Study on epidemic dynamics model with time delay to eliminate measles in China

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Abstract. Measles is an infectious illness and especially harmful to children. Although the national immunization program is implemented, measles remains to be an important public health issue in China. This paper is devoted to modelling the combined effects of the first dose of Measles rubella combination vaccines (MR1) and the second dose of Measles mumps rubella combination vaccines (MMR2) coverage rates on the controlling of measles. To do that, we propose and study a robust time delayed compartment measles epidemic model where MMR2 is followed after an interval time $\tau$ by MR1. Via simulation method, we find $R_0$ is a decreasing function on the coverage rates of MR1 $\eta_1$ and the coverage rates of MMR2 $\eta_2$, but an increasing function on the interval time $\tau$. We also find $R_0 > 1$ based on the Chinese current situation of $\eta_1 = 0.95$, $\eta_2 = 0.95$ and $\tau = 1.25$. In order to completely eliminate measles in China, $\eta_1$ should be more than 0.9643, or $\eta_2$ should be more than 0.9586, or $\tau$ should be within 8 month. By comparison, it is easier to shorten the interval time $\tau$ by revising the Chinese national immunization program.

1. Introduction
Measles is one of the highly contagious viral diseases caused by paramyxovirus, spreading especially rapidly in populations that are dense and/or exhibit low immunity. Measles virus is transmitted via droplets of respiratory secretions, characterized by fever, upper respiratory tract inflammation, conjunctivitis, or red maculopapule seen on skin with spots. Measles is often associated with respiratory diseases like otitis media, laryngotracheitis, pneumonia etc. [1] The children are more susceptible to measles especially in the children’s gathering areas like schools or kindergartens. During that period measles immunization program had been not yet implemented, outbreak of measles took place every 2 or 3 years in big cities, and was one of the leading causes of death in children under 5 years old. For now, because it is lack of specific treatment, the pre-exposure vaccination acts as the only reasonable measure to control measles [2].

In 1963, the United States approved measles virus vaccine (MV). In 1970s, MV was widely applied in other parts all around the world. The vaccine can provide the protection longer than 20 years, and its immunity can be seen as life-long time. Because the maternal transferred measles antibody may interfere the vaccine antibody, the efficiency of measles vaccine gradually improves after 6 months and would peak 95%-98% in 12-15 months old [3]. In 1980s, most countries have listed measles vaccine to their regular immune plans and the coverage of the vaccines achieves a huge improvement.
In 1990, reported coverage of measles vaccine for 2-year-olds reaches 70% of all infants under 2. Since 1990, in World Health Organization (WHO) Americas, the eliminating measles plan has reduced cases by 99% and higher. Strategies for the plan include maintaining a high coverage rate by carrying out children’s vaccine plan. In WHO West Pacific, WHO Africa, WHO Europe, WHO East Mediterranean, and WHO Southeast Asia, controlling on measles has also made big process [4].

There was a high incidence of measles in China before vaccines. For example, the reported measles cases in 1959 were about 10 million, and its death tolls were about three hundred thousand. Since 1965 China began to the immunization program for measles, the morbidity reduced 200 per million until 1986. In 2006, the national committee for measles elimination of China executed the National Measles Elimination Plan (NMEP) which includes the second injection is to be administered at 18-24 months, and all measles vaccinations are free of charge, which aimed to reduce the morbidity to 1 per million in 2012 [5]. Although measles has been farther controlled, the aim is still not achieved and measles exploded to 28 per million in 2014, as shown in Figure 1 according to the statistics from Chinese Centre for Public Health Sciences Data [6]. China will shoulder heavy responsibilities for eliminating measles.

The measles problems also exit in many other countries such as Angola, Ethiopia, India, and Russia as China. Therefore, the research on measles has attracted a lot of scholars in and out of China, including works via mathematical model [7-12]. However, these studies only give a conclusion on immune results, but not on the second injection vaccine effects and the influences of the interval time between the first injection and second injection. In this paper, the epidemic dynamics model with time delay has been illustrated and analyzed by numerical simulation to study the important factors influence the measles spreading. The paper also provides the strategies for Chinese immunization program to ultimately eliminate measles.

2. The model descriptions
Since China issued the latest national immunization programme on Dec. 6, 2016, the Chinese current strategy for measles becomes that infants get a first dose vaccine when they are 8 months old. Measles rubella combination vaccines (MR) used for this denotes as MR1. To ensure immunity, a second dose of Measles mumps rubella combination vaccines (MMR) denoted as MMR2 is recommended in the 18-24 month of age. The interval time between MR1and MMR2 is applied the structured model with time delay to addressing the dynamical changes.

The model of this paper is based on that of SIR epidemic model with susceptible-infectious-recovered structure and bilinear incidence. Before giving our mathematical model, we assume that the measles infections only occur among the children aged less than 14 years old since most of the reported measles cases in China are under that age. For the infants within 8 months, they are maternally immune to measles. We assume that they have constant birth and death rates. The measles epidemic model with time delayed combined effects of MR1and MMR2 is established, which takes the form as the system (1).
The variables in the system (1) includes: $S$ is the number of susceptible individuals between MR1 at the age of 8 months and 14 years old; $I$ is the number of infected individuals at the age under 14 years; $R$ is the number of recovered individuals under the age of 14 years; $V_1$ is the number of vaccinated individuals with MR1-induced immunity between MR1 and MMR2; $V_2$ is the number of vaccinated individuals with MMR2-induced immunity between MMR2 and 14 years old; $\tilde{V}_1$ is the number of individuals with the loss of MR1-induced immunity between MMR2 and 14 years old; $N$ is the number of new born susceptible individuals less than 8 months old.

\[
\begin{aligned}
\frac{dN(t)}{dt} &= \lambda_0 - d'N - N, \\
\frac{dS(t)}{dt} &= (1 - \rho_1\eta)N + \delta\tilde{V}_1 - (1 - \rho_1\eta)\rho_2\eta_2'N_1e^{\int_{t_1}^{t}(\delta + \rho_1\eta')d\sigma} - dS - \beta SI, \\
\frac{dI(t)}{dt} &= \beta SI + \beta'\tilde{V}_1I - \gamma I - dI, \\
\frac{dR(t)}{dt} &= \gamma I - dR, \\
\frac{dV_1(t)}{dt} &= \rho_1\eta_1N - \rho_1\eta_1\rho_2\eta_2'N_1e^{-\delta\tilde{V}_1} - \rho_1\eta_1(1 - \rho_2\eta_2')N_1e^{-\delta\tilde{V}_1} - dV_1, \\
\frac{dV_2(t)}{dt} &= \rho_1\eta_1\rho_2\eta_2'N_1e^{-\delta\tilde{V}_1} + (1 - \rho_1\eta_1)\rho_1'\eta_1'N_1e^{\int_{t_1}^{t}(\delta + \rho_1\eta')d\sigma} - dV_2, \\
\frac{d\tilde{V}_1(t)}{dt} &= \rho_1\eta_1(1 - \rho_2\eta_2')N_1e^{-\delta\tilde{V}_1} - \delta\tilde{V}_1 - d\tilde{V}_1 - \beta'\tilde{V}_1I.
\end{aligned}
\]

The parameters in the system (1) are explained in Table 1, and $N$ means $(N-d)$. 

**Table 1.** Parameters using in system.

| Symbol | Definition | Unit | Symbol | Definition | Unit |
|--------|------------|------|--------|------------|------|
| $\lambda_0$ | Birth rate | People $/$ Years $^{-1}$ | $d$ | Nature death and mature rate | Years $^{-1}$ |
| $\beta$ | Infection rate for $S$ | People $/$ Years $^{-1}$ | $\beta'$ | Infection rate for $\tilde{V}_1$ | People $/$ Years $^{-1}$ |
| $\gamma$ | Recovery rate | Years $^{-1}$ | $\delta$ | Rate of $\tilde{V}_1$ degenerated into $S$ | Years $^{-1}$ |
| $d'$ | Childhood mortality rate | Years $^{-1}$ | $\tau$ | Interval time between MR1 and MR1 | Years |
| $\eta_1$ | Injection rate for MR1 | - | $\rho_1$ | Effective rate for MR1 | - |
| $\eta_2$ | Injection rate of $V_1$ for MMR2 | - | $\rho_2$ | Effective rate of $V_1$ for MMR2 | - |
| $\eta_2'$ | Injection rate of $S$ for MMR2 | - | $\rho_2'$ | Effective rate of $S$ for MMR2 | - |

The more details about this model have been displayed in our previous studies (reference [13]), including to getting a unique disease-free equilibrium and a unique endemic equilibrium and the basic reproductive number $R_0$, demonstrating the stability of equilibriums, analyzing the coverage rates of MR1 $\eta_1$ and the coverage rates of MMR2 $\eta_2$ for eliminating the measles in China. Based on the
achievements that have been acknowledged, the paper will furthermore research the interval time between MR1 and MMR2.

3. Numerical simulations

Based on the theory of epidemic dynamics model, China wants to eliminate measles completely on the conditions that $R_0 < 1$ and it is the global stability of the free-equilibrium. In the reference [13], we know that when the interval time $\tau$, considering China’s current immunization situation, is constant 1.25, we should have MR1 coverage rates larger than 88.01% based on perfect MMR2 coverage, and have MMR2 coverage rates larger than 92.63% based on perfect MR1 coverage. In this paper, we will conduct numerical simulations to discuss $R_0$ with the variable interval time. The model uses some of the parameter values chosen from the data in [5, 6, 14, 15] and references here: $\lambda = 20.6$, $\beta = 0.1$, $\gamma = 0.9$, $d = 0.069$, $d’ = 0.00743$, $\eta_1 = 0.95$, $\delta = 0.02$, $\rho_1 = 0.98$, $\rho_2 = \rho_2’ = 0.94$.

According to the result in the ref. 13, $R_0$ determines the threshold dynamics of the model. We can find the local stability of the endemic equilibrium when $R_0 > 1$; and global stability of the free-equilibrium when $R_0 < 1$.

Observing $R_0$, we detect that the parameters in that equation are only $\eta_1$, $\eta_2$, and $\tau$ which are easier to make sure $R_0 < 1$. So we assume the basic values of $\eta_1$ and $\eta_2$ are 0.95 [5] and $\eta_2 = \eta_2’$. Moreover the paper will analyze the influence of the interval time which changes from 3 months to 24 months (0.25-2 years). The simulation results are shown in Figure 2.

![Simulations of $R_0$ Values](image)

Figure 2. Simulations of $R_0$ Values
Figure 2 show that \( \mathcal{R}_0 \) always decreases when \( \eta_1, \eta_2 \) increase and \( \tau \) decreases. In Figure 2(a), we know if China wants to eliminate measles on the current situation of \( \eta_1 = 0.95 \) and \( \tau = 1.25 \) (15 months of interval time), MR1 coverage rate \( \eta_1 \) must be larger than 0.9643. Figure 2(b) indicates MMR2 coverage rate \( \eta_2 \) must be larger than 0.9586 with \( \eta_1 = 0.95 \) and \( \tau = 1.25 \). That is the reason China has made great progress in measles control, but still far above the WHO recommended rate of 1 per million. If the interval time between MR1 and MMR2 is three months, \( \eta_1 \) can reduce to 0.9326 for \( \eta_2 = 0.95 \), and \( \eta_2 \) can reduce to 0.9436 for \( \eta_1 = 0.95 \). These mean \( \eta_2 \) has more important influence on \( \mathcal{R}_0 \) than \( \eta_1 \), so it is more effective to improve MMR2 coverage rate for eliminating measles. Figure 2 (c) and (d) suggest that the interval time should be within 8 months if we want \( \mathcal{R}_0 < 1 \) on the conditions of \( \eta_1 = \eta_2 = 0.95 \). That is more easily realized by revising the Chinese national immunization program. Figure 2 (c) and (d) also tell us the interval time can exceed two years when \( \eta_1 = 0.95, \eta_2 = 0.97 \) or \( \eta_1 = 0.97, \eta_2 = 0.95 \), and the interval time can exceed three years when \( \eta_1 = 0.95, \eta_2 = 0.99 \) or \( \eta_1 = 0.99, \eta_2 = 0.95 \). This means the interval time can be lengthened with the higher coverage rates of measles vaccine.

4. Conclusions

In this paper, we construct and study a time delayed compartment measles epidemic model with combined vaccination effects of MR1 and MMR2 implemented in China. The following conclusions are obtained:

The basic reproductive number \( \mathcal{R}_0 \) is a decreasing function on the coverage rates of MR1 \( \eta_1 \) and the coverage rates of MMR2 \( \eta_2 \), but an increasing function on the interval time \( \tau \) between MR1 and MMR2.

\( \eta_2 \) has more important influence on \( \mathcal{R}_0 \) than \( \eta_1 \), and it is more effective to improve MMR2 coverage rate for eliminating measles.

Based on the current situation of \( \eta_1 = 0.95, \eta_2 = 0.95 \) and \( \tau = 1.25 \), measles can’t be eliminated in China, unless \( \eta_1 \) is more than 0.9643, or \( \eta_2 \) is more than 0.9586, or \( \tau \) reduces to 8 months. Among them, Reducing \( \tau \) is more easily realized by revising the Chinese national immunization program.

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