However, the extent and periodicity of rubella epidemics is highly variable in both industrialized and developing countries. Susceptibility for rubella lowers after an epidemic among young adults and it generally lies in between 10% to 20% (Reef & Plotkin, 2018; WHO, 2020).

A serological evidence of CRS was found in infants investigated for congenital malformation in India (Chauhan, Sen, Jhanda, & Grover, 2016). Also, infection of Rubella with a serological evidence of rubella specific antibodies in infants was confirmed in congenital cataract cases in India and Nigeria (Cutts & Vynnycky, 1999) (Dewan & Gupta, 2012; Otaigbe, Tabansi, & Agbedey, 2012). Several other studies from India showed (Ballal & Shivananda, 1997; Chandy et al., 2011; Eckstein, Vijayalakshmi, Killedar, Gilbert, & Foster, 1996; Johar, Savalia, Vasavada, &

Gupta, 2004; Mahalakshmi et al., 2010) that 6% to 25% of children with non-traumatic cataracts and 15% of infants suspected of having congenital infection had rubella-specific antibodies. The CRS rate was observed in between 0.6 and 2.2 per 1000 live births before universal vaccination in developed countries and it is also similar to developing countries (Reef & Plotkin, 2018).

The risk of CRS is greater in infants of young mothers, child of woman in contacts with military recruits and school-age children in area of frequent rubella outbreak. Pregnant women with older children are also at greater risk (Reef & Plotkin, 2018). Women who enter in pregnancy in rubella seronegative state are more susceptible for infection (Reef & Plotkin, 2018).

2. **Economic evaluations of rubella vaccine:**

A more recent economic analysis of the impact of CRS has calculated the disability-adjusted life-years and cost of care. For a CRS child in a low-income country, 29 disability-adjusted life-years and US$11,266 in cost of care would be incurred, whereas for a high-income country the figures are 19 disability adjusted life-years and US$ 934,000 in cost of care (K. M. Thompson & Odahowski, 2016). The Global Alliance for Vaccines and Immunizations (GAVI) supported an economic evolution of vaccinations conducted in years 2001–2020 and 2011–2020 against 10 diseases in 73 low- and middle-income countries which shows a value of life year of disability averted 1.5 billion of US$ and 25 million of DALYs averted due to rubella vaccination (Ozawa et al., 2017). A cost utility analysis study shows an average of 22.9 QALYs has gained due to prevention of a complication of rubella infection during pregnancy (Lugnér, Mollema, Ruijs, & Hahné, 2010). No studies related to cost-effectiveness of rubella vaccination are being done in India.

3. **Rubella Vaccine**:

There is no treatment for Rubella infection as on today and the vaccination has been demonstrated as the successful approach and strategy to control and eliminate rubella (WHO, 2020). Before vaccine development, on exposure to rubella virus, immune serum globulin (ISG) was often used in expectation to prevent fatal infection (Reef & Plotkin, 2018). A hyperimmunoglobulin was prepared to overcome the deficiency of ISG from the serum of normal peoples with high rubella antibody titre (Reef & Plotkin, 2018). The isolation of rubella virus in tissue culture boosts vaccine development and consequently results in different strains of vaccine (S.A. Plotkin, 1996). During

1969 to 1970, three Rubella vaccines were licensed in US. HPV-77 (human papillomavirus 77) was developed originally by passaging virus culture 77 times in monkey kidney cells and then adapted to duck embryo cells (Hilleman, Buynak, Whitman, Weibel, & Stokes, 1969). Also one of the HPV-77 strains were similar procedure but adapted to dog kidney cells (Meyer et al., 1969), and in Cendehill to rabbit kidney cells (A. Prinzie, C. Huygelen, J. Gold, J. Farquhar, & J. McKee, 1969). Meanwhile, in early 1965 RA27/3 was isolated from a foetus infected with rubella and vaccine developed from this strain got approval in Europe in 1969 (S. A. Plotkin, J. D. Farquhar, M. Katz, & F. Buser, 1969). The RA27/3 strain is produced as a vaccine strain between the 25th and 33rd passages in human diploid cells (Stanley A. Plotkin, Farquhar, & Ogra, 1973). The nucleic acid sequence analysis of RA27/3 envelope gene with wild type revealed difference of 31 amino acid (Nakhasi, Thomas, Zheng, & Liu, 1989). The RA27/3 strain is also the most widely used throughout the world, except in Japan and China (Perkins, 1985). In Japan, five Japanese strains were attenuated by passage(Ueda, 2009). While In China a strain called BRD-II is in use (Chang et al., 2015).

The vaccine dose of RA27/3 is required to be at least 1000 plaque-forming units (PFU) of virus delivered subcutaneously. In most countries, rubella vaccination is accomplished with a triple vaccine that also contains measles and mumps vaccine viruses (MMR). The American triple formulation contains the Moraten attenuated measles, and the RA27/3 rubella virus, the Jeryl Lynn mumps virus (Reef & Plotkin, 2018). A measles and rubella combination is produced by Sanofi Pasteur and the Serum Institute of India, which manufactures three different rubella-containing formulations: rubella-only vaccine (Wistar RA27/3; 1000 TCID50) Measles-rubella (MR) with the addition of Edmonston Zagreb measles virus; 1000 TCID50), and MMR (Tresivac, with the addition of L-Zagreb mumps strain; 5000 TCID50). Rubella vaccine is highly stable in the frozen state at approximately −70°C or approximately 20°C (McAleer, Markus, McLean, Buynak, & Hilleman, 1980).

3.1 Immune Responses- Vaccination by Rubella vaccines induces antibodies of both IgM and IgG classes and cellular immune responses. Secretory IgA responses are also induced. By the hemagglutination inhibition (HI) assay, 95% to 100% of RA27/3 vaccines experience seroconversion by 21 to 28 days after vaccination, with geometric mean antibody titres ranging from 1:30 to 1:300, depending on the method of titration (Reef & Plotkin, 2018). A vaccination

study conducted in India using MMRV showed 99% to 100% seroconversion to rubella after one dose (Lalwani et al., 2015). Vaccination induces antibodies predominantly binding the E1 protein as detected by immunoblot, but those antibodies mature in avidity less rapidly than after natural infection and do not reach the same level (Nedeljkovic, Jovanovic, & Oker-Blom, 2001). Antibodies to the E1 protein bearing neutralizing epitopes persist for at least 3 years as confirmed by Immunoblot analysis (Reef & Plotkin, 2018). Persistence of antibodies to the C protein also confirmed unlike to antibodies to E2 which is often absent (Cusi, Metelli, & Valensin, 1989).

A crucial property of RA27/3 is its ability to induce secretary IgA antibody in the nasopharynx, which, as discussed subsequently, may prevent re-infection with wild virus. This property makes vaccination with RA27/3 similar to natural infection, which also induces local immunity. Although secretory IgA responses are higher after intranasal vaccination, they also are induced by subcutaneous vaccination with RA27/3 because of replication of the virus in the nasopharynx (Reef & Plotkin, 2018) which effects on the distribution of lymphocyte classes, but no functional changes (Rager-Zisman et al., 2003). Responses to rubella as part of MMR combinations are equal to those seen after rubella vaccination as a single antigen is taken from a study by Weibel and colleagues (Weibel et al., 1980). Seroconversion to rubella vaccination with any of the Bivalent measles-rubella and other triple combinations is usually 97% to 98%. Effectiveness of RA27/3 against clinical rubella was 90-97% as observed in various studies (Jossy van den Boogaard, 2019; Reef & Plotkin, 2018). The presence of rubella IgG antibodies greater than or equal to 10 IU/mL is commonly considered to provide evidence of protection (WHO immunologic basis).

The recommended age of administration of RCV (as a combined MR or MMR vaccine) is from 9 months in countries with a high incidence and mortality from measles. Manufacturers recommend shifting the age of vaccination to 12–15 months in countries with a low measles incidence and consequently a lower risk to infants and with use of MMRV. A second dose of MR, MMR or MMRV should be given to ensure protection against measles (WHO, 2020).

4. Study Rationale

The effectiveness of the RA 27/3 vaccine has been demonstrated by elimination of rubella and CRS from Region of the Americas (AMR), 39 countries in European Region (EUR), 4 countries in Western Pacific Region (WPR) and 3 countries in Eastern Mediterranean Region (EMR) (Grant, Desai, Dumolard, Kretsinger, & Reef, 2019). As a part of the strategy to eliminate rubella and CRS in the Region of the Americas, >250 million adolescents and adults were vaccinated in mass campaigns with MR vaccine. The Region of the Americas established the goal of eliminating rubella and CRS by 2010. Building on the regional measles elimination strategy of a 1-time campaign targeted at children in a wide range of ages (that is, a catch-up campaign), achieving high coverage of routine immunization (that is, keep-up vaccination) and regular follow-up campaigns targeting recent birth cohorts, countries in the Americas added MR vaccination campaigns for adult men and women (known as speed-up campaigns) to accelerate achievement of elimination. Over the past 20 years, the number of countries that have introduced a RCV into their routine immunization programmes has increased significantly, from 99 (51%) countries in 2000 to 173 (89%) in December 2019 (WHO, 2020). By the end of 2019, rubella was eliminated from 81 countries. AMR eliminated rubella in 2009 and in 2015, the International Expert Committee for Measles and Rubella Elimination verified the Region as free of endemic rubella and CRS. The European Region (EUR) set a rubella elimination target of 2015; however, in 2019, 21% (11/53) of countries in the Region were considered endemic for rubella (WHO, 2020).

The South-East Asian Region (SEAR), which includes India has set a target for rubella elimination of 2023, and the Western Pacific Region (WPR) has pledged to eliminate rubella but has not set a target date. In AFR and EMR, no targets have been set for control or elimination of rubella (WHO, 2020). While, SEAR set a goal to achieve and maintain elimination of measles and rubella with interruption of the transmission of indigenous measles and rubella viruses by 2023 (WHO, 2019b). If vaccination coverage is sufficiently high (generally estimated to be >80% in each birth cohort), rubella transmission will be markedly reduced or interrupted, thereby reducing the risk of exposure of pregnant women. However, as it is recommended that RCV be provided in combination with measles vaccine, and measles elimination requires >95% coverage, the goal for rubella vaccination coverage should also be >95% (WHO, 2020). India has adopted the goal of measles elimination and rubella/CRS control by 2020 along with other countries of WHO South-East Asia Region (Shastri, 2019).

India has made progress towards achieving these goals, including:

- In 2010, Measles containing Virus 2 (MCV2) was introduced into the routine immunization schedule.
- In between 2017-2019, a wide-age range Measles and Rubella Supplementary Immunization catch-up campaign (MR-SIA) has been conducted in 33 states, and is ongoing in two states and yet to be completed in two more states (Delhi and West-Bengal). Approximately, 32.36 crore children have been vaccinated as part of the campaign with a coverage of 97.04% (Welfare, 2020a).
- In 2018, Measles and Rubella vaccine (MR vaccine) was introduced in routine immunization as the first and second doses across the country (Welfare, 2020b).
- India is transitioned from outbreak to case-based MR surveillance, which has been initiated in 32 states, and now implemented across the entire country.(Welfare, 2020a).
- Fever-rash surveillance has been piloted in three states (Karnataka, Madhya Pradesh and Odisha). Evidence generated from this pilot will provide guidance on operational feasibility, and is likely to inform policy decisions regarding further expansion across the country.

Considering the conclusions of the midterm review on measles elimination and rubella/CRS control, a high-level consultation was planned with all Member States and partners to revise the target for measles elimination and establish a new goal for rubella elimination as well as develop strategies to combat challenges faced during the implementation of the current strategy (Shastri, 2019).

As suggested by the WHO, when vaccination at high coverage (e.g. >85%–90%) is provided only to young children (such as those aged 1–4 years) (follow-up campaigns) rubella and CRS will be eliminated in approximately 20–30 years; it will be eliminated within approximately 10–20 years when vaccination at high coverage is provided to young children and adolescents (for example, children aged 1–14 years) (A catch-up campaign), and within 10 years when vaccination at high coverage is provided to young children, adolescents and adults (for example, people aged 1–39 years) (A speed-up campaign) (WHO, 2011). India already implemented catch-up campaign and now its need to go for speed up campaign to achieve goal of measles and rubella elimination.

In high-income and middle-income countries, caring for CRS cases is costly, and rubella vaccination has been found to be cost–effective (Babigumira, Morgan, & Levin, 2013). To eliminate CRS, considering the vaccination in adult age group, particularly women in child bearing age group (15-49), will be the promising way. However, due to different fertility rate in different age group, the cost and effects will be varied in different age group. The cost effectiveness study to compare vaccination scenarios at different age groups is necessary to implement speed up campaign for CRS elimination.

The present study will be helpful for generating evidence related to cost-effectiveness of rubella vaccination to support rational decision making regarding the Rubella vaccination in Maharashtra state.

5. **Hypothesis:** Rubella vaccination by speed-up campaign among reproductive age group women will eliminate the Congenital Rubella Syndrome cases in Maharashtra.

Research question:

1. Will the rubella vaccination among reproductive age group women by speed-up campaign cost effective?
2. What will be the budget impact of providing rubella vaccination for reproductive age group women population in Maharashtra?

Aim: To evaluate cost effectiveness of speed up campaign strategy of rubella vaccination among reproductive age group women (20-39 years) in Maharashtra so as to eliminate the Congenital Rubella Syndrome.

Objectives:

1. To estimate the cost- effectiveness of rubella vaccination (MR vaccine) compared to no vaccination strategy among reproductive age group women (20-39 years) in Maharashtra, India.

2. To assess the budget impact of providing rubella vaccination among reproductive age group women (20-39 years) in Maharashtra, India.

6. Methods:

PICO

- Population: Reproductive age group eligible women (20-39 years)
- Intervention: Rubella vaccination (MR vaccine, one dose)
- Comparator: No vaccination of MR vaccine
- Outcome: Congenital rubella syndrome cases averted
- Study design: Decision analytical model
- Perspectives: Health care perspective

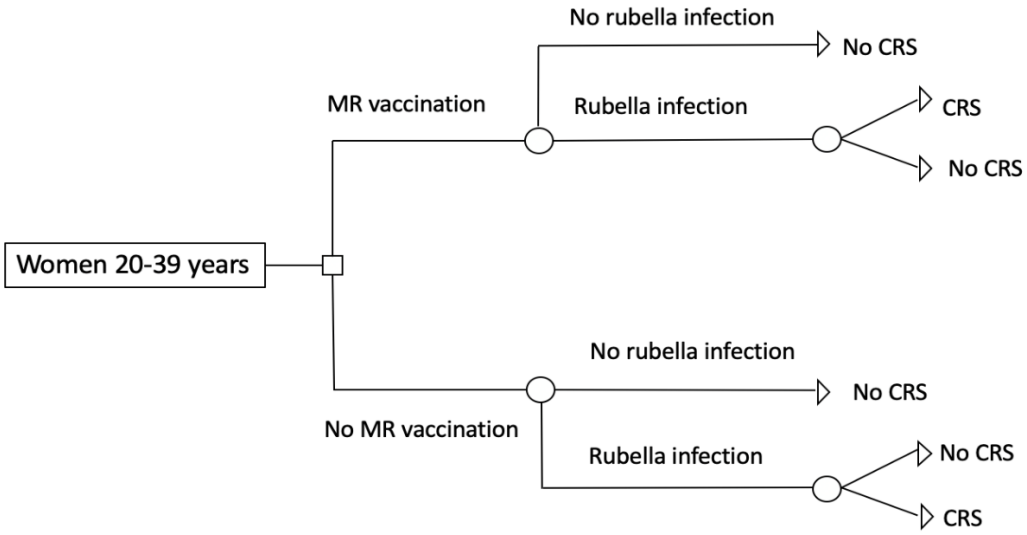


Figure1: Decision tree for rubella vaccination among reproductive age group women.

Study outline and description of decision analysis tree: The cost-effectiveness study was analyzed by decision analytic model.

The decision tree analysis started with the decision regarding whether to give MR vaccination to women of reproductive age group (20-39 years).

MR vaccine cohort:

Two probabilities were taken into account for MR vaccination cohort which are as follows.

1. This is the cohort of women who will receive the MR vaccine, develop the antibodies against rubella and will not acquire rubella infection and as a result there will not be any complications due to rubella infection. The CRS cases will get averted in this cohort.
2. This is the cohort of women who will receive MR vaccine but will not develop the antibodies against rubella infection and will acquire the rubella infection. This group would be divided into two categories based on two possible probabilities. One group will develop CRS and other will not develop CRS. It is assumed that there will be no natural infections of Rubella among remaining 3% women (vaccine efficacy 97%) who will develop vaccine induced antibodies and will be considered as susceptible for rubella infection.

No MR vaccine cohort:

Two probabilities were taken into account for "No MR vaccination cohort" which were as follows.

1) This cohort of women who will not receive the MR vaccine and will get the natural infection of rubella. Due to the natural infection, they will develop the natural antibodies against rubella and will not have complications of CRS. For calculating rubella susceptible women, the seroprevalence of rubella for Maharashtra from ICMR report (Unpublished data) was considered
2) This cohort includes the women who will not receive rubella vaccine and get the rubella infection and will have complication of rubella (CRS) as per the probability of having the CRS.

The number of CRS cases averted in both branches of decision tree were analyzed by passing cohort of women of age group 20-39 years from Maharashtra population through decision tree model. The cost required for MR vaccination of the study population/target population and lifetime treatment of CRS was taken from published literature. The cost effectiveness was analyzed based on CRS cases averted in each branch. For Estimation of total number of pregnant women in Maharashtra General fertility rate obtained from Sample registration survey statistical report for Maharashtra population was considered. The costs taken from references were first adjusted

according to US inflation rate and in the next step, these values were converted from US$ to INR according to US$ exchange rate.

Eligible study population: The women who belong to the age group 20-39 years were selected as study population considering the high fertility rate in this age group. The women of age group 20-39 years who have undergone female sterilization or hysterectomy and the women of age group 20-39 years whose husbands have undergone male sterilization were excluded from study population cohort.

In Maharshatra, as on August 2022, the age group 15-19 years (Male and female population) has already been vaccinated by MR vaccine in year 2017-18 during mass vaccination campaign. Hence in this study age group 20-39 years was only considered. The general fertility rate of specific for Maharashtra population was considered for the study population. The maximum disabilities for CRS were considered (Central nervous system + heart defect + hearing disability+ ocular defect) for QoL weight. The deterministic approach was used for calculating the cost-effectiveness.

Sensitivity analysis: A one way sensitivity analysis was performed to check elasticity of cost-effectiveness results. The parameters were varied in between the upper and lower limit mentioned in the source references and the variation in cost per QALY gained was observed. In absence of upper and lower limit for parameters, the values fluctuated by 20% on upper and lower side.

Table 1: Parameters description for decision tree:

Parameters	Base Value	Source/reference
Demographic parameters		
Maharashtra population 2021	12,44,37,000	(Projection, 2020)
Females	5,97,35,000	(Projection, 2020)
Females in age group 20-39	2,03,76,000	(Projection, 2020)
Maharashtra GFR 2018	55.1	(Commissioner, 2018)
% of Female sterilization in 20-39 age woman	32.33	(ICF., 2021)
% of Male sterilization in 20-39 age men	0.35	(ICF., 2021)

% Hysterectomy in 15-39 age group	1.4	(ICF., 2021)
Efficacy Parameters		
Effectiveness of MR Vaccine (%)	97	(Jossy van den Boogaard, 2019)
Probability of rubella infection in vaccinated cohort	0.03	1-vaccine effectiveness
Epidemiological Parameters		
Probability of natural infection of rubella, Constant force of infection	0.069	(Shanmugasundaram et al., 2021)
Percentage seropositivity of rubella among woman's in Maharashtra	91.0	Serosurvey data for Palghar Maharashtra, ICMR
Percentage Rubella Susceptible woman in Maharashtra	9.0	Serosurvey data for Palghar Maharashtra, ICMR
Probability of rubella infection Mother to child transmission (MTCT)	0.90	(Shanmugasundaram et al., 2021)
Probability of the risk of child being born with CRS in infected woman	0.65	(Shanmugasundaram et al., 2021)
Percentage of Foetal loss in rubella infection to mother	5.60	(Kimberly M. Thompson, Simons, Badizadegan, Reef, & Cooper, 2016)
Percentage of Medical termination of pregnancy in case of rubella infection to mother	36.00	(Kimberly M. Thompson et al., 2016)
Percentage of CRS mortality	3.60	(Kimberly M. Thompson et al., 2016)
Percentage of CRS surviving birth	14.00	(Kimberly M. Thompson et al., 2016)
Percentage of normal surviving birth in case of rubella infection in mother	40.00	(Kimberly M. Thompson et al., 2016)
Probability of abortion in case of rubella infection in mother	0.04	(ICF., 2021)
Probability of Stillbirth in case of rubella infection in mother	0.004	(ICF., 2021)

Utility/Quality of life (QoL) weights		
QoL healthy Child	1	Assumption
QoL healthy female	1	Assumption
QoL weight CRS child (CNS + heart defect + hearing disability)	0.405	(Lugnér et al., 2010)
Cost Parameters		
Expected cost of CRS from LMI countries	US$ 14,759	(K. M. Thompson & Odahowski, 2016)
Expected cost of rubella infection with home care from LMI countries	US$340	(K. M. Thompson & Odahowski, 2016)
Vaccine adverse events Cost (with home care cost in LMI country)(per dose)	US$0.87	(K. M. Thompson & Odahowski, 2016)
Inflation, consumer prices (annual %) 2020 USA	1.2	https://data.worldbank.org/country/india
Exchange Rate (INR to USD) in 2020	74.13	https://www.exchangerates.org.uk/

7. Results:

Cost: The cost of MR vaccination among study population of women of age group 20-39 years in Maharashtra state estimated to INR 90,31,58,213/-. The lifetime CRS cost in the newborn were estimated to be INR 2,28,58,430/-. While in the alternate scenario of the cohort containing women of age group 20-39 years with "No MR vaccination", the lifetime management cost for infants born with CRS is estimated to INR 76,19,47,674/-. Lower treatment cost in vaccination scenario was because of reduced number of children born with CRS.

The cost in INR 15,213/- could be saved per QALY gained and the cost saved for per CRS cases averted would be nearly INR 39,01,601 (Table 2)

Table 2: Results of deterministic decision analytical model

	Cost (INR)	QALY	ICER	CRS Cases	ICER
Intervention (MR vaccination)	1,10,84,49,010	5,08,74,106		17	
Control (No vaccination)	3,30,48,29,391	5,07,29,733		580	
INR	-2,19,63,80,382	1,44,374	**-15,213**	-563	**INR 39,01,601** saved per CRS case averted
			cost per QALY gained		
US$	-2,96,28,765.44	1,947	-205.2		52,632

Consequences: Study analysis showed that in "No vaccination scenario", among the 1,34,31,859 eligible women of age group 20-39 years, a total of 83,593 women may have natural rubella infection which can result into 580 CRS cases, suggesting risk of CRS childbirth to be 0.004 % among women in Maharashtra.

Analysis also shows that the vaccination in this cohort will reduce the total number of rubella infections to 2,508 among which the CRS cases would be 17 suggesting reduction of 563 cases. As a result, we can state that one CRS case would be prevented for every 23,860 women vaccinated. The reduced burden of CRS among the newborns gains overall 1,44,374 QALY because of MR vaccination among eligible study population. This indirectly suggests an increase of 256 QALY per rubella case averted.

Cost-Effectiveness: MR Vaccination in the cohort of women of age group 20-39 years in Maharashtra would save INR 15,213/- per QALY gained. Similarly, INR 39,01,601/- (Table 2) would be saved per CRS cases averted due to MR vaccination of the study cohort.

Budget Impact: One time total cost of MR vaccination campaign (Speed up campaign) for the cohort of women of age group 20-39 years in Maharashtra is about INR 1,00,93,04,128/- which includes vaccination cost (INR 90,31,58,213/-) and vaccine adverse event cost with minor reactions & home care (INR 10,61,45,915/-) which is 0.51% of total health budget of Maharashtra (year 2022-2023). However, accounting the total cost (cost for CRS treatment, rubella infection,

MTP, vaccination cost including adverse event), INR 2,19,63,80,382/- would be saved in lifetime horizon due to MR vaccination, which amounts to 1.1% of total state health budget 2022-23 in Maharashtra.

Table 3: Costs of MR Vaccination and CRS Treatment in Different Arms of the Cost-Effectiveness Model

Costs	Base Case	
	INR	US$ (in millions)
Costs: no MR vaccination scenario		
CRS Treatment cost	76,19,47,674	10.27
Medical termination of pregnancy cost	1,46,02,774	0.19
Rubella infection cost	252,82,78,944	34.10
Total cost	330,48,29,391	**44.58**
Costs: MR vaccination scenario		
Vaccination cost	90,31,58,213	12.18
CRS Treatment cost	2,28,58,430	0.30
Medical termination of pregnancy cost	4,38,083	0.005
Rubella infection cost	7,58,48,368	1.02
Vaccine adverse event cost	10,61,45,915	1.43
Total cost	1,10,84,49,009	**14.9**
Incremental costs in MR vaccination		
Vaccination cost (including adverse events)	1,00,93,04,127	13.6
CRS Treatment cost	-73,90,89,243	-9.97
Medical termination of pregnancy cost	-1,41,64,690	-0.19
Rubella infection cost	-2,45,24,30,575	-33.08
Total cost	**-2,19,63,80,382**	**-29.6**

Sensitivity Analysis:

In one way sensitivity analysis, we varied different parameters by min/max or 95% CI provided in source otherwise by 20%, to determine the plausible range over which the MR vaccination continues to be cost-effective. The 20% variation in the percentage of susceptible women, the probability of rubella infection in vaccinated cohort and probability of MTCT of rubella infection have minimal influence on cost-effectiveness of MR vaccination among women in the study cohort. Likewise, even with the variation in vaccination as well as treatment cost in minimum and maximum range provided in source reference, vaccination strategy continues to be cost-effective. The Quality-of-Life weight of CRS varied 20% on upper and lower side has least effect on cost-effectiveness of MR vaccination among women of study cohort. Sensitivity analysis suggests that the ICER for QALY gained is most sensitive to MTCT, life expectancy at birth, , expected CRS+ Rubella cost and the QoL of rubella (Figure 2).

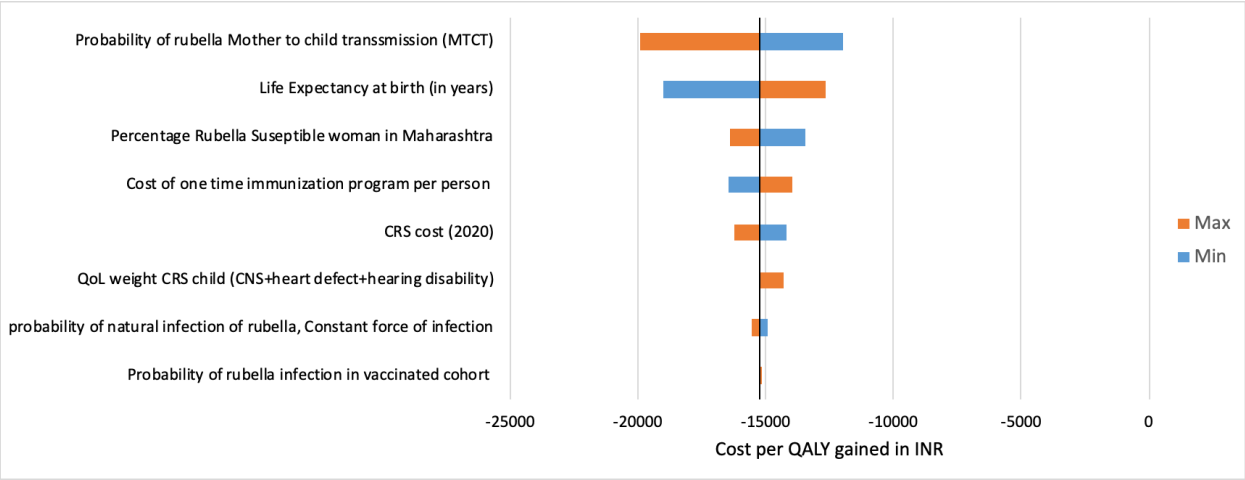
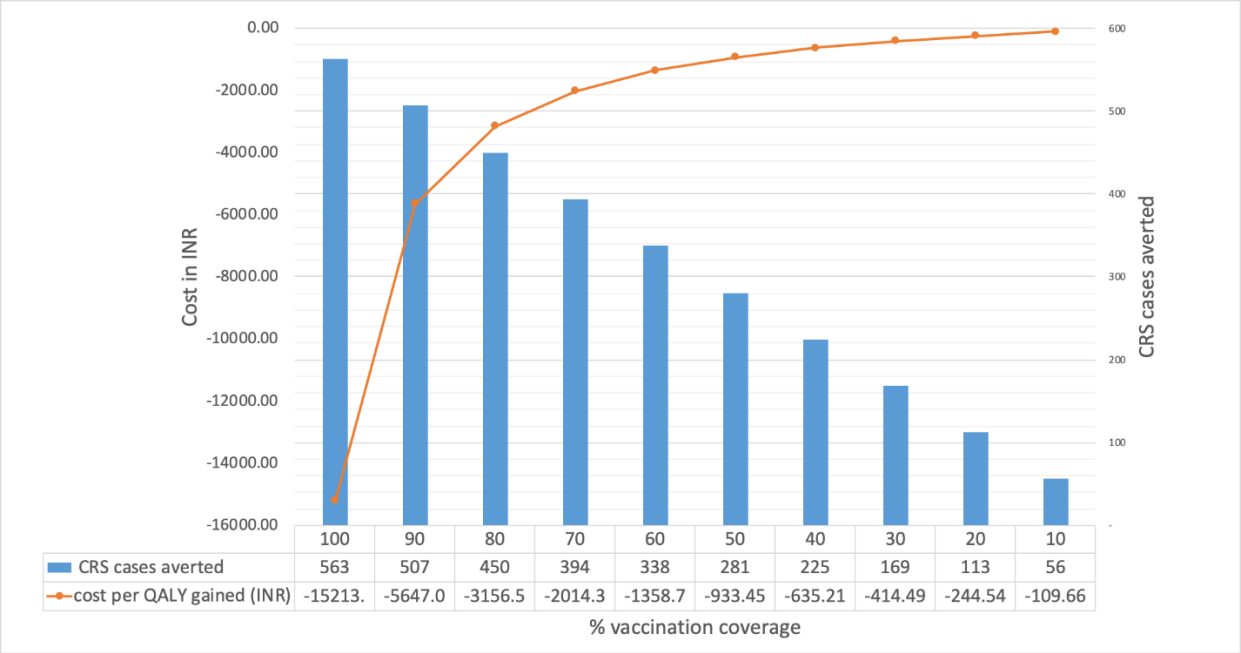


Figure 2: Tornado diagram showing sensitivity analysis of for the input parameters used in decision analytical model.

Impact of vaccination coverage on cost per QALY gain and number of CRS cases averted:

The cost effectiveness was calculated based on the assumption that vaccination coverage would be 100% among study population (20-39 years age eligible women). However, achievement 100% vaccination coverage may not be possible due to many reasons. Hence, the cost effectiveness was assessed considering lower coverage of vaccination. The results of the assessment show that as the vaccination coverage reduces, the number of CRS cases increases and the cost saved per CRS cases decreases (Fig 4). The saved cost per QALY gained drastically increases after 80% of vaccination coverage. This implies the importance of vaccination coverage. More we vaccinate

more cost will be saved per QALY gained and even with lower vaccination coverage, the intervention “Rubella vaccination” remains to be cost saving.



	100	90	80	70	60	50	40	30	20	10
CRS cases averted	563	507	450	394	338	281	225	169	113	56
cost per QALY gained (INR)	-15213.	-5647.0	-3156.5	-2014.3	-1358.7	-933.45	-635.21	-414.49	-244.54	-109.66

Figure 3: Impact of vaccination coverage on cost per QALY gain and number of CRS cases averted

8. Discussion:

The results of the current analysis demonstrate that MR vaccination in women of age group 20-39 years in Maharashtra would be a cost saving option with saving of approximately INR 3.9 million by considering the lifetime CRS management cost. Reduction in CRS cases due to decrease in rubella infections saves approximately INR 15,213 per QALY gained, suggesting a high cost-effectiveness in cost saving manner. Vaccination continues to be cost-effective among women of age group 20-39 years, even if disease burden and force of rubella are decreased by 20% as revealed in one way sensitivity analysis. The lifetime cost of CRS management and rubella infection in women have less impact on cost-effectiveness MR vaccination and it remains cost-effective even if cost is decreased by 15%. Even with lower vaccination coverage, the intervention “Rubella vaccination” remains to be cost saving (Figure 3).

Findings in Context of Existing Evidence

Several other countries studies have published the analysis of Rubella vaccination. A Systematic review of 27 studies between 1970 and 2012 was conducted in high-income, upper-middle income, and lower-middle income countries to assess the value of rubella vaccination (Babigumira et al., 2013).

This study concluded that CRS is costly and different rubella vaccination programs, including the vaccination of health workers, children, and women have favorable cost-effectiveness, cost-utility, or cost-benefit ratios in high and middle-income countries.

The finding from the review suggests that vaccine prices have fallen over the years; blind vaccination has become more favorable compared to targeted vaccination. Both, the campaigns in conjunction with routine immunization and the routine programs, regardless of the vaccine presentation used, were cost-beneficial.

One of the studies conducted in Guyana in 1998, suggests that $3,335 per CRS case prevented for rubella eradication and which is highly cost-effective. In the current study, the cost saved due to CRS cases averted estimated to be USD$ 52,631.88 in 2020 for the lifetime CRS cost. The major difference in comparison to previous results is due to time horizon in study conducted in Guyana was 5 years' time horizon while in our study we have taken lifetime horizon. The study conducted in US in 2012 estimated that vaccination program saves $6,83,813 per CRS case prevented, which is in correlation with our current results.

Large variation was found in the cost of CRS among the studies reviewed (Babigumira et al., 2013). The annual cost of CRS in Upper middle income countries estimated to be $4,261, $58,023, and $57,010 as per 2012 US$ in three studies, while in high income country the life time CRS cost was estimated to be $139,910 (Babigumira et al., 2013). We have considered the cost of CRS as US$14,759 as per US$ 2013 which is in the range of previous estimated cost.

9. Assumptions & limitations:

1. It was assumed that one pregnant woman will give birth to the single child.
2. It was assumed that the treatment of Rubella was given to only those mothers who delivered child with CRS. This implies the percentage of women receiving Rubella treatment was same as MTCT rate (65%).
3. We have taken lifetime CRS treatment cost for CRS cases. The cost of rubella infection was estimated from societal perspective in source reference.
4. The QoL weight was derived from disability weights in the source reference.

10. Conclusion:

The MR vaccination among the women of age group 20-39 years in Maharashtra would be a cost saving strategy. The cost burden of CRS will be huge if the MR vaccination intervention will not be implemented. The MR vaccination among the high reproductive rate group women will assure a major step toward Rubella elimination.

Recommendations:

The MR vaccination may be considered by health services, Govt. of Maharashtra among the women of reproductive age with high fertility rate (i.e.,20-39 years) in Maharashtra as the MR vaccine can be made available at various health facilities easily. Awareness among women's regarding CRS will encourage them to take the MR vaccination in the health facilitates which can reduce the CRS burden among children and rubella infection among women. Al though large human resources would be required for MR vaccination among eligible women, one-time vaccination would help to reduce CRS cases among children and Rubella infection among women considerably.

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