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Modeling and analysis of the secondary routine dose against measles in China

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Abstract

Measles remain to be an important global public health issue in China. In spite of large coverage rates of the first dose of Measles mumps rubella (MMR) combination vaccines (MMR1), large numbers of measles cases continue to be reported in China in recent years due to the high incidence and the low coverage of the second MMR vaccine dose (MMR2). This paper is devoted to modeling the combined effects of MMR1 and MMR2 coverage rates on the controlling of measles. To do that, we propose and study a robust time-delayed compartment measles infection model where MMR2 is followed after a fixed time interval of MMR1, and the combined elements of infection and mass immunization are also considered. By using the methods of Lyapunov functional and the uniform theory for infinite-dimensional dynamical systems, a threshold dynamics determined by the basic reproduction number $\Re_0$ is established: the measles can be eradicated if $\Re_0 < 1$, whereas the disease persists if $\Re_0 > 1$. Moreover, it is shown that the endemic equilibrium is locally asymptotically stable once $\Re_0 > 1$. Numerical simulations are performed to support the theoretical results and to consider the effects of MMR2 on the controlling of measles. Our results show that to eliminate measles in China, we should have MMR1 coverage rates larger than 88.01% based on perfect MMR2 coverage, and have MMR2 coverage rates larger than 92.63% based on perfect MMR1 coverage; Moreover, our simulations suggest that there is a risk that paradox of vaccination against measles in China may occur: that is, the final size of infected individuals may even increase in spite of the increase of MMR2 coverage rates.

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Keywords: measles model; second dose; Lyapunov function; globally asymptotic stability; basic reproductive number

1 Introduction

Measles is one of the most contagious viral diseases, spreading especially rapidly in populations that are dense and/or exhibit low immunity [1, 2]. In 1963, the United States approved measles virus vaccine (MV), and in the 1970s, MV were widely applied in other parts all around the world [3, 4]. The vaccine can provide with protection longer than 20 years, and its immunity can be seen as life-long time, the efficiency of the vaccine reaches above 80% [3, 5]. Because the antibodies produced by the vaccine are interfered by maternal-transferred one, the efficiency of vaccine, which reaches 95%-98%, improves after six months and reaches the peak when the infant becomes 12-15 months old [5, 6]. In the late 1980s, most countries have listed measles vaccine to their regular immune

plans, and the coverage of the vaccines sees a huge improvement. In 1990, reported coverage of measles vaccine for 2-year-olds has taken up 70% of all infants under 2 years old [2, 6]. Since 1990, in World Heath Organization (WHO) Americas, plan on eliminating measles has reduced cases by 99% and higher, and the cases for death are close to zero [4, 7]. Strategies for the plan include maintaining a high coverage rate by carrying out children's vaccine plan. In WHO West Pacific, and WHO Africa, WHO Europe, WHO East Mediterranean, and WHO Southeast Asia, controlling on measles has also made big process [7, 8].

In China, the national Expanded Program on Immunization (EPI) of a 2-dose monovalent MV schedule was implemented in 1986, with the first dose of vaccine at 8 months (monovalent attenuated vaccine, HU-191 or CHANG-47 strain) and the second dose at 7 years of age average [1, 5]. In 2006, the national committee for measles elimination of China executed the National Measles Elimination Plan (NMEP) [7, 9], which includes the MMR2 is to be administered at 18-24 months, and all measles vaccinations are free of charge. Although China has made great progress in measles control in the framework of the NMEP, its reported rate of measles was 28 cases per million in 2010, still far above the WHO's recommended rate of one case per million [2, 10, 11]. The key contributors of measles outbreaks in China include the mobility and complexity of population, the age structure changing of measles cases and the own limitations of MV, which induce the recurrence and epidemic of measles. Especially in the communities of floating population where coverage rates of MMR1 and MMR2 are much lower than the national average rates [2, 12], the measles rate continuously increases or keeps at higher level [7, 12]. Besides, the efficiency of vaccine cannot reach 100%, many children have never been vaccinated and are still susceptible to measles, and a small number children are susceptible because of the primary immunity fail [6, 13].

For the overall world, WHO suggested an MMR2 based on MMR1 to ensure the validity of immune and the prevention of the breakout, and WHO proposed the plan to achieve the regional measles elimination goals in 2015. However, new data show that overall progress toward increasing global immunization coverage has stagnated in recent four years and the 2015 measles elimination goals set by WHO Member States will not be achieved on time [7, 14]. Furthermore, comments on MMR2 are different both domestically and internationally, and problems are also exposed for the monitoring and management of measles cases, which include miss out of case report, error for case report, lack of enough information put monitor, and control on measles breakout of very difficult situation [7, 12]. Although the total of measles cases in some regions had gone down, measles still breaks out in other countries such as Angola, Ethiopia, India, Russia, and China. Therefore, the problem on the effects of MMR on measles prevention has attracted many studies in recent years, including works via mathematical model [15–19]. Baucha et including works via mathematical model [15–19]. Baucha et al. [20] developed an age-structured MSEIRV compartmental model, whereby individuals are allocated into one of a number of mutually exclusive categories based on their epidemiological status and age. Babad et al. [15] employed a discrete age-specific mathematical model to predict the impact of measles vaccination in England and Wales. Motivated by these interesting works, in this paper, we introduce a discrete time delay to describe the fixed time interval between MMR1 and MMR2, and we consider the effects of MMR2 on the measles prevention in China. Our study seems to be the first attempt in applying the structured model with time delay to

addressing the dynamical changes of those susceptible and those MMR1 during the time interval between MMR1 and MMR2.

The rest of this paper is organized as follows. In Section 2, based on the epidemic model of SIR, we formulate a structured mathematical model to examine the effects of MMR2 on measles prevention. In Section 3, we identify the basic reproduction number and establish a global threshold dynamics for our model. In Section 4, we conduct numerical simulations to confirm our analytical results. We conclude this paper in Section 5 with a summary and discussion.

2 The model

In this section, we model the combined effects of MMR1 and MMR2 coverage rates on the controlling of measles in China. Without MMR, our model is based on that of SIR epidemic model with susceptible-infectious-recovered structure and bilinear incidence. Before giving our mathematical model, we make the following assumptions:

- 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 at the age of less than 14 years [7, 10].
- For the infants N at the age of less than 8 month, they are maternally immune to measles. We assume that they have constant birth and death rates. Moreover, when they survive at the age of 8 months, they receive MMR1 with constant vaccination rate $\rho_1\eta_1$ to get MMR1-induced immunity for measles, where ρ_1 is the effective rate for MMR1, and η_1 is the injection rate for MMR1.
- For those vaccinated individuals with MMR1-induced immunity, that is, V_1, we suppose they are always immune to measles before the MMR2 scheduled time and they has constant death rate d'; moreover, we assume that there is a fixed time interval τ between the MMR1 and MMR2 scheduled time [1, 2].
- For those the infants N who do not receive MMR1 at the age of 8 months, or who get MMR1 failure, they are assumed to lose the maternal immunity and become the susceptible compartment S to measles unless they receive MMR2 in future. From our assumptions it follows that the covering rate of these infants is $1 - \rho_1\eta_1$.
- Since the incubation period of measles is only from 9 to 12 days, which is too short compared with the whole immunity period of 1.5 years, the effect of incubation period on the measles immune control is ignored.
- Those V_1 who survived in the fixed time interval τ take MMR2 with constant vaccination rate $\rho_2\eta_2$ to get MMR2-induced immunity for measles, where ρ_2 is the effective rate of V_1 for MMR2, and η_2 is the injection rate of V_1 for MMR2.

  To calculate the surviving probability, we have that $V_1(t)$ satisfies the following equation for all t between the age of 8 month and 8 months + τ:

$$\frac{dV_1(t)}{dt} = -d'V_1(t),$$

  and thus we have $V_1(t+\tau) = V_1(t)\cdot e^{-d'\tau}$, and we get the surviving rate $V_1(t+\tau)/V_1(t) = e^{-d'\tau}$.
- Those V_1 who do not receive MMR2 at scheduled time or who get MMR2 failure become the compartment $\tilde{V}_1$ with waning MMR1-induced immunity.

- The vaccinated individuals with MMR2-induced immunity, that is, V_2, are always immune to measles before they become 14 years old.
- Those S who survived at the period before MMR2 scheduled time have constant rate $\rho_2'\eta_2'$ to get MMR2-induced immunity for measles, where ρ_2' is the effective rate of S for MMR2, and η_2' is the injection rate of S for MMR2.

To calculate the surviving probability, we have that $S(t)$ satisfies the following equation for all t between the age of 8 month and 8 months + τ:

$$\frac{dS(t)}{dt} = -dS(t) - \beta S(t)I(t),$$

thus, we have

$$S(t+\tau) = S(t) \cdot e^{-\int_{t-\tau}^{t}(d+\beta I)\,d\sigma},$$

so that the surviving rate is $e^{-\int_{t-\tau}^{t}(d+\beta I(\sigma))\,d\sigma}$, which is the probability remaining for susceptible persons.

Based on these assumptions, a flow chart of measle infection model with MMR1 and MMR2 is sketched in Figure 1, where N_τ means $N(t-\tau)$. Variables and parameters are summarized in Tables 1 and 2, respectively.

Based on the flow chart in Figure 1, we obtain the time delayed compartment measles infection model with both MMR1 and MMR2 models, which takes the form as the following

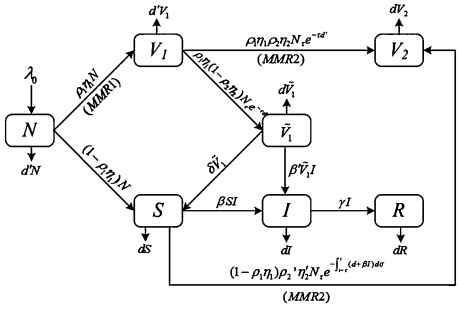

Figure 1 Flow chart of the secondary routine dose in measles vaccination.

Table 1 Variables of the models given by assumptions

Symbol	Definition
S	Number of susceptible individuals (between the age of 8 months-14 years)
I	Number of infected individuals (at the age under 14 years)
R	Number of recovered individuals (under the age of 14 years)
V_1	Number of vaccinated individuals with MMR1-induced immunity (between the age of 8-24 months)
V_2	Number of vaccinated individuals with MMR2 (between the age of 18 months-14 years)
$\tilde{V}_1$	Number of individuals with waning MMR1-induced immunity between the age of 18 months-14 years
N	Number of new born susceptible individuals less than 8 months old

Table 2 Parameters and values used in assumptions

Symbol	Definition	Range	Baseline	Unit	Reference
$\overline{N}$	Total population	-	$\lambda_0/(d'+1)$	People	[21, 22]
λ_0	Birth rate	-	20.75	People Years^{-1}	[21, 22]
d	Nature death and mature rate	-	0.069	Years^{-1}	[21, 22]
β	Infection rate for S	0.08-0.3	0.1	People^{-1} Years^{-1}	[23, 24]
β'	Infection rate for $\tilde{V}_1$	0.0088-0.099	0.011	People^{-1} Years^{-1}	[23, 24]
γ	Recovery rate	0-1	0.9	Years^{-1}	[22, 25]
δ	The proportion of $\tilde{V}_1$ degenerated into S	0.02-0.05	0.02	Years^{-1}	[2, 6]
d'	Childhood mortality rate	-	0.00743	Years^{-1}	[21, 22]
η_1	Injection rates for MMR1	0.723-1	0.91	-	[1, 2]
η_2	Injection rates of V_1 for MMR2	0.3-1	-	-	[1, 2]
η_2'	Injection rates of S for MMR2	0.3-1	-	-	[1, 2]
τ	Time interval between MMR1 and MMR2	1.3-1.5	1.5	Years	[10, 11]
ρ_1	Effective rate for MMR1	0.724-1	0.98	-	[13, 26]
ρ_2	Effective rate of V_1 for MMR2	0.857-1	0.94	-	[13, 26]
ρ_2'	Effective rate of S for MMR2	0.857-1	0.94	-	[13, 26]

system:

$$\begin{cases} \frac{dN(t)}{dt} = \lambda_0 - d'N - \rho_1\eta_1 N - (1-\rho_1\eta_1)N, \\ \frac{dS(t)}{dt} = (1-\rho_1\eta_1)N + \delta\tilde{V}_1 - (1-\rho_1\eta_1)\rho_2'\eta_2' N_\tau e^{-\int_{t-\tau}^{t}(d+\beta I)\,d\sigma} - dS - \beta SI, \\ \frac{dI(t)}{dt} = \beta SI + \beta'\tilde{V}_1 I - \gamma I - dI, \\ \frac{dR(t)}{dt} = \gamma I - dR, \\ \frac{dV_1(t)}{dt} = \rho_1\eta_1 N - \rho_1\eta_1\rho_2\eta_2 N_\tau e^{-\tau d'} - \rho_1\eta_1(1-\rho_2\eta_2)N_\tau e^{-\tau d'} - d'V_1, \\ \frac{dV_2(t)}{dt} = \rho_1\eta_1\rho_2\eta_2 N_\tau e^{-\tau d'} + (1-\rho_1\eta_1)\rho_2'\eta_2' N_\tau e^{-\int_{t-\tau}^{t}(d+\beta I)\,d\sigma} - dV_2, \\ \frac{d\tilde{V}_1(t)}{dt} = \rho_1\eta_1(1-\rho_2\eta_2)N_\tau e^{-\tau d'} - \delta\tilde{V}_1 - d\tilde{V}_1 - \beta'\tilde{V}_1 I. \end{cases} \tag{1}$$

Since model (1) is rather challenging in analysis, we would just consider its reduced case. According to Zhao et al., the infection rate β' of $\tilde{V}_1$ is much smaller than β [23, 24], and hence we may ignore the infection of $\tilde{V}_1$ by denoting $\beta' = 0$; then from system (1), we have that $\frac{dN(t)}{dt} = \lambda_0 - d'N - \rho_1\eta_1 N - (1-\rho_1\eta_1)N = \lambda_0 - d'N - N$, $\lim_{t\to\infty} N(t) = \lambda_0/(d'+1)$. Denoting

$$\overline{N} = \frac{\lambda_0}{(d'+1)}$$

and using the limit system theory engaged in [27, 28], we have that the asymptotical dynamics of system (1) is equivalent to that of the following limit system:

$$\begin{cases} \frac{dS(t)}{dt} = \overline{N}(1-\rho_1\eta_1) + \delta\tilde{V}_1 - \overline{N}(1-\rho_1\eta_1)\rho_2'\eta_2' e^{-\int_{t-\tau}^{t}(d+\beta I)\,d\sigma} - dS - \beta SI, \\ \frac{dI(t)}{dt} = \beta SI - \gamma I - dI, \\ \frac{dR(t)}{dt} = \gamma I - dR, \\ \frac{dV_1(t)}{dt} = \overline{N}\rho_1\eta_1 - \overline{N}\rho_1\eta_1 e^{-\tau d'} - d'V_1, \\ \frac{dV_2(t)}{dt} = \overline{N}\rho_1\eta_1\rho_2\eta_2 e^{-\tau d'} + \overline{N}(1-\rho_1\eta_1)\rho_2'\eta_2' e^{-\int_{t-\tau}^{t}(d+\beta I)\,d\sigma} - dV_2, \\ \frac{d\tilde{V}_1(t)}{dt} = \overline{N}\rho_1\eta_1(1-\rho_2\eta_2)e^{-\tau d'} - \delta\tilde{V}_1 - d\tilde{V}_1. \end{cases} \tag{2}$$

For system (2), we get

$$\lim_{t\to\infty} V_1(t) = \frac{\overline{N}\rho_1\eta_1(1-e^{-\tau d'})}{d'}, \qquad \lim_{t\to\infty} \tilde{V}_1(t) = \frac{\overline{N}\rho_1\eta_1(1-\rho_2\eta_2)e^{-\tau d'}}{\delta+d}.$$

To obtain the asymptotical dynamics of system (2), we only need to consider its subsystem

$$\begin{cases} \frac{dS(t)}{dt} = \overline{N}(1-\rho_1\eta_1) + \frac{\delta\overline{N}\rho_1\eta_1(1-\rho_2\eta_2)e^{-\tau d'}}{\delta+d} - \overline{N}(1-\rho_1\eta_1)\rho_2'\eta_2' e^{-\int_{t-\tau}^{t}(d+\beta I)d\sigma} - dS - \beta SI, \\ \frac{dI(t)}{dt} = \beta SI - \gamma I - dI. \end{cases} \tag{3}$$

Letting

$$A = \overline{N}(1-\rho_1\eta_1) + \frac{\delta\overline{N}\rho_1\eta_1(1-\rho_2\eta_2)e^{-\tau d'}}{\delta+d}, \qquad B = \overline{N}(1-\rho_1\eta_1)\rho_2'\eta_2' e^{-d\tau},$$

system (3) takes the form

$$\begin{cases} \frac{dS(t)}{dt} = A - Be^{-\int_{-\tau}^{0}\beta I(t+\sigma)\,d\sigma} - dS - \beta SI, \\ \frac{dI(t)}{dt} = \beta SI - \gamma I - dI. \end{cases} \tag{4}$$

Next, we consider the asymptotical behavior of (4).

3 Mathematical analysis

In this section, we analyze the stability of system (4).

3.1 Positiveness and boundedness of solutions

Throughout this paper, we set $\phi(\theta) \in C$ for $-\tau \le \theta \le 0$, with norm $\|\phi\| = \sup_{-\tau\le\theta\le 0}|\phi(\theta)|$ for $\phi \in C$. The nonnegative cone of C is defined as $C^+ = C([-\tau, 0], R_+)$. The initial conditions for system (4) are chosen at $t = 0$ as

$$\big(S(0), \phi\big) \in R_+ \times C^+, \quad S(0) > 0, \phi_2(0) > 0. \tag{5}$$

Let $X(t) = (S(t), I(t))$ be a solution to system (4), Using similar methods to [29, 30], it is clear that it suffices to verify that the set $X(t)$ is positively invariant for system (4).

Proposition 1 *Let $X(t) \in R_+ \times C^+$ be the solution of system* (4) *with the initial condition* (5). *Then $S(t) > 0$ and $I(t) > 0$ for all $t > 0$.*

Proof By the second equation of (4) we have $I(t) = I(0)e^{\int_0^t(\beta S-\gamma-d)\,d\sigma} > 0$ for all $t > 0$. From the first equation of (4), noting that $A > B$, by similar arguments we have $S(t) > 0$ for all $t > 0$. □

Proposition 2 *Let $X(t) \in R_+ \times C^+$ be the solution of system* (4) *with the initial condition* (5). *Then $S(t)$ and $I(t)$ are ultimately bounded.*

Proof For system (4), we have $\dot{S}(t) < A - dS$, $t \ge 0$, and thus $\limsup_{t\to+\infty} S(t) \le A/d$. By constructing the similar function $\bar{W} = S + I$ and using similar arguments to [29, 30], we can prove that (4) is ultimately bounded. Thus, we get that $I(t)$ is eventually bounded. □

3.2 The equilibria

It is easy to see that system (4) has a unique disease-free equilibrium

$$E_0 = (S_0, 0) = \left(\frac{A-B}{d}, 0\right) = \left(\frac{\overline{N}(1-\rho_1\eta_1)(1-\rho_2'\eta_2'e^{-\tau d})}{d} + \frac{\delta\overline{N}\rho_1\eta_1(1-\rho_2\eta_2)e^{-\tau d'}}{d(\delta+d)}, 0\right).$$

To prove the existence and uniqueness of endemic equilibrium, we identify the basic reproduction number. Following the method and notation of [31] and [32], we obtain that the basic reproduction number for system (4) is

$$\Re_0 = \frac{\beta S_0}{\gamma+d} = \frac{\beta\overline{N}(1-\rho_1\eta_1)(1-\rho_2'\eta_2'e^{-\tau d})}{d(\gamma+d)} + \frac{\beta\overline{N}\delta\rho_1\eta_1(1-\rho_2\eta_2)e^{-\tau d'}}{d(\gamma+d)(\delta+d)},$$

which decreases with the increase of η_2, η_2'. Therefore, we can reduce $\Re_0$ by increasing the probability of secondary vaccination η_2, η_2'.

Proposition 3 *If* $\Re_0 > 1$, *then system* (4) *has a unique endemic equilibrium*

$$E^* = (S^*, I^*) = \left(\frac{\gamma+d}{\beta}, I^*\right),$$

and I^* *satisfies* $f(I^*) = 0$ *with*

$$f(I) = A - Be^{-\beta I\tau} - dS^* - \beta S^* I = 0.$$

Proof Note that $f'(I) = \beta\tau Be^{-\beta I\tau} - \beta S^*$. Letting $f'(I) = 0$, we have

$$I = \frac{1}{\beta\tau}\ln\frac{\tau B}{S^*} \triangleq I_1 > 0.$$

Thus, it is easy to see that $f(I)$ is decreasing when $I > I_1$ and increasing when $I < I_1$. Recalling that $\Re_0 = \frac{S_0}{S^*}$, we have $f(0) = d(S_0 - S^*) > 0$ for $\Re_0 > 1$; moreover, $f(I) < 0$ as $I \to +\infty$. Hence, we get that the equation $f(I) = 0$ has a unique positive solution $I^* > I_1$, which proves the proposition. □

3.3 Main results

In this section, we consider the asymptotical dynamics of system (4). We will construct a Lyapunov functional, and using the LaSalle-Lyapunov theorem, we will study the characteristic equation of system (4).

We obtain the local stability of a steady state of (4) by linearization. We linearize system (4) and obtain the characteristic equation evaluated at the infected steady state [33], given by the following determinant:

$$\begin{vmatrix} \zeta + (d+\beta I) & \beta S - B\beta e^{-\beta I\tau}\int_{-\tau}^{0} e^{\zeta\sigma}\,d\sigma \\ -\beta I & \zeta - \beta S + \gamma + d \end{vmatrix} = 0,$$

where ζ is an eigenvalue. We have the following results for the disease-free and endemic steady states.

Theorem 1 *The disease-free equilibrium* $E_0 = (S_0, I_0)$ *is globally asymptotically stable when* $\Re_0 < 1$ *and unstable when* $\Re_0 > 1$.

Proof The characteristic equation of (4) at the infection-free steady state E_0 is

$$P(\zeta) = (\zeta + d)\big[\zeta + (\gamma + d)(1 - \Re_0)\big] = 0. \tag{6}$$

Thus, from (6) we get that E_0 is locally asymptotically stable when $\Re_0 < 1$ and unstable when $\Re_0 > 1$.

Define the Lyapunov functional

$$W = S - S_0 - S_0 \ln \frac{S}{S_0} + I.$$

Then it is obvious that $W(t)$ is defined and continuous for all $t \geq 0$, $S(t), I(t) > 0$, and $W(t) \geq 0$ for all $t \geq 0$ with $W(t) = 0$ only at E_0. The time derivative of $W(t)$ along the solution of (4) is given by

$$\begin{aligned}
\left.\frac{\mathrm{d}W}{\mathrm{d}t}\right|_{(4)} &= \left(1 - \frac{S_0}{S}\right)\dot{S} + \dot{I} \\
&= \frac{S - S_0}{S}\big[d(S_0 - S) + \overline{N}(1 - \rho_1\eta_1)\rho_2'\eta_2'\big(e^{-d\tau} - e^{-\int_{t-\tau}^{t}(d+\beta I)\,dt}\big) - \beta SI\big] \\
&\quad + \beta SI - (\gamma + d)I \\
&= -\frac{d}{S}(S - S_0)^2 + (\gamma + d)I(R_0 - 1) \\
&\quad + \overline{N}(1 - \rho_1\eta_1)\rho_2'\eta_2'\big(e^{-d\tau} - e^{-\int_{t-\tau}^{t}(d+\beta I)\,dt}\big)\frac{S - S_0}{S}.
\end{aligned}$$

From Proposition 2 we see that $S \leq S_0$ for sufficiently large t. Thus, the function $\frac{dW}{dt}|_{(4)}$ is always nonpositive for any functions $S(t), I(t) > 0$ when $\Re_0 < 1$, and $\frac{dW}{dt}|_{(4)} = 0$ if and only if $S = S_0$, $I = I_0$. By the LaSalle-Lyapunov theorem ([34], Thm. 3.4.7), the largest compact invariant set of $\{\mathcal{F} = \frac{dW}{dt}|_{(4)} = 0\}$ is the singleton point E_0. Thus, we conclude that E_0 is globally attractive in $\mathcal{F}$. From the above we see that the disease-free equilibrium $E_0 = (S_0, 0)$ is globally asymptotically stable when $\Re_0 < 1$. This completes the proof. □

By applying the methods and techniques of persistence theory introduced in Zhao [28] for infinite-dimensional systems, which have been recently employed in [29, 30, 35], we have the following:

Theorem 2 *Suppose the basic reproduction number* $\Re_0 > 1$. *Then system* (4) *is uniformly persistent, that is, there exists a positive constant* $\epsilon > 0$ *such that every solution* $(S(t), I(t))$ *of* (4) *satisfies* $\liminf_{t\to\infty} I(t) \geq \epsilon$.

We omit the proofs for Theorem 2 since they are very similar to those for [29], Thm. 5, [35], Thm. 2, and [30], Thm. 3.3; we refer the interested readers to these references.

Furthermore, by studying the stability of the endemic equilibrium of model (4), we have the following:

Theorem 3 *The endemic equilibrium* $E^* = (S^*, I^*)$ *is locally asymptotically stable when* $\Re_0 > 1$.

Proof At the infected steady state E^* the characteristic equation of model (4) is given by

$$P(\zeta) = \zeta^2 + \big(d + \beta I^*\big)\zeta + \beta^2 S^* I^* - B\beta^2 I^* e^{-\beta I^* \tau} \int_{-\tau}^{0} e^{\zeta\sigma}\, d\sigma = 0. \tag{7}$$

Step 1. We prove that the roots of the polynomial $P(\zeta) = 0$ only have negative real parts when $\tau = 0$.

When $\tau = 0$, the characteristic equation reduces to

$$P(\zeta) = \zeta^2 + \big(d + \beta I^*\big)\zeta + \beta^2 S^* I^* = 0. \tag{8}$$

Assume that ζ_1, ζ_2 are two roots of equation (6), which implies that

$$\zeta_1 + \zeta_2 = -\big(d + \beta I^*\big) < 0, \qquad \zeta_1\zeta_2 = \beta^2 S^* I^* > 0,$$

and thus the real parts of roots of the polynomial $p(\zeta)$ are all negative.

Step 2. We prove that $\zeta = 0$ is not a root for $p(\zeta) = 0$ for any $\tau > 0$.

Assume that $\zeta = 0$ is a root of the equation $p(\zeta) = 0$, which implies that

$$\beta^2 S^* I^* - B\beta^2 I^* e^{-\beta I^* \tau}\tau = 0.$$

This equation implies that $S^* = Be^{-\beta I^* \tau}\tau$, which contradicts the proof of Proposition 3. Thus, we have that $\zeta = 0$ is not a root of $p(\zeta) = 0$ when $\tau > 0$.

Step 3. We prove that there is no imaginary root for the characteristic equation evaluated at the infected steady state of system (3) when $\tau > 0$.

Assume that $\zeta = i\omega$ is a root of the characteristic equation. Then we have

$$\begin{aligned}&\left(\beta^2 S^* I^* - \omega^2 - \frac{B\beta^2 I^* e^{-\beta I^* \tau}\sin\omega\tau}{\omega}\right)\\ &\quad + \left[\big(d + \beta I^*\big)\omega + \frac{B\beta^2 I^* e^{-\beta I^* \tau}}{\omega} - \frac{B\beta^2 I^* e^{-\beta I^* \tau}\cos\omega\tau}{\omega}\right] i = 0.\end{aligned}$$

This equation implies that

$$\big(d + \beta I^*\big)\omega + \frac{B\beta^2 I^* e^{-\beta I^* \tau}}{\omega} - \frac{B\beta^2 I^* e^{-\beta I^* \tau}\cos\omega\tau}{\omega} = 0.$$

Thus,

$$\cos\omega\tau = \frac{(d + \beta I^*)\omega + \frac{B\beta^2 I^* e^{-\beta I^* \tau}}{\omega}}{\frac{B\beta^2 I^* e^{-\beta I^* \tau}}{\omega}} > 1,$$

a contradiction, which shows that there is no imaginary root for the characteristic equation.

With all these three steps, we have proved that as τ increases from $\tau = 0$, the real parts of roots for $p(\zeta) = 0$ cannot be zero; indeed, ζ can neither be a zero root nor be an imaginary root. Therefore, we show that the real roots of the polynomial $p(\zeta) = 0$ must always be negative for any $\tau \geq 0$. This completes the proof. □

4 Numerical simulations

In this section, we conduct numerical simulations to confirm and extend our analytical results.

Figure 2(a,b) confirms the results of Theorems 1-3, indicating that $\Re_0$ determines the threshold dynamics of system (4). Figure 2(c) shows that given $\eta_2 = \eta_2'$, the number of infected individuals I decreases with the increase of η_2, η_2' and that I will finally get eliminated when η_2 and η_2' are sufficiently close to 1. When η_2 and η_2' increase from 0 to 0.8, the peak time is delayed. In addition, when $\eta_2 = \eta_2' = 0$, $I_{\max} = 14.5$ and $I^* = 8.912$; when $\eta_2 = \eta_2' = 1$, $I_{\max} = 4.25$ and $I^* \approx 0$. The values of η_2 and η_2' have a very important impact on the immune control of measles. Figure 2(a,b) also confirms the local stability of the endemic equilibrium when $\Re_0 > 1$ and the global stability of the free-equilibrium when $\Re_0 < 1$. This verifies the results of Theorem 1-3. From Figure 2(c) we know that I is more volatile when changing the range from $\eta_2, \eta_2' \in (0.192, 0.5)$ to $\eta_2, \eta_2' \in (0.8, 1)$. The annual reported incidence rate of measles is 287 per 100,000, that is, about 7.956 per 2772 (total population $\tilde{N}$). Meanwhile the range of η_2 is from 0.024 to 0.394 in Hefei City in 2009 [7]. The result is similar to that in Figure 2(c) with $\eta_2 = 0.192$ and $I = 7.954$.

Figure 3 shows the complicated relationship between the final size of the infected I^* and the increase of MMR2 rate η_2, based on different MMR1 rates η_1. From Figure 3(a) we find $I^* = 0$ as (4) satisfies $\eta_1 = 1$, $\eta_2 = \eta_2' \geq 0.9263$ or $\eta_1 = 0.8801$, $\eta_2 = \eta_2' = 1$. This means that even if MMR1 rate is 100%, then MMR2 rate should be larger than 92.63% to eliminate the measles. If the MMR1 rate η_1 is only 88%, then MMR2 rate has to reach 100%. This suggests that we should have MMR1 coverage rates η_1 larger than 0.8801 to eliminate measles. From Figure 3(b) we get the following conclusions. First, it indicates that if MMR1 rate η_1 is rather small, then the measles could not be eliminated even with large η_2. Second, it is shown that if η_1 is large enough such as $\eta_1 \geq 0.8$ approximately, then I^* decreases with the increase of η_2, indicating the positive effect of increasing MMR2 coverage rate on the measles control. Third, if η_1 is rather small, say, $\eta_1 = 0.4$, then it comes from Figure 3 (left) that I^* will even increase as η_2 increases from 0.3 to 1, which implies some kind of paradox of MMR2 vaccination.

From Figure 4 we know that $\Re_0$ always decreases when η_1, η_2, η_2' increase. From Figure 4(a) we find that $\Re_0 < 1$ when $\eta_1 = 1$, $\eta_2 = \eta_2' > 0.9263$ or $\eta_1 = 0.8801$, $\eta_2 = \eta_2' = 1$, suggesting that we must have MMR1 coverage rates η_1 larger than 0.8801 to eliminate measles. The calculation result shows that $\Re_0 < 1$ when $\eta_1 = 0.95$, $\eta_2 = \eta_2' > 0.9623$. Although we have MMR1 coverage rates η_1 larger than 0.95 in most of China, MMR2 coverage rates $\eta_2 = \eta_2' < 0.9623$ [3, 7], which is the reason that China has made great progress in measles control in the framework of the NMEP, but it still far above the WHO's recommended rate of one case per million [2, 10, 11].

5 Summary and discussion

In this paper, we construct and study a robust time delayed compartment measles infection model with combined vaccination effects of MMR1 and MMR2 implemented in

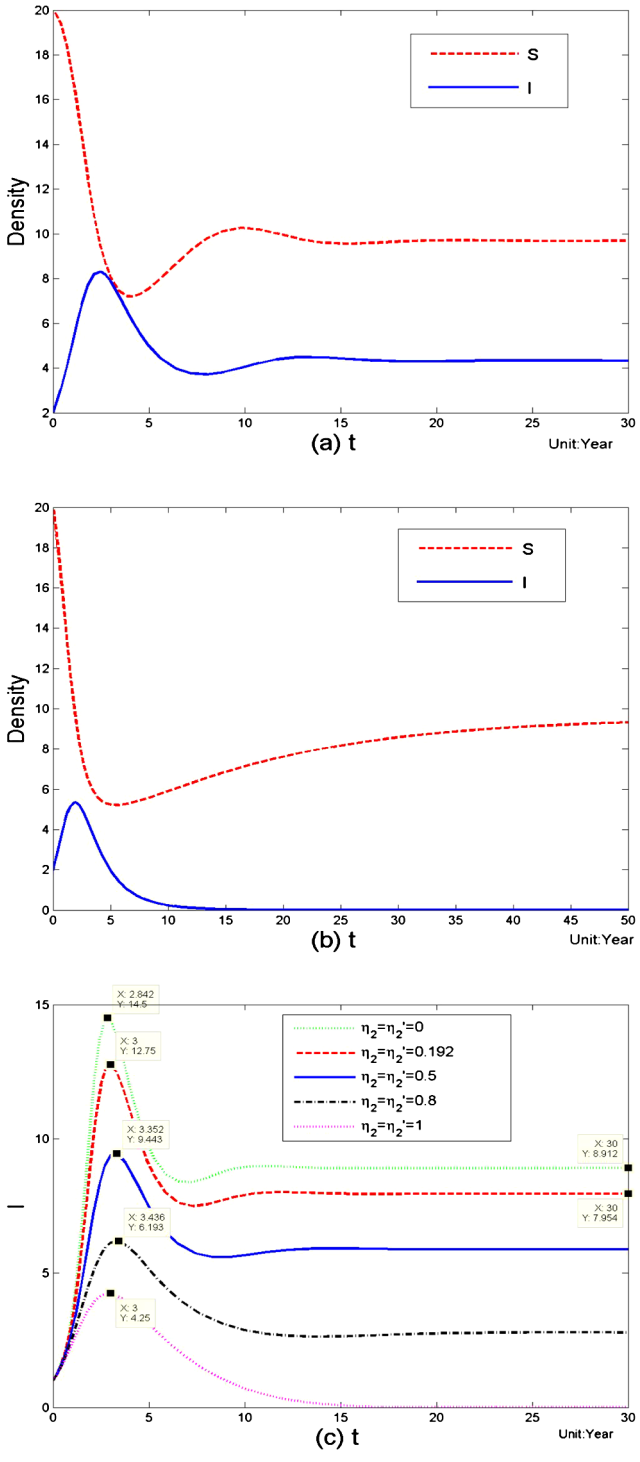

Figure 2 Numerical simulations of system (4) showing *S*, *I* vs time *t*. (a) $\eta_2 = \eta_2' = 0.3$, $\Re_0 = 6.8702 > 1$; (b) $\eta_2 = \eta_2' = 0.99$, $\Re_0 = 0.9601 < 1$.

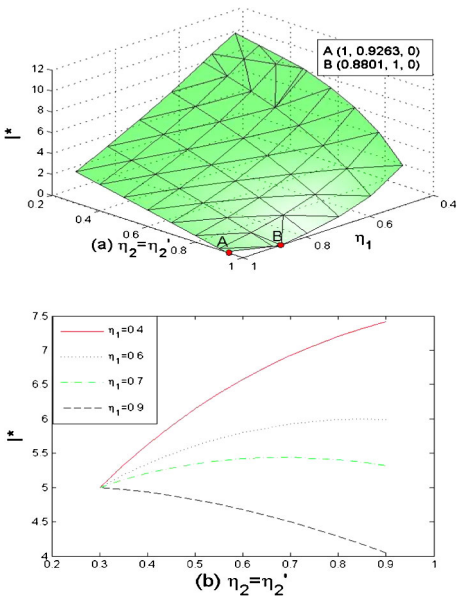

Figure 3 I^* **according to the increase of** η_1, η_2, η_2'.

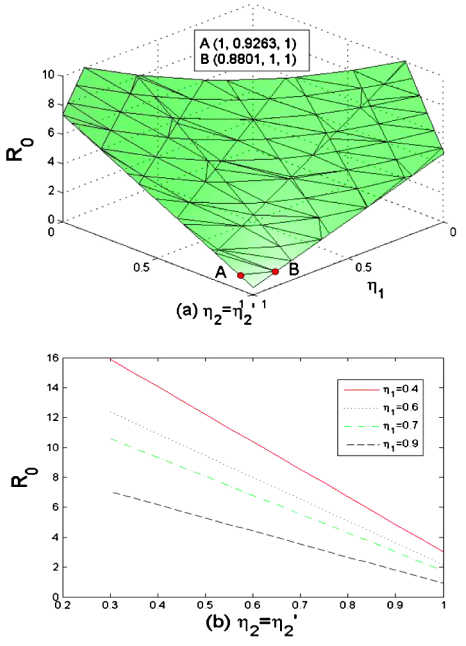

Figure 4 $\Re_0$ **according to the increase of** η_1, η_2, η_2'.

China. By using the methods of Lyapunov functional and the uniform theory for infinite-dimensional dynamical system we establish the asymptotical behaviors for the model and try to apply our results to investigate the effects of MMR1 and MMR2 on the measles control in China. We have the following conclusions:

- Our Theorems 1, 2, and 3 show that the measles-free or measles-endemic only depends on the basic reproductive number $\Re_0$.
- The basic reproductive number $\Re_0$ is a decreasing function on η_1, that is, the coverage rates of MMR1, and on η_2, η_2', that is, the coverage rates of MMR2 for V_1 and S. By

increasing MMR2 rate we can reduce the basic reproductive number $\Re_0$ and achieve the goal of control disease outbreaks by making $\Re_0 < 1$.

- Our results show that to eliminate measles in China, we should have MMR1 coverage rates $\eta_1 \geq 88.01\%$ based on $\eta_2 = \eta_2' = 100\%$; on the other hand, for MMR2, we should have $\eta_2 \geq 92.63\%$ based on $\eta_1 = 100\%$. A recent study on migrant children in east China shows that the MMR2 coverage rates are 44.7% [2], which will surely result in outbreak of measles.
- We have also performed numerical studies of system (4). The parameter values are taken mainly from [2, 22, 25, 35]. We can observe that system (4) has 13 parameters, and discussing the impact of each in detail is neither relevant nor revealing. However, as observed in the uniform persistence and stability conditions, the epidemiological parameter β is also important and may provide significant variations in the system dynamics.
- Interesting results from our simulations show that, given low coverage of MMR1 (say, $\eta_1 < 0.7$), the final size of infected individuals I^* may even increase in spite of the increase of MMR2 coverage rates, indicating some kind of paradox of vaccination, which had been found and studied in [36] for vaccination against avian flu epidemics. A recent study in [2] on migrant children in east China shows that the MMR1 coverage rates on these special groups are 0.769, which is close to 0.7, suggesting that there is a risk that paradox of vaccination against measles in China may occur.

Finally, we see that there are many other valuable problems in this area. For example: (1) We ignore the significant variance on MMR2 coverage rate for some different communities [7]; (2) We ignore the influences of subsequent supplementary immunization on measles control; (3) We ignore the influences of incubation period on measles control. We leave these questions for our future work.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
YL and JW performed the mathematical analysis of the model and also wrote and typeset the manuscript. SB, JT, SP, and XX conducted the numerical simulations and discussions. YL proofread the final document. YL and JW formulated the model. All authors read and approved the final manuscript.

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