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THE DYNAMICS OF RUBELLA VIRUS WITH TWO-DOSE VACCINATION STRATEGY

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Abstract. An age-structured SEIR model were constructed to study the transmission of rubella virus. The study investigated the impact of 2-dose vaccination strategy to eradicate the virus transmission. The population were focused on women population and due to the implementation of 2-dose vaccination, the population were divided into two age groups, namely age group 1 of girls who received MMR1 at age 12 – 15 months old and age group 2 of girls who received MMR2 at age 4 years old or older. The analysis was started with determining the equilibria of the system and then used it to calculate the basic reproduction ratio ($\mathscr{R}_0$) of the system. The basic reproduction ratio was used to identify the stability of the equilibria. Some numerical simulations were undertaken to confirm the analytical calculations. From the results of the study it can be concluded that the model is well fitted to the facts that 2-dose vaccination strategy for elimination rubella virus transmission really makes sense to be applied by countries all over the world.

Keywords: rubella; two-dose vaccination; basic reproduction ratio; stability.

2010 AMS Subject Classification: 37N25, 92B05.

1. INTRODUCTION

Rubella is one of Vaccine-preventable Diseases (VPDs) that can cause serious disease and complications of disease. The most feared complication due to rubella virus infection is Congenital Rubella Syndrome (CRS), an illness in infants that results from maternal infection with

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rubella virus during pregnancy. Rubella was considered as a variant of measles or scarlet fever, until firstly described in 1814 that it was different disease in German medical literature. Since then many efforts had been undertaken to prevent the transmission of the disease [5, 13].

As implemented to other VPDs, the use of vaccine to eliminate rubella transmission has a long history since the Rubella-Containing Vaccines (RCVs) had been introduced in 1969 in the United States. Later, the monovalent vaccines were substituted with combined measles and rubella -containing (MR) vaccines and measles, mumps, and rubella -containing (MMR) vaccines which are used worldwide nowadays. ([3, 16]).

World Health Organization (WHO) strongly recommended the use of MMR vaccines to eradicate mumps, measles, and rubella virus in the countries implementing large-scale immunization program [15]. This was as a result of extensive studies on the result of numerous clinical trials. The studies reported that the use of multivalent vaccines, such as MMR vaccine was recommended to interrupt rubella virus transmission and also eliminate both rubella and CRS. A thorough review had been conducted by Vynnicky et al. [13] on seroprevalence and immunization coverage to estimate CSR burden globally. The review result concluded that the estimated CRS incidence remains high after vaccination worldwide, except in the Americas, Europe and the Eastern Mediterranian.

As a follow up to the Global Vaccine Action Plan [17] that do not mention specifically global measles or rubella eradication goal, WHO published the Global Measles and Rubella Strategic Plan 2012-2020 [18]. In this plan, one of the strategies to eradicate measles, rubella and CRS is that countries should achieve and maintain high level coverage immunization coverage (at least 80%) with 2-dose MCV-RCV or combined vaccines (MR or MMR). 2-dose vaccination strategy is recommended because rubella antibodies level that most people had after 1 dose rubella-containing vaccine might be decreased over time. It is apparent that among persons with 2 doses, approximately 91-100% had detectable antibodies after 12 to 15 years after receiving the second dose [11].

The schedule of 2-dose MMR vaccination are routinely recommended for children age 12 months or older. The first dose should be given at age 12 – 15 months and the second dose is

given based on observations of failure to generate an immune response rubella following the first dose. Dose 2 is routinely given at age 4 – 6 years, before a child enters school. [4].

Many studies on rubella virus transmission, including various vaccination strategies has been conducted by many authors. There are some studies in some WHO regions that can be mentioned regarding the efforts of rubella eradication. For example, in 2013 Gao et al. [9] informed that the use of vaccine in Australia had succeeded to reduce by 99% in 2010 compared to the pre-vaccination period (1960-70). Meanwhile, Lambert et al. [10] reported that despite the success of rubella vaccines implementation in the Americas since 2009, incomplete rubella immunization programs resulted in the continuation of the virus transmission as evidenced new outbreaks in Japan and other regions. In addition, they also informed about new policies on controlling rubella and about rubella vaccine immunogenetics for the development of novel vaccine candidate which is affordable, easy to administer, and does not require any complex process for an optimal result. In 2016, Wu et al. [19] reported their study on age-structured transmission model of rubella with seven vaccination strategies in East Java, Indonesia. Their results stated that replacing the existing 2-dose measles vaccination with MR vaccines might be more effective to achieve about 99% annual reduction of rubella transmission after 20 years, provided that the vaccination coverage is maintained at least the same with the previous one.

The importance of second dose rubella vaccination (MMR2) was strengthen by the study of LeBaron et al. [11] that evaluated the short- and long-term rubella immunogenicity of MMR2. They evaluated rubella antibody levels of two groups children who received MMR2 at age 4-6 years and at age 10-12 years from serum specimens that were collected during a 12-year period. The finding of their study stated that the response of rubella antibody to MMR2 was strong, but the level of the antibody tends to decrease after 12 years.

Regarding studies on virus transmission model, most authors refer to the standard model by Kermack-McKendrick (see in [2]) and its modifications, depending on additional factors that are put in the model. Zhou et al. [20] studied a SIR measles transmission model with age-structure. They investigated the global stability of endemic equilibria of SIR epidemic models with discrete age structures in both susceptible and infectious populations. In addition, they developed a vaccination model with four age groups to analyze different vaccination strategies

for measles epidemics in India. Sun and Hsieh [12] studied a SEIR model considering varying population size and vaccination strategy. Rigorous results on the investigation of the basic reproduction ratios of the system were presented and then used them to determine the stability the disease-free equilibrium and the endemic equilibrium. They also conjectured that low vaccination rate and low efficacy of the vaccine may lead to a more complicated dynamics of the system.

This paper aimed to study the transmission models of rubella virus with age-structure and vaccination. The model followed the one studied by Sun and Hsieh [12], particularly its vaccination modeling, combined with the one studied by Zhou et al. [20] for age structure modeling. The study started with the analysis for determining equilibria of the system, and then used the disease-free equilibrium to determine the basic reproduction ratio ($\mathscr{R}_0$) following the procedures explained in [7]. Using the basic reproduction ratio, the stability of the equilibria could be determined. These results then were confirmed through numerical simulations. Finally, the interpretation of the solutions of the system were drawn.

2. Materials and Methods

This study is a continuation of the previous study in [1] where vaccination and seasonality were considered. This study proposes a similar model as in [1] but more focuses on the the implementation of 2-dose vaccination strategy as recommended by WHO [14] and Center for Disease Control and Prevention ([3, 4]).

The mathematical model still focused on women population as discussed in [1], however due to the implementation of 2-dose vaccination strategy the population was divided into two groups of population, namely 12 - 15 months old girls and 4 years old girls and older populations. In this study we used Susceptibles (S) – Exposed/Latent (E) – Infectives (I) – Recovered (R) model for both groups. The assumptions used in the model are the followings.

i. The dynamics of susceptible women population is affected by contant influx due to natural birth rate, the natural death rate and contacts between infective women with susceptible individuals,
ii. The infection rate is the same at each age group,

iii. There is an incubation rate before exposed individuals become infective individuals,

iv. Dose 1 vaccine (MMR1) is implemented to age group 1 of 12 - 15 months old girls with a certain efficacy level.

v. Dose 2 vaccine (MMR2) is implemented to age group 2 of 4 years old girls and older with a certain efficacy level.

3. Results and Discussion

Based on the assumptions above, the structure of transmission model is illustrated by compartment diagram in Figure 1 that follows. The model structure implements 2-dose rubella

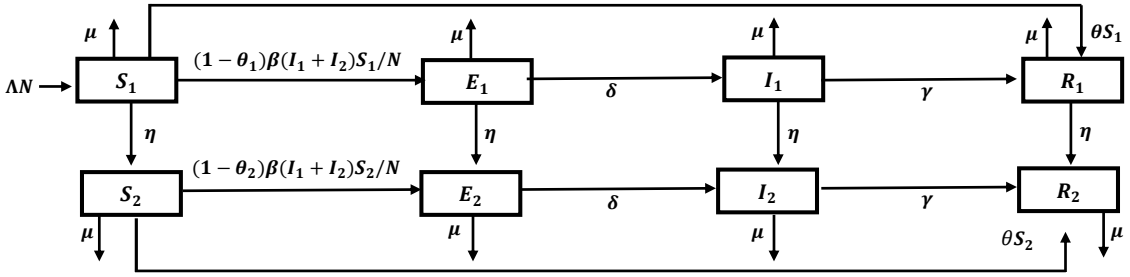


FIGURE 1. Compartment diagram of 2-dose vaccination strategy with two age groups.

vaccination strategy: MMR1 for age group 1 and MMR2 for age group 2. The model is further formulated by the following system of differential equations.

$$
\begin{aligned}
\frac{dS_1}{dt} &= \Lambda N - \frac{(1-\theta_1)\beta S_1(I_1+I_2)}{N} - (\mu+\eta+\theta_1)S_1 \\
\frac{dE_1}{dt} &= \frac{(1-\theta_1)\beta S_1(I_1+I_2)}{N} - (\mu+\eta+\delta)E_1 \\
\frac{dI_1}{dt} &= \delta E_1 - (\mu+\eta+\gamma)I_1 \\
\frac{dR_1}{dt} &= \gamma I_1 - (\mu+\eta)R_1 + \theta_1 S_1 \\
\frac{dS_2}{dt} &= \eta S_1 - \frac{(1-\theta_2)\beta S_2(I_1+I_2)}{N} - (\mu+\theta_2)S_2 \\
\frac{dE_2}{dt} &= \eta E_1 + \frac{(1-\theta_2)\beta S_2(I_1+I_2)}{N} - (\mu+\delta)E_2 \\
\frac{dI_2}{dt} &= \eta I_1 + \delta E_2 - (\mu+\gamma)I_2 \\
\frac{dR_2}{dt} &= \eta R_1 + \gamma I_2 - \mu R_2 + \theta_2 S_2.
\end{aligned}
\tag{1}
$$

where S_i, E_i, I_i, and $R_i, i = 1,2$ are Susceptibles-Exposed-Infectives-Recovered sub-population, respectively. The index $i = 1$ indicates age group 1 and $i = 2$ indicates age group 2.

In system (1) susceptibles increases by a constant influx Λ due to natural birth rate. The probability of susceptible individuals get infected when have a contact with infective ones is at the rate of β. The rate of aging of every sub-population is the same at the rate of η, while vaccines effectiveness in each age group at the rate of θ_1 and θ_2, respectively. In this study vaccines effectiveness is multiplication of vaccination coverage and vaccines efficacy that are not considered explicitly in the model. The natural death rate of each sub-population is the same at a rate of μ. Once the virus infects individuals in each age group, it needs to incubate at a rate of δ. It is assumed that infected individuals in each age group will recover at a rate of γ. All parameters of the system are assumed to be non-negative.

Using the following re-scaling

$$\bar{S}_1 = \frac{S_1}{N},\ \bar{E}_1 = \frac{E_1}{N}, \bar{I}_1 = \frac{I_1}{N}, \bar{R}_1 = \frac{R_1}{N}, \bar{S}_2 = \frac{S_2}{N},\ \bar{E}_2 = \frac{E_2}{N}, \bar{I}_2 = \frac{I_2}{N}, \bar{R}_2 = \frac{R_2}{N}$$

and after dropping the bars, we obtained the following system.

$$\begin{aligned}
\frac{dS_1}{dt} &= \Lambda - (1-\theta_1)\beta S_1(I_1+I_2) - (\mu+\eta+\theta_1)S_1 \\
\frac{dE_1}{dt} &= (1-\theta_1)\beta S_1(I_1+I_2) - (\mu+\eta+\delta)E_1 \\
\frac{dI_1}{dt} &= \delta E_1 - (\mu+\eta+\gamma)I_1 \\
\frac{dR_1}{dt} &= \gamma I_1 - (\mu+\eta)R_1 + \theta_1 S_1 \\
\frac{dS_2}{dt} &= \eta S_1 - (1-\theta_2)\beta S_2(I_1+I_2) - (\mu+\theta_2)S_2 \\
\frac{dE_2}{dt} &= \eta E_1 + (1-\theta_2)\beta S_2(I_1+I_2) - (\mu+\delta)E_2 \\
\frac{dI_2}{dt} &= \eta I_1 + \delta E_2 - (\mu+\gamma)I_2 \\
\frac{dR_2}{dt} &= \eta R_1 + \gamma I_2 - \mu R_2 + \theta_2 S_2.
\end{aligned} \tag{2}$$

In the analysis, both recovered sub-populations ($R_1$and R_2) were not considered because they do not contribute to the other sub-populations. Therefore, the analysis focused on the following

reduced system.

$$
\begin{aligned}
\frac{dS_1}{dt} &= \Lambda - (1-\theta_1)\beta S_1(I_1+I_2) - (\mu+\eta+\theta_1)S_1 \\
\frac{dE_1}{dt} &= (1-\theta_1)\beta S_1(I_1+I_2) - (\mu+\eta+\delta)E_1 \\
\frac{dI_1}{dt} &= \delta E_1 - (\mu+\eta+\gamma)I_1 \\
\frac{dS_2}{dt} &= \eta S_1 - (1-\theta_2)\beta S_2(I_1+I_2) - (\mu+\theta_2)S_2 \\
\frac{dE_2}{dt} &= \eta E_1 + (1-\theta_2)\beta S_2(I_1+I_2) - (\mu+\delta)E_2 \\
\frac{dI_2}{dt} &= \eta I_1 + \delta E_2 - (\mu+\gamma)I_2.
\end{aligned} \tag{3}
$$

By taking the right hand sides of (3) equal zeroes, the equilibria were obtained as follow.

The disease-free equilibrium

$$
E_0 := (S_1^0, E_1^0, I_1^0, S_2^0, E_2^0, I_2^0) = \left(\frac{\Lambda}{\eta+\mu+\theta_1}, 0, 0, \frac{\Lambda\eta}{(\eta+\mu+\theta_1)(\mu+\theta_2)}, 0, 0\right), \tag{4}
$$

while, the endemic equilibrium is given by

$$
E^* := (S_1^*, E_1^*, I_1^*, S_2^*, E_2^*, I_2^*). \tag{5}
$$

that cannot be presented here due to its lengthy expression.

Using Next Generation Matrix method, the basic reproduction ratio for rubella virus was obtained as follows.

Linearization of *infected states* of (3) to obtain

$$
\begin{aligned}
\frac{dE_1}{dt} &= -(\mu+\eta+\delta)E_1 + (1-\theta_1)\beta S_1 I_1 + (1-\theta_1)\beta S_1 I_2 \\
\frac{dI_1}{dt} &= \delta E_1 - (\mu+\eta+\gamma)I_1 \\
\frac{dE_2}{dt} &= \eta E_1 + (1-\theta_2)\beta S_2 I_1 - (\mu+\delta)E_2 + (1-\theta_2)\beta S_2 I_2 \\
\frac{dI_2}{dt} &= \eta I_1 + \delta E_2 - (\mu+\gamma)I_2.
\end{aligned} \tag{6}
$$

Setting $\mathbf{x} = (E_1, I_1, E_2, I_2)^T$, the linearized infection subsystem (6) can be written

$$
\dot{\mathbf{x}} = (\mathbf{T}+\Sigma)\mathbf{x}, \tag{7}
$$

where

$$\mathbf{T}=\begin{pmatrix} 0 & (1-\theta_1)\beta S_1 & 0 & (1-\theta_1)\beta S_1 \\ 0 & 0 & 0 & 0 \\ 0 & (1-\theta_2)\beta S_2 & 0 & (1-\theta_2)\beta S_2 \\ 0 & 0 & 0 & 0 \end{pmatrix}, \Sigma=\begin{pmatrix} -\mu-\eta-\delta & 0 & 0 & 0 \\ \delta & -\eta-\gamma-\mu & 0 & 0 \\ \eta & 0 & -\mu-\delta & 0 \\ 0 & \eta & \delta & -\gamma-\mu \end{pmatrix}$$

are *transmissions* and *transitions* matrices, respectively.

Since matrix $\mathbf{T}$ has two zero rows of rows 2 and 4, an auxiliary matrix corresponding to non zero rows of matrix $\mathbf{T}$ (which are rows 1 and 3) is defined as follows.

$$\mathbf{E}=\begin{pmatrix} 1 & 0 \\ 0 & 0 \\ 0 & 1 \\ 0 & 0 \end{pmatrix}.$$

Now, we are ready to calculate the basic reproduction ratio ($\mathscr{R}_0$) from the following next generating matrix with large domain. Evaluating

$$\begin{aligned} \mathbf{K}_L &= -\mathbf{E}^T \times T \times \Sigma^{-1} \times \mathbf{E} \\ &= -\begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 \end{pmatrix} T\Sigma^{-1} \begin{pmatrix} 1 & 0 \\ 0 & 0 \\ 0 & 1 \\ 0 & 0 \end{pmatrix} \\ &= \begin{pmatrix} \frac{(1-\theta_1)\beta S_1\delta}{(\eta+\gamma+\mu)(\mu+\eta+\delta)} + \frac{(1-\theta_1)\beta S_1\delta\eta(\gamma+\delta+\eta+2\mu)}{(\mu+\eta+\delta)(\eta+\gamma+\mu)(\mu+\delta)(\gamma+\mu)} & \frac{(1-\theta_1)\beta S_1\delta}{(\gamma+\mu)(\mu+\delta)} \\ \frac{(1-\theta_2)\beta S_2\delta}{(\eta+\gamma+\mu)(\mu+\eta+\delta)} + \frac{(1-\theta_2)\beta S_2\delta\eta(\gamma+\delta+\eta+2\mu)}{(\mu+\eta+\delta)(\eta+\gamma+\mu)(\mu+\delta)(\gamma+\mu)} & \frac{(1-\theta_2)\beta S_2\delta}{(\gamma+\mu)(\mu+\delta)} \end{pmatrix}. \end{aligned}$$

Substituting the values of $S_1 = S_1^0$ and $S_2 = S_2^0$ of the disease-free equilibrium (4) to matriks $\mathbf{K}_L$ and then evaluating for its eigenvalues, the largest eigenvalue corresponding to the basic reproduction ratio is obtained as follows.

$$\mathscr{R}_0 = \frac{\beta\delta\Lambda((1-\theta_1)(\mu+\theta_2)+(1-\theta_2)\eta)}{(\delta+\mu)(\gamma+\mu)(\mu+\theta_2)(\eta+\mu+\theta_1)}. \tag{8}$$

(See Diekmann et. al [6, 7] or van den Driessche and Watmough [8] for the procedure to calculate the threshold quantities of the expected second cases produced).

From [8] it follows that

Proposition 1. *The disease-free equilibrium E_0 is locally asymtotically stable if $\mathscr{R}_0 < 1$, and it is unstable if $\mathscr{R}_0 > 1$.*

3.1. Simulation. Considering the basic reproduction ratio (8), for the purpose of numerical simulation we choose parameter values mostly taken from [20] as presented in Table 1.

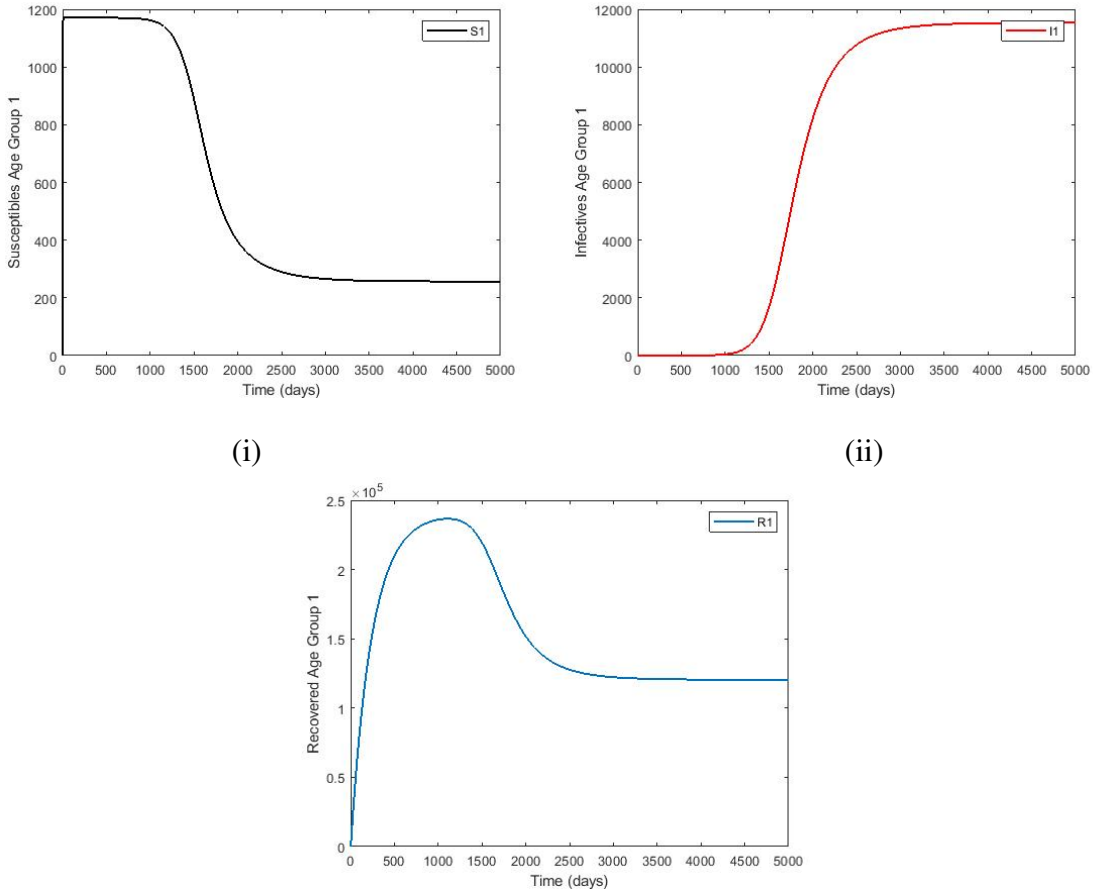
TABLE 1. Parameter values.

Description	Parameter	Values	Unit
Influx of susceptibles	Λ	1,000	1,000/week
Contact/infection rate	β	0.0007	
aging rate	η	0.00385	week^{-1}
incubation rate	μ	0.3	
Recovery rate	γ	0.0243	week^{-1}
Natural death rate	μ	0.00029	week^{-1}
Effectiveness of MMR1	θ_1	0.85	
Effectiveness of MMR2	θ_2	0.95	

For the set of parameter values in Table 1, the basic reproduction ratio $\mathscr{R}_0 = 4.564709774 > 1$, i.e. an endemic equilibrium takes place. Figure 2 and 3 illustrate that the endemic equilibrium is asymptotically stable. Comparing the dynamics of the solutions in the two age groups, it can be seen that the susceptibles in age group 2 much lower than that in age group 1. This is a result of the effectiveness of MMR1 implemented to age group 1. Meanwhile the number of recovered individuals of age group 2 is much higher than that of age group 1. This shows the effectiveness of 2-dose vaccination strategy being implemented to the population.

Figure 2 shows that to converge to the equilibrium age group 1 needs about 3000 days (or $\pm$ 8 years). This means that there will be no additional recovered individuals after the period. Also, there are still about 200 individuals which are susceptibles (Figure 2 (i)). These individuals are treated with MMR2 and belong to age group 2 in which the number of susceptible individuals is much lower than that in age group 1. (See Figure 3 (i)).

Figure 3 shows that the number of recovered individuals of age group 2 is much higher than that of age group 1. It needs about 10,000 days (or $\pm$ 27 years) until there is no more additional



(i) (ii)

(iii)

FIGURE 2. Stable Endemic Equilibrium ($\mathscr{R}_0 = 4.564709774 > 1$) of age group 1. (i) Susceptibles, (ii) Infectives, (iii) Recovered.

recovered individuals. Meanwhile, the persistence of infective individuals after that period indicates that vigilance is still required to assure continued elimination of the disease.

4. CONCLUSIONS

The SEIR transmission model of rubella virus refines the model proposed by Zhou et al. [20], particularly in considering exposed stage during the transmission of the virus. This implies that the system only gets constant influx into susceptibles of age group 1 (S_1) .

The determination of the basic reproduction ratio of the system under study plays a central role in the analysis, particularly for identifying the stability of both disease-free and endemic equilibrium.

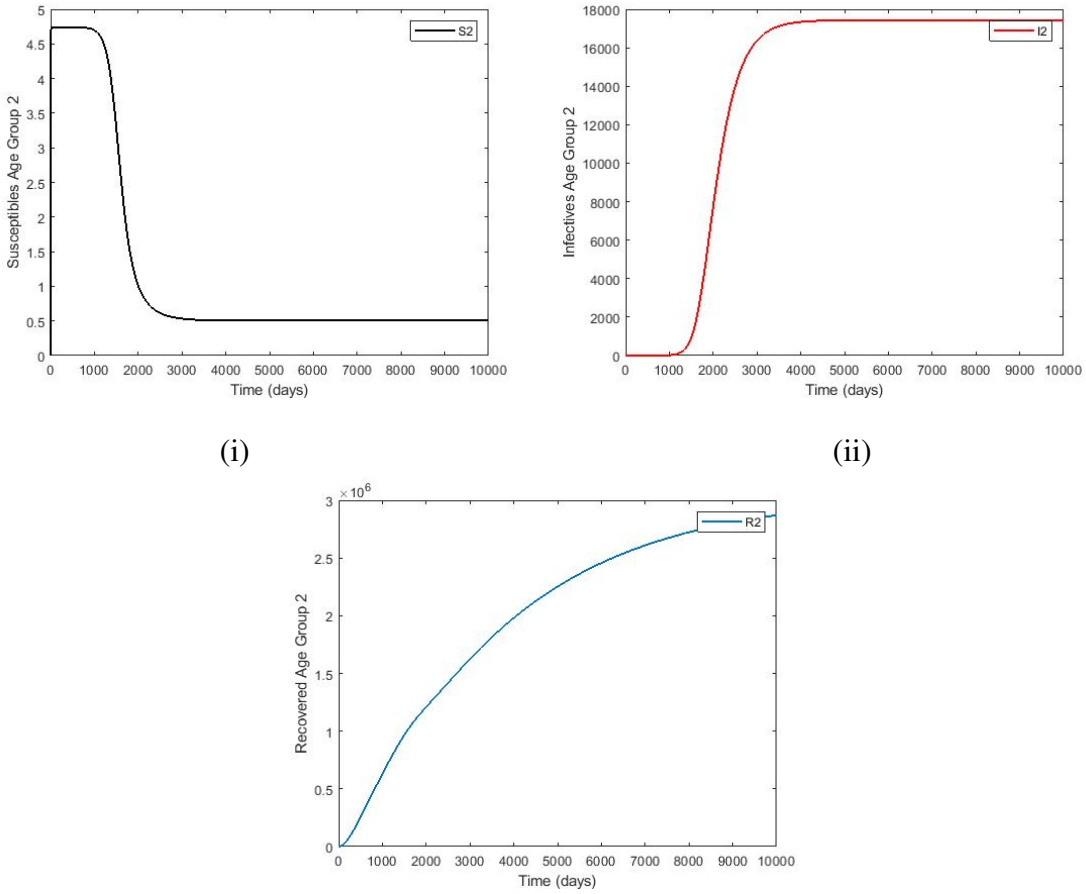


FIGURE 3. Stable Endemic Equilibrium ($\mathscr{R}_0 = 4.564709774 > 1$) of age group 2. (i) Susceptibles, (ii) Infectives, (iii) Recovered.

The model of rubella virus transmission under study gives a good confirmation about WHO recommendation to implementation 2-dose vaccination strategy in order to interrupt the transmission of the virus. The results show that it is true that the immunity being obtained due to the first dose vaccination will last not more than 12 years period. This proves the need of the second dose of the vaccine to assure continued elimination of the virus [11]. It is interesting to further study about the impact of vaccination coverage and routine immunization service which are also key factors in eliminating rubella and CRS. [18, 13].

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CONFLICT OF INTERESTS

The author(s) declare that there is no conflict of interests.

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