Informing rubella vaccination strategies in East Java, Indonesia through transmission modelling

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Abstract

An estimated 110,000 babies are born with congenital rubella syndrome (CRS) worldwide annually; a significant proportion of cases occur in Southeast Asia. Rubella vaccine programs have led to successful control of rubella and CRS, and even the elimination of disease in many countries. However, if vaccination is poorly implemented it might increase the number of women reaching childbearing age who remain susceptible to rubella and thereby paradoxically increase CRS. We used an age-structured transmission model to compare seven alternative vaccine strategies for their impact on reducing CRS disease burden in East Java, a setting which is yet to implement a rubella vaccine program. We also investigated the robustness of model predictions to variation in vaccine coverage and other key epidemiological factors. Without rubella vaccination, approximately 700 babies are estimated to be born with CRS in East Java every year at an incidence of 0.77 per 1,000 live births. This incidence could be reduced to 0.0045 per 1,000 live births associated with 99.9% annual reduction in rubella infections after 20 years if the existing two doses of measles vaccine are substituted with two doses of measles plus rubella combination vaccine with the same coverage (87.8% of 9-month-old infants and 80% of 6-year-old children). By comparison a single dose of rubella vaccine will take longer to reduce the burden of rubella and CRS and will be less robust to lower vaccine coverage. While the findings of this study should be informative for settings similar to East Java, the conclusions are dependent on vaccine coverage which would need consideration before applying to all of Indonesia and elsewhere in Asia.

Highlights

- Transmission models are helpful for predicting the burden of rubella and CRS disease in settings lacking recent and specific epidemiological data, and for informing potential vaccination strategies.
- Introducing rubella vaccine to East Java children at both 9 months and 6 years old could virtually eliminate CRS within 20 years, and would result in a more rapid decline in CRS cases and be more robust to lower achieved vaccine coverage compared to a single dose strategy at 9 months.

Keywords

Modelling

Rubella vaccine

Immunisation

Congenital rubella syndrome

Developing countries

South-East Asia

1. Introduction

Rubella infection usually causes a mild self-limiting illness. However infection during pregnancy can result in foetal death or *congenital rubella syndrome (CRS)* which refers to a range of congenital defects including sensorineural deafness, heart abnormalities, cataracts and intellectual disability [1, 2].

Despite major reductions in both rubella and *CRS* in many countries owing to rubella vaccination [1, 3-5], an estimated *110,000* annual births remain affected by *CRS* worldwide with almost half in South-East Asia [6]. In countries that have not implemented national rubella vaccination programs, the risk of *CRS* epidemics remains high [7, 8], constituting a leading cause of preventable congenital disorders [9]. Well-implemented rubella vaccination programs generally have a marked impact on the incidence of *CRS* and are usually considered highly cost-effective [3, 6, 10]. Three of the six World Health Organization (WHO) regions have set control or elimination targets for rubella and *CRS* with the Americas reaching its elimination goal [11]. Indonesia belongs to the WHO South-East Asian (SEA) Region which has resolved to control rubella/*CRS* by 2020 [12].

CRS surveillance in most developing settings is insufficient to reliably estimate burden or monitor disease trends [13]. Mathematical modelling can play an important role in understanding the epidemiology of rubella and *CRS* in such countries and in predicting the potential impact of vaccination strategies, taking into account the observed experience in other settings [3, 14-17].

Both modelling and epidemiological studies have shown that a poorly implemented infant or early childhood vaccination campaign with low vaccine coverage has the potential to cause a paradoxical increase in the incidence of *CRS* [2, 14, 18-20]. This can occur if transmission is reduced rather than eliminated, resulting in the peak incidence occurring after early-mid childhood and increasing the incidence of rubella among women of childbearing age [14, 21]. Some have argued targeting vaccination to girls in early adolescence minimises the risk of paradoxical increases in *CRS* [2, 14, 22]. However, this can leave the population vulnerable to on-going epidemics of rubella and *CRS* as has been observed in Japan [6, 23].

Because of these concerns, the WHO recommends rubella vaccine be introduced to the routine immunization program with a wide age range campaign if a country has maintained at least 80% coverage with measles-containing vaccine [2, 11]. While Indonesia has only recently exceeded 80% coverage, this requirement has been met for a number of years in East Java, a province of 37.5 million people [24]. In the absence of recent and specific rubella and CRS surveillance in this location, we applied an age-structured transmission model to inform the effectiveness of alternative rubella vaccine strategies in East Java, a setting with no existing rubella vaccine program nor stated detailed plan to introduce one, supported by Indonesian demographic data and informed by estimates of key epidemiological parameters from comparable settings.

2. Methods

2.1 Model description

We used a deterministic compartmental model based on an *SEIR* structure (Susceptible, Latent, Infectious, and Recovered or Vaccinated) stratified by single years of age, as in Anderson and May [14], Hethcote [25] and Gao *et al.* [3] with additional heterogeneity in contacts among age groups. The model was applied to estimate the current burden of disease from rubella and CRS in East Java and to investigate the impact of alternative vaccination strategies on reducing this burden from both direct benefit of vaccine and indirect benefit through herd immunity. A constant population was considered with all deaths occurring at 70 years informed by recent demographic and health survey data for East Java (Table 1) [26, 27]. A detailed description of the model is provided in Appendix 1.

2.2 Model outputs

Results are presented as the number of rubella infections, the incidence (per 1000 live births) and number of CRS cases, the number and cost of vaccine doses implemented in a given program based on published MR vaccine prices by UNICEF [28], and the incremental cost-effectiveness ratio of a given rubella vaccination strategy beyond the cost of the existing program per case of CRS prevented.

The incidence of CRS cases per 1000 live births, *Incd*, has been used to measure the burden of CRS and to evaluate the impact of implemented vaccine programs. *Incd* at time *t* was estimated using a catalytic model [3, 8, 29, 30]:

$$Incd(t) = 0.65 \sum_{a=15}^{49} F(a)S(a, t) [1 - \exp(-\theta \lambda(a, t))] \times 1000$$

where *F(a)* is the age-specific birth rate for women between 15 and 49 years old in Indonesia [26]; θ is 16/52 years representing the first 16 weeks of pregnancy which is the risk period for infection. *S(a, t)* and $\lambda(a, t)$ are model derived parameters reflecting the age-specific proportion of women susceptible to rubella infection and the age-specific force of infection respectively at time *t*. The estimated risk of CRS among infected pregnant women is 0.65 with assumed negligible risk in late pregnancy [15].

The cumulative number of CRS cases over a given period of time *T* (in years) is:

$$CRS_T = \sum_{t=1}^T \frac{\text{mean}(Incd(t) \text{ over the } t^{th} \text{ year})}{1000} \times 0.023 \times N ,$$

where t is the time (in years) after vaccine introduction, and $Incd(t)$ is used to estimate the cumulative number of *CRS* cases, based on the population in East Java N and an estimated *crude birth rate* of 0.023 for Indonesia [26].

The incremental cost-effective ratio (*ICER*) of a given vaccine scenario n over a comparator scenario m over time horizon T was calculated as the additional cost of vaccination to prevent one additional case of *CRS* (assuming no additional costs to the delivery of the vaccine program):

$$ICER_T(\text{scenario } n \text{ over } m) = \frac{CRS_T(\text{scenario } m) - CRS_T(\text{scenario } n)}{Cost_T(\text{scenario } n) - Cost_T(\text{scenario } m)}$$

A 5% annual discount rate was applied to both prevented cases of *CRS* and vaccine costs in each subsequent year after the vaccine introduction (at $t = 0$) over the nominated time horizon.

2.3 Scenario design

The existing measles vaccination program utilizes a single attenuated virus vaccine produced in Indonesia. This is scheduled at 9 months and 6 years old, with its coverage reported at 80% (95% CI 78.1% - 82.2%) nationally and 87.8% (95% CI 81.8% - 93.8%) in East Java in 2010 estimated from provincial-level survey data on representative samples stratified by gender, age and urban-rural areas [26]. A modification to the national vaccination campaign to replace measles-only vaccine with a *MR* vaccine would require minimal change to the program. Under the base case assumption that actual *MR* coverage would be the same as currently reported for measles vaccine, we considered seven alternative rubella vaccine strategies based on the schedule of the existing measles program.

In *Scenario 1, Universal Infant* program, *MR* is substituted for measles-only vaccine at age 9 months while children at age 6 years continue to receive a measles-only vaccine. In *Scenario 2, School 6* program, *MR* is substituted for measles-only vaccine at age 6 years while infants at age 9 months continue to receive a measles-only vaccine. In *Scenario 3, Measles Modification* program, a *MR* vaccine substitutes for measles-only vaccine at both age 9 months and 6 years. In *Scenarios 4 to 6*, we consider three catch-up programs (*Catch-up 6*, *Catch-up 15*, and *Catch-up 40*) where in addition to routine *MR* vaccination at 9 months and 6 years, a broad catch-up campaign where *MR* is implemented at the same time for all those younger than 6, 15, or 40 years old respectively. In *Scenario 7, Adolescent 12* program, *MR* vaccine is introduced for girls only at age 12 years. In Appendix 2, we provide a detailed description of each strategy. If a country introduces combined *MR* vaccine, WHO recommends all future vaccine doses should use the combined vaccine; however, we have aligned those scenarios (1, 2 and 7) against this recommendation with their alternatives to provide a more comprehensive comparison.

2.4 Sensitivity analyses

We conducted sensitivity analyses to assess the robustness of our predictions to variations in vaccine coverage. This variation was applied to the scenarios with the additional assumption that vaccine coverage in older age groups (above 1 year old) is always lower than that in infants (aged 9 months). In the absence of local contact pattern data, we investigated the

impact of various age-specific transmission patterns in urban and rural areas associated with different R_0 . Finally, we investigated the impact of varying the rate of imported rubella cases on scenarios of interest.

3. Results

3.1 Burden of disease in East Java

Due to the lack of recent applicable data from Indonesia, the modelled population immunity from natural infection was used to estimate the current burden of disease from rubella and CRS in East Java. Our model estimates were similar to the observed age-specific proportion immune to rubella in South-East Asian and Western Pacific countries before rubella vaccine introduction (Figure 1, left) including a seroepidemiology study of East Java from 1968 [31]. The right panel in Figure 1 shows the annual incidence of rubella infections by age in East Java, 517,293 cases in total assuming disease equilibrium and no rubella vaccine program. With an estimated mean age of infection at approximately 10.2 years old (dashed), the infection rates are approximately 10-fold higher in children than adults, with a substantial rate of rubella infection in women of child-bearing age. The estimated incidence of CRS per 1,000 live births is approximately 0.77 at equilibrium (Figure 2, thick solid light grey), which corresponds to approximately 700 CRS cases annually in East Java.

3.2 Scenario analysis

Seven alternative vaccine strategies were simulated to be introduced at $t=0$, and their impacts on $Incd(t)$ over 50 years are presented in Figure 2. Compared with the control target $> 95\%$ annual reduction in rubella burden planned to be adopted by WHO SEA region by 2020 [32], under the *Universal Infant* program (*Scenario 1*), we expect 99.8% annual reduction in rubella infection 50 years after vaccine introduction, and $Incd(t)$ fluctuates before it monotonically decreases to a value below 0.01 at 19 years (Figure 2, blue). Under both *School 6* (*Scenario 2*) and *Adolescent 12* (*Scenario 7*) programs, a significant number of rubella and CRS cases would still be expected 50 years after implementation (Figure 2, red and dash-dot black curves, with 77.3% and 11.6% annual reduction in rubella, respectively). By contrast, under the *Measles Modification* and its *Catch-up* programs (*Scenarios 3 to 6*), rubella burden drops by 99.9% at 50 years since the vaccine implementation and CRS incidence decreases to below 0.01 within 13 years (Figure 2, solid black and dashed grey curves). *Scenarios 1* and *3 to 6* are most likely to meet the rubella control target within 20 years.

Compared with the no vaccine scenario (Table 2), the smallest number of accumulated CRS cases in the first 20 years after rubella vaccine introduction (260) is achieved in the comprehensive *Catch-up 40 program* at a discounted ICER of \$US1098 per CRS case prevented. We estimate the discounted ICER of the *Universal Infant* program would be only \$US357 for each case of CRS prevented but due to on-going fluctuations in CRS incidence 4,547 CRS cases would still occur over the first 20 years. The *Measles Modification* program would prevent almost 4,000 more cases of CRS than the *Universal Infant* program over this period, at a discounted ICER of \$US591 over the *Universal Infant* program and a discounted ICER of \$US440 over the no vaccine scenario (Table 2). In Appendix 3, we compared

vaccine scenarios using a cost-effectiveness frontier, and showed how the discounted *ICERs* vary over a range of parameters including the time horizon and vaccine coverage.

3.3 Sensitivity analyses

The impact of vaccine coverage was assessed for the *Universal Infant* and *Measles Modification* programs. For the *Measles Modification* program, we assumed that the vaccine coverage among 6-year-old children is less than that in infants (aged 9 months) and the additive vaccine immunity for 2 doses was adjusted accordingly. The cumulative incidence of rubella infections over 100 years would greatly increase from approximately 2.5 to more than 11 million if the actual coverage of the *Universal Infant* program was reduced from the base case estimate of 87.8% to 70% or lower (Figure 3, top); and this would be associated with a significant increase in *CRS* incidence and failure in rubella control (less than 80.6% annual reduction compared with the target > 95%). Similar patterns were observed for lower vaccine coverage of the *Measles Modification* program (Figure 3, bottom), however this strategy appeared more robust to reductions in vaccine coverage. Control of rubella would be achieved by this program if no less than 70% 9-months and 60% 6-year-old children are vaccinated. The potential impact of low vaccine coverage on *ICERs* and the average age of infection is discussed in detail in Appendix 4.

Assuming an Italy-derived contact pattern resulted in a different age distribution of infection compared with the Kenya-derived contact pattern in the absence of vaccine [33, 34], with small differences in the modelled impact of the universal infant and measles modification strategies at different coverage levels (Figure 4). However, the Kenya scenario is less robust to drops in vaccine coverage. The rate of imported rubella cases appeared to have a small impact (Appendix 5).

4. Discussion

There is a strong need to introduce rubella vaccine to developing regions and countries. Our modelling analysis of implementing rubella vaccination in East Java suggests that modifying the current measles vaccination program to include a combined measles-rubella vaccine for infants at 9 months and children at 6 years is likely to be an effective strategy for reducing annual rubella burden > 95% and *CRS* incidence to <0.01 per 1,000 live births in 20 years with little risk of a paradoxical increase. A > 95% reduction in annual rubella burden is a control target that has been proposed for adoption by SEA region [32] and a *CRS* incidence to <0.01 per 1,000 live births was set by the European Region for the elimination of *CRS* by 2015 [35]. However, control and elimination of rubella/*CRS* might only be achieved if *MR* vaccines are delivered with similar coverage to the existing measles vaccine program. Wide age-range supplementary immunization activities should be considered to accelerate the disease elimination process by improving vaccine coverage. This proposed strategy concords with the recommendations of the Strategic Advisory Group of Experts Working Group [5, 9], and its age schedule for vaccination is similar to those in the WHO American Region [36, 37] where rubella and *CRS* elimination has been achieved. The findings of this study can be generalised to developing country settings similar to East Java. The coverage achieved for the

existing measles vaccine is expected to be the major barrier for such adaptation of our proposed strategy, in particular given that WHO South-East Asia appears to experience the lowest reported infant coverage (75%) worldwide [24].

In countries that have not yet implemented rubella vaccination, the seroprevalence of anti-rubella antibodies increases with age according to the intensity and pattern of circulation of rubella in the population. Current standard surveillance of rubella in Indonesia massively underestimates the disease burden; compared with the approximately 3,000 cases of rubella infection reported for all of Indonesia each year [24], there are over half a million cases in East Java annually predicted in our model. 5 to 15% of pregnancies are at risk of rubella infection [10, 15], resulting in our estimate of approximately 700 babies born with CRS in East Java annually at an incidence of 0.77 per 1,000 live births. This CRS incidence is comparable to surveillance conducted across a number of developing countries and at the conservative end of a range between 0.5 and 2.2 per 1,000 live births [7, 38].

If the existing measles vaccine program is modified to replace all measles-only vaccines with MR vaccines (*Measles Modification* program), approximately 99.9% of rubella infections and 94% (12,593/13,357) of CRS cases could be prevented at an incremental cost of \$US5.4 million in direct vaccine costs over a 20-year time period. The discounted ICER estimated for the *Measles Modification* program over the no vaccine scenario of \$US440 per CRS case prevented is much less than the lifetime cost for treating a child with CRS which has been estimated at \$US50,000 in developing countries [10]. However, the cost-effectiveness is influenced by the achieved vaccine coverage. Our model showed that providing rubella vaccine only at age 9-months (the *Universal Infant* program) without a second scheduled dose is less robust to reduced vaccine coverage and fails to meet the rubella control target if the coverage drops below 80%. Highly effective elimination of CRS may also be achieved by high vaccine coverage in routine infant vaccination program together with catch-up to age 14 years, this has been shown through a recent modelling study in Vietnam[17].

An infant or early childhood vaccine program with low coverage might also lead to an increase in the mean age of infection if transmission is slowed but not interrupted [2]. Similar to modelling studies in other settings [14, 39], we found that low levels of vaccine coverage would be much less effective, with potential for paradoxical increase in CRS cases as a result of shifting the burden of rubella infection into older age-groups. We showed that the mean age of rubella infection could increase from 10 to the early childbearing ages (over 15 years old) if the vaccine coverage drops from the current 87.8% for 9-month-old infants and 80% for 6-year-old children to 70% and 60%, respectively. Although East Java has had good coverage with measles vaccine for several years [26], Indonesia currently does not report cases of CRS to the WHO, and the lack of sufficient surveillance on rubella and CRS may undermine efforts to control and eliminate rubella disease. Since early 2000, surveillance networks have been established in countries like Bangladesh which has introduced routine rubella vaccine (as MR at 9 months) since 2014 [38, 40, 41]. The maintenance of high coverage together with effective and ongoing disease surveillance have been considered vital for successful rubella control and eradication [13].

The mathematical models used here help provide an understanding of the relative impacts of alternative vaccine strategies. The estimates under each scenario are affected to varying degrees by the uncertainty in the measurement of various disease, geographical and cultural

factors [42, 43]. For example, the value of R_0 of rubella infection during an epidemic (the expected number of secondary cases per infected individual) can range widely from 3 to 12 in different settings [6, 16, 21], being largely influenced by region-specific social contact patterns. Given the limited local data, we compared the empirical contact patterns observed in two contrasting countries (Italy [33] and Kenya [34]), with both analyses suggesting vaccination would be highly cost-effective at existing levels of vaccine coverage. As documented elsewhere [16], the pre-vaccination burden of CRS and the benefit from immunisation tend to decrease with higher R_0 and if this were significantly higher, the cost-effectiveness of vaccine program may become poorer. High- R_0 settings are likely to face a higher risk of breakthrough rubella epidemics [17]. This underscores the importance of maintaining high vaccine coverage and sufficient disease surveillance in East Java once a rubella vaccine program has been successfully implemented, given the potential future source of rubella infections from inter-province importation [44]. The number of CRS cases due to imported rubella may decrease if rubella vaccination is introduced nationwide across Indonesia. However, there are potential delays in nationwide introduction due to high spatial heterogeneity in the coverage of relevant vaccine programs within Indonesia (the lowest reported coverage is 49% in Papua [26]). As recommended by WHO and SAGE group, wide age-range SIAs could help to close this vaccine coverage and immunity gaps across provinces [9].

There were a number of limitations to the modelling study in addition to those discussed above. We did not have data to reliably inform the total costs and utilities associated with the treatment of CRS in Indonesia. For simplicity, we ignored the protective effect of passively acquired maternal antibodies against infection in infancy [14], assuming instead that infants are susceptible from birth. The relatively simple modelling framework applied here could be extended to be structurally more realistic depending on potential questions of interest. For instance, demographic change such as declining birth rates can be investigated using an *SEIR* model with varying population [45, 46], where reduced fertility rate will be associated with delayed infection due to reduced influx of susceptibles. The impact of heterogeneity in achieved vaccine coverage for example caused by supplementary immunisation activities could be studied using more sophisticated contact patterns.

5. Conclusions

In support of the WHO recommendation for introducing rubella vaccine to countries that achieve 80% coverage of measles vaccine, this study found that substituting either the 9-month or both the 9-month and 6-year-old measles vaccine with a combined measles-rubella vaccine is highly likely to be effective and cost-effective. The latter approach would result in a more rapid decline in CRS cases and would be more robust to lower achieved vaccine coverage under contact patterns in both developed and developing settings.

Conflicts of interests

None declared.

Author contributions

YW contributed to model development, analysis and manuscript writing; JW contributed to model development and manuscript; GK provided expertise for the study and contributed to manuscript; CW supervised the project and contributed to the manuscript; TS initiated and supervised the project, and contributed to manuscript writing. All authors approve the submission of the manuscript.

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1. Plotkin, S.A., *The History of Rubella and Rubella Vaccination Leading to Elimination*. Clinical Infectious Diseases, 2006. **43**(Supplement 3): p. S164-S168.
2. *Rubella vaccines: WHO position paper*. 2011, World Health Organization: Weekly Epidemiological record. p. 301-316.
3. Gao, Z., et al., *Models of strategies for control of rubella and congenital rubella syndrome—A 40 year experience from Australia*. Vaccine, 2013. **31**(4): p. 691-697.
4. CDC, *Rubella and congenital rubella syndrome control and elimination - global progress, 2000-2012*. Morbidity & Mortality Weekly Report, 2013. **62**(48): p. 983-986.
5. Grant, G.B., et al., *Global Progress Toward Rubella and Congenital Rubella Syndrome Control and Elimination — 2000–2014*. Morbidity and Mortality Weekly Report, 2015. **64**(37): p. 1052-1055.
6. Lambert, N., et al., *Rubella*. The Lancet, 2015(0).
7. Cutts, F.T., et al., *Control of rubella and congenital rubella syndrome (CRS) in developing countries, Part 1: Burden of disease from CRS*. Bulletin of the World Health Organization, 1997. **75**(1): p. 55-68.
8. Miyakawa, M., et al., *Seroprevalence of rubella in the cord blood of pregnant women and congenital rubella incidence in Nha Trang, Vietnam*. Vaccine, 2014. **32**(10): p. 1192-1198.
9. *Status Report on Progress Towards Measles and Rubella Elimination*. 2013, SAGE working group, World Health Organization.
10. Hinman, A.R., et al., *Economic analyses of rubella and rubella vaccines: a global review*. Bulletin of the World Health Organization, 2002. **80**: p. 264-270.
11. *Global measles and rubella strategic plan: 2012-2020*. 2012, World Health Organization: Switzerland.
12. *Resolution SEA/RC66/R5: measles elimination and rubella/congenital rubella syndrome control*. 2013, World Health Organization: New Delhi, India.
13. *Status report on progress towards Measles and Rubella Elimination*. 2012, SAGE working group, World Health Organization: Switzerland.
14. Anderson, R.M. and R.M. May, *Vaccination against rubella and measles: quantitative investigations of different policies*. Journal of Hygiene, 1983. **90**(02): p. 259-325.
15. Cutts, F.T. and E. Vynnycky, *Modelling the incidence of congenital rubella syndrome in developing countries*. International Journal of Epidemiology, 1999. **28**(6): p. 1176-1184.
16. EDMUNDS, W.J., et al., *The pre-vaccination epidemiology of measles, mumps and rubella in Europe: implications for modelling studies*. Epidemiology & Infection, 2000. **125**(03): p. 635-650.

17. Vynnycky, E., et al., *Modelling the impact of rubella vaccination in Vietnam*. Human Vaccines & Immunotherapeutics, 2015: p. 00-00.
18. Miller, C.L., *Rubella in the developing world*. Epidemiology & Infection, 1991. **107**(01): p. 63-68.
19. Gill, O., *Greece paid a price for an inadequate vaccination programme against rubella infection*. Euro. Surveill. , 1999. **3**(50): p. pii=1286.
20. Panagiotopoulos, T. and T. Georgakopoulou, *Epidemiology of rubella and congenital rubella syndrome in Greece, 1994-2003*. Euro. Surveill. , 2004. **9**(4): p. pii=461.
21. Metcalf, C.J.E., et al., *Implications of spatially heterogeneous vaccination coverage for the risk of congenital rubella syndrome in South Africa*. Journal of The Royal Society Interface, 2013. **10**(78).
22. Robertson, S.E., et al., *Control of rubella and congenital rubella syndrome (CRS) in developing countries, Part 2: Vaccination against rubella*. Bulletin of the World Health Organization, 1997. **75**(1): p. 69-80.
23. Minakami, H., T. Kubo, and N. Unno, *Causes of a nationwide rubella outbreak in Japan, 2012–2013*. Journal of Infection, 2014. **68**(1): p. 99-101.
24. *WHO vaccine-preventable diseases: monitoring system. 2016 global summary*. 2016, World Health Organization: Switzerland.
25. HETHCOTE, H.W., *MEASLES AND RUBELLA IN THE UNITED STATES*. American Journal of Epidemiology, 1983. **117**(1): p. 2-13.
26. *Indonesia Demographic and Health Survey 2012*. 2013, Statistics Indonesia (Badan Pusat Statistik - BPS), National Population and Family Planning Board (BKKBN), and Kementerian Kesehatan (Kemenkes - MOH), and ICF International.
27. Budiantara, I.N., et al., *Analysis of Factors that Influence Life Expectancy in East Java (Indonesia) Using Semiparametric Spline Regression Approach*. International Journal of Basic & Applied Sciences, 2014. **14**(02): p. 22-25.
28. *Vaccine projections: quantities and pricing*. 2011 [cited 2014 24/08]; Available from: http://www.unicef.org/supply/files/2011_Vaccine_Projection_final.pdf.
29. Griffiths, D.A., *A Catalytic Model of Infection for Measles*. Journal of the Royal Statistical Society. Series C (Applied Statistics), 1974. **23**(3): p. 330-339.
30. Ades, A.E., *Methods for estimating the incidence of primary infection in pregnancy: a reappraisal of toxoplasmosis and cytomegalovirus data*. Epidemiology & Infection, 1992. **108**(02): p. 367-375.
31. Hotta, S., et al., *Virologic-epidemiological studies on Indonesia IV. Anti-influenza and anti-rubella HI antibodies in sera collected in Surabaya, East Java, in 1968*. Kobe J. Med. Sci., 1970. **16**: p. 251-259.
32. *Measles elimination and rubella control*. 2013, Regional Committee for South-East Asia Region, World Health Organization.
33. Mossong, J., et al., *Social Contacts and Mixing Patterns Relevant to the Spread of Infectious Diseases*. PLoS Med, 2008. **5**(3): p. e74.
34. Kiti, M.C., et al., *Quantifying age-related rates of social contact using diaries in a rural coastal population of Kenya*. PloS one, 2014. **9**(8): p. e104786.
35. *Eliminating measles and rubella: Framework for the verification process in the WHO European region*. 2014, World Health Organization: Denmark.
36. CDC, *Recommended immunization schedule for persons aged 0 through 18 years, United States 2016*.
37. Domingues, C.M.A.S., A.M.d.S. Teixeira, and S.M.D. Carvalho, *National immunization program: vaccination, compliance and pharmacovigilance*. Revista do Instituto de Medicina Tropical de São Paulo, 2012. **54**: p. 22-27.
38. Van Bang, N., et al., *Surveillance of congenital rubella syndrome (CRS) in tertiary care hospitals in Hanoi, Vietnam during a rubella epidemic*. Vaccine, 2014. **32**(52): p. 7065-7069.

39. Gabutti, G., et al., *Epidemiology of measles, mumps and rubella in Italy*. Epidemiology & Infection, 2002. **129**(03): p. 543-550.
40. Featherstone, D.A., et al., *Expansion of the Global Measles and Rubella Laboratory Network 2005–09*. Journal of Infectious Diseases, 2011. **204**(suppl 1): p. S491-S498.
41. Imam, H., et al., *Pregnant Women in and Around Dhaka City: Are Their Children at Risk of Developing Congenital Rubella Syndrome?* Indian Journal of Microbiology, 2010. **50**(4): p. 443-448.
42. Amaku, M., et al., *Vaccination against rubella: Analysis of the temporal evolution of the age-dependent force of infection and the effects of different contact patterns*. Physical Review E, 2003. **67**(5): p. 051907.
43. Lessler, J. and C.J.E. Metcalf, *Balancing Evidence and Uncertainty when Considering Rubella Vaccine Introduction*. PLoS ONE, 2013. **8**(7): p. e67639.
44. Lu, Y., *Rural-urban migration and health: Evidence from longitudinal data in Indonesia*. Social Science & Medicine, 2010. **70**(3): p. 412-419.
45. Li, M.Y., et al., *Global dynamics of a SEIR model with varying total population size*. Mathematical Biosciences, 1999. **160**(2): p. 191-213.
46. Merler, S. and M. Ajelli, *Deciphering the relative weights of demographic transition and vaccination in the decrease of measles incidence in Italy*. Proceedings of the Royal Society of London B: Biological Sciences, 2014. **281**(1777).

Table 1. Model variables and parameters

Variables	Description	
$S(a, t)$	Susceptible individuals	
$E(a, t)$	Exposed individuals in the latent period	
$I(a, t)$	Infected individuals	
$R(a, t)$	Immunised individuals after recovery or vaccination	
Parameters	Description	Default estimate
N	East java Population	37.5×10^6 [1]
$\beta(a, a')$	Contact coefficient of age a with all age classes a'	Italian all-contact data from Mossong <i>et al.</i> , 2008 [2]
$\lambda(a, t)$	Force-of-infection of an age a at time t	Calculated upon $\beta(a, a')$, $I(t)$ and imported cases of infection
R_0	Basic reproductive number during pre-vaccination period	4.2 for Italy [3]
v_c	Vaccine coverage for infants at age 0	87.8% [1]
	Vaccine coverage for age groups 1 to 12	80% [1, 4]
	Vaccine coverage for age groups 13 and 14	60%
	Vaccine coverage for age groups above 14	40%
v_e	Vaccine efficacy for single-dose <i>MR</i> vaccine	95% [5]
	Vaccine efficacy for two-dose <i>MR</i> vaccine	99% [5]
$P(a)$	Proportion effectively immunised by vaccination in an age group a	Calculated upon v_c and v_e
$1/\sigma$	Duration of latent period in days	10 [3, 6]
$1/\alpha$	Duration of infectious period in days	11 [3, 6]
$\phi(t)$	Predicted susceptible proportion in the risk group (aged 15-40)	Calculated from the model
θ	Risk period of gestation	16/52 years
c_1	Cost of a measles vaccination in \$US ₂₀₁₁	0.23 [7]
c_2	Cost of a measles and rubella combination vaccination in \$US ₂₀₁₁	0.53 [7]

Table 2: Comparing outcomes of alternative vaccine strategies over 20 years

Scenario \ Estimates	9 month	6 year	Catch-up	Rubella in millions	Annual reduction in rubella to no vaccine	CRS ₂₀	Total reduction in CRS cases	Total number of doses in millions	Incremental costs (\$US in millions)	Undiscounted ICER ₂₀ to no vaccine (\$US/ prevented CRS case)	Discounted ICER ₂₀ to no vaccine (\$US/ prevented CRS case)
<i>No Rubella Vaccine</i>	N	N	N	10.34	0	13,357	0	0	0	N/A	N/A
<i>1. Universal Infant</i>	Y	N	N	2.40	99.7%	4,547	66.0%	9.41	2.82	320.35	357.22
<i>2. School 6</i>	N	Y	N	2.10	77.7%	4,067	69.6%	8.57	2.57	276.79	277.39
<i>3. Measles Modification</i>	Y	Y	N	0.45	99.9%	764	94.3%	17.98	5.39	428.32	440.15
<i>4. Catch-up 6</i>	Y	Y	Y	0.28	99.9%	600	95.5%	20.12	6.53	511.83	571.33
<i>5. Catch-up 15</i>	Y	Y	Y	0.17	99.9%	314	97.6%	23.33	8.23	631.24	761.65
<i>6. Catch-up 40</i>	Y	Y	Y	0.16	99.9%	260	98.1%	28.69	11.07	845.43	1,098.29
<i>7. Adolescent 12</i>	N	N	N	9.36	10.8%	9,860	26.2%	4.29	2.27	649.59	739.93

1. *Indonesia Demographic and Health Survey 2012*. 2013, Statistics Indonesia (Badan Pusat Statistik - BPS), National Population and Family Planning Board (BKKBN), and Kementerian Kesehatan (Kemenkes - MOH), and ICF International.
2. Mossong, J., et al., *Social Contacts and Mixing Patterns Relevant to the Spread of Infectious Diseases*. PLoS Med, 2008. **5**(3): p. e74.
3. EDMUNDS, W.J., et al., *The pre-vaccination epidemiology of measles, mumps and rubella in Europe: implications for modelling studies*. Epidemiology & Infection, 2000. **125**(03): p. 635-650.
4. *Rubella vaccines: WHO position paper*. 2011, World Health Organization: Weekly Epidemiological record. p. 301-316.
5. Lambert, N., et al., *Rubella*. The Lancet, 2015(0).
6. EDMUNDS, W.J., et al., *Modelling rubella in Europe*. Epidemiology & Infection, 2000. **125**(03): p. 617-634.
7. *Vaccine projections: quantities and pricing*. 2011 [cited 2014 24/08]; Available from: http://www.unicef.org/supply/files/2011_Vaccine_Projection_final.pdf.

Figure 1: Estimated burden of rubella in absence of vaccine introduction. Left: Age-specific seropositivity for rubella in East Java and comparable settings. The solid blue curve represents the estimated proportion of East Java population in each age group immune to rubella virus at the model equilibrium. Estimated prevalence of anti-rubella antibodies in Surabaya, East Java in 1968 was presented as circles in blue [1]. Proportion of women with protective rubella antibody in Taipei, Taiwan, 1979 is shown using circles in black [2]. Observed data of both genders at age 0 to 60 from Papua New Guinea between 2006 and 2008 [3] is shown as triangles in dark grey. Observed data of pregnant women between 17 and 45 from Nha Trang, Vietnam in 2009 [4] is presented as crosses in grey. Immunity to rubella in women of child-bearing age in Cambodia, 2012, is shown using squares in light grey [5]. Right: Estimated annual rubella incidence by age at equilibrium with no vaccine, with total annual estimate in parenthesis. The mean age of infection calculated from these simulated data is approximately 10.2 years as indicated using a dashed black vertical line. All parameter values used are given in Table 1.

Figure 2. Incidence of *CRS* per 1,000 live births (*Incd*) under alternative vaccine strategies over 50 years. The vaccine coverage of each alternative vaccine program is as described in Appendix 2. The annual reduction in rubella infection (compared with pre-vaccination equilibrium) and the value of *Incd* at 50 years after the introduction of rubella vaccine is provided for each scenario in parentheses. All parameter values used are given in Table 1.

Figure 3. CRS incidence per 1,000 live births ($Incd$) over time under different levels of vaccine coverage. The vaccine coverage for newborns at age 0, $v_c(0) = 87.8\%$, 80% , 70% , 60% and 50% ; and that for 6-year-old children $v_c(6) = 80\%$, 70% , 60% , 50% and 40% , respectively. Top: The *Universal Infant* program. Bottom: The *Measles Modification* program. The cumulative incidence (in millions) of rubella infections over 100 years, and the reduction in annual rubella cases compared with no vaccine for each scenario is provided in parentheses. Under the *Measles Modification* program, the additive vaccine efficiency on patients who receive two doses was adjusted accordingly with dropped vaccine coverages as describe in Appendix 2. All other parameter values used are given in Table 1.

Figure 4. Age-specific cumulative number of rubella infections under the *Universal Infant* program (left) and the *Measles Modification* program (right) and different contact patterns (top: Italy with $R_0=4.2$, bottom: Kenya with $R_0=8$ [6-8]). The results demonstrated are for the risk age group over 20 years since the vaccine introduction. The vaccine coverage for newborns at age 0, $V_c(0) = 87.8\%$, 80% , 70% , 60% and 50% ; and that for 6-year-old children $V_c(6) = 80\%$, 70% , 60% , 50% and 40% . All other parameter values used are given in Table 1.

1. Hotta, S., et al., *Virologic-epidemiological studies on Indonesia IV. Anti-influenza and anti-rubella HI antibodies in sera collected in Surabaya, East Java, in 1968*. Kobe J. Med. Sci., 1970. **16**: p. 251-259.
2. Black, F.L., et al., *Geographic variation in infant loss of maternal measles antibody and in prevalence of rubella antibody*. American Journal of Epidemiology, 1986. **124**(3): p. 442-452.
3. Riddell, M., et al., *Rubella control in Papua New Guinea: Age-specific immunity informs strategies for introduction of rubella vaccine*. Vaccine, 2012. **30**(52): p. 7506-7512.
4. Miyakawa, M., et al., *Seroprevalence of rubella in the cord blood of pregnant women and congenital rubella incidence in Nha Trang, Vietnam*. Vaccine, 2014. **32**(10): p. 1192-1198.
5. Mao, B., et al., *Immunity to polio, measles and rubella in women of child-bearing age and estimated congenital rubella syndrome incidence, Cambodia, 2012*. Epidemiology & Infection, 2014. **FirstView**: p. 1-10.
6. Mossong, J., et al., *Social Contacts and Mixing Patterns Relevant to the Spread of Infectious Diseases*. PLoS Med, 2008. **5**(3): p. e74.

7. Kiti, M.C., et al., *Quantifying age-related rates of social contact using diaries in a rural coastal population of Kenya*. PloS one, 2014. **9**(8): p. e104786.
8. Metcalf, C.J.E., et al., *Implications of spatially heterogeneous vaccination coverage for the risk of congenital rubella syndrome in South Africa*. Journal of The Royal Society Interface, 2013. **10**(78).

Supplemental Files

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