Vaccine xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

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

Yue Wu [b], James Wood [c], Gulam Khandaker [d], Claire Waddington [a,b], Thomas Snelling [a,b,e,*]

[a] Princess Margaret Hospital, Perth, Western Australia, Australia
[b] Wesfarmers Centre of Vaccines & Infectious Diseases, Telethon Kids Institute, University of Western Australia, Australia
[c] School of Public Health and Community Medicine, University of New South Wales, Australia
[d] Sydney Medical School, University of Sydney, Australia
[e] Menzies School of Health Research, Charles Darwin University, Darwin, Australia

ARTICLE INFO

Article history:
Received 22 March 2016
Received in revised form 12 September 2016
Accepted 14 September 2016
Available online xxxx

Keywords:
Modelling
Rubella vaccine
Immunisation
Congenital rubella syndrome
Developing countries
South-East Asia

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 1000 live births. This incidence could be reduced to 0.0045 per 1000 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.

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

* Corresponding author at: Wesfarmers Centre of Vaccines & Infectious Diseases, Telethon Kids Institute, University of Western Australia, Australia.
E-mail address: Tom.Snelling@telethonkids.org.au (T. Snelling).

http://dx.doi.org/10.1016/j.vaccine.2016.09.010
0264-410X/

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 immunisation 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:

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

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):

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 et al. (2008) [33]
$\lambda(a, t)$	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 1–12	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 *MR* vaccine	95% [5]
	Vaccine efficacy for two-dose *MR* 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]

Please cite this article in press as: Wu Y et al. Informing rubella vaccination strategies in East Java, Indonesia through transmission modelling. Vaccine (2016), http://dx.doi.org/10.1016/j.vaccine.2016.09.010