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The impact of supplementary immunization activities on measles transmission dynamics and implications for measles elimination goals: A mathematical modelling study

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ABSTRACT

Background: Measles has re-emerged globally due to the accumulation of susceptible individuals and immunity gap, which causes challenges in eliminating measles. Routine vaccination and supplementary immunization activities (SIAs) have greatly improved measles control, but the impact of SIAs on the measles transmission dynamics remains unclear as the vaccine-induced immunity wanes.

Methods: We developed a comprehensive measles transmission dynamics model by taking into account population demographics, age-specific contact patterns, seasonality, routine vaccination, SIAs, and the waning vaccine-induced immunity. The model was calibrated by the monthly age-specific cases data from 2005 to 2018 in Jiangsu Province, China, and validated by the dynamic sero-prevalence data. We aimed to investigate the short-term and long-term impact of three-time SIAs during 2009–2012 (9.68 million and 4.25 million children aged 8 months-14 years in March 2009 and September 2010, respectively, and 140,000 children aged 8 months-6 years in March 2012) on the measles disease burden and explored whether additional SIAs could accelerate the measles elimination.

Results: We estimated that the cumulative numbers of measles cases from March 2009 to December 2012 (in the short run) and to December 2018 (in the long run) after three-time SIAs (base case) were 6,699 (95% confidence interval [CI]: 2,928–10,469), and 22,411 (15,146–29,675), which averted 45.0% (42.9%-47.0%) and 34.3% (30.7%-37.9%) of 12,226 (4,916–19,537) and 34,274 (21,350–47,199) cases without SIAs, respectively. The fraction of susceptibles for children aged 8–23 months and 2–14 years decreased from 8.3% and 10.8% in March 2009 to 5.8% and 5.8% in April 2012, respectively. However, the fraction of susceptibles aged 15–49 years and above 50 years increased gradually to about 15% in 2018 irrespective of SIAs due to the waning immunity. The measles elimination goal would be reached in 2028, and administrating additional one-off SIAs in September 2022 to children aged 8–23 months, or young adolescents aged 15–19 years could accelerate the elimination one year earlier.

Conclusions: SIAs have greatly reduced the measles incidence and the fraction of susceptibles, but the benefit may wane over time. Under the current interventions, Jiangsu province would reach the measles elimination goal in 2028. Additional SIAs may accelerate the measles elimination one year earlier.

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1. Introduction

Although measles is preventable through two doses of a safe and effective vaccine, there still existed 9.8 million measles cases and 207,500 measles deaths in 2019 globally (Patel et al., 2020; Mulholland et al., 2020). The annual measles incidence worldwide decreased from 145 cases per million in 2000 to 18 per million in 2016, but increased to 120 per million in 2019 (Patel et al., 2020). In China, the annual measles incidence decreased from 99 cases per million in 2008 to 5 per million in 2012 (Ma et al., 2014), but increased to 20 and 39 per million in 2013 and 2014, and then decreased to 3 per million in 2018 (Ma et al., 2019), which was close to achieving measles elimination goal (Papania and Orenstein, 2004; Ma et al., 2011; World Health Organization Regional Office for South-East Asia, 2015). However, the measles antibody level has declined (Hu et al., 2018; Liu et al., 2008), especially in those aged >14 years old, and the resulted increase in population susceptibility and measles immunity gap may threaten measles elimination (Wagner et al., 2016; Li et al., 2017; Chong et al., 2018; Hao et al., 2019; Trentini et al., 2017; Yang et al., 2019). When the measles elimination can be achieved and how to accelerate its elimination even with an accumulation of susceptibles are important to guide the measles control policy in China. Moreover, once there are reintroduced infections by imported cases, how to predict the local outbreak risk is also challenging.

Mathematical modelling has played an important role in evaluating the measles transmission dynamics in China. Yang et al. (Yang et al., 2019) estimated the age-specific susceptibility during 1950–2004 in Beijing, Guangzhou city and Shandong Province. Li et al. (Li et al., 2017) evaluated the impact of age-targeted (<15 years old) supplementary immunization activities (SIAs) on measles immunity and the age distribution of measles susceptibility during 1980–2011 in six provinces. As the adult infections increased, Chong et al. (Chong et al., 2018) predicted the effect of 2- or 4-year cycle SIAs targeting adults aged above 20 years old on the incidence from 2020 to 2035 in Hubei Province. Hao et al. (Hao et al., 2019) predicted the effect of SIAs targeting adolescents (15–19 years old) and young adults (20–29 years old) on the incidence during September of three successive years from 2018 to 2025 in 31 provinces. However, most of these studies did not consider the waning vaccine-induced immunity (Mossong et al., 1999; Mossong et al., 2001; Kremer et al., 2006) or validate the results based on the dynamic serological survey data. Moreover, with the accumulation of susceptible individuals, the potential outbreak risk remains unclear.

In this paper, we propose an age- and time-dependent compartmental model including the seasonality and waning immunity. We calibrate this model by the number of monthly age-specific diagnosed measles cases from 2005 to 2018 in Jiangsu Province, China, and validate it by the age-specific sero-prevalence data during 2009–2015. We estimate the effectiveness of three SIAs during 2009–2012 in Jiangsu Province in the short and long term and investigate the strategies to eliminate the measles. We also predict the outbreak risk given measles importation.

2. Methods

2.1. Data sources

We obtained the monthly measles surveillance data between January 2005 and December 2018 from the Center for Disease Control and Prevention (CDC) in Jiangsu Province, China. The reported measles cases were confirmed by laboratory testing, epidemiological linkage or clinical criteria (Ma et al., 2014). We extracted the measles cases data from 27 age groups, i.e., 0–7 months (non-vaccinated infants), 8–17 months (routine vaccinated children with the first dose), 18–23 months (routine vaccinated children with the second dose), 2–9 years with the age interval of one year (8 age groups), 10–84 years with the age interval of five years (15 age groups), 85 years and above. The data of three SIAs during 2009–2012 (Appendix Table S1), i.e., catch-up vaccination for 9,679,489 children aged 8 months-14 years in March 2009, 4,254,194 children aged 8 months-14 years in September 2010, and 141,430 children aged 8 months-6 years in March 2012, were also obtained from Jiangsu CDC. The demographic data about population size and age distribution were obtained from Jiangsu Statistical Yearbook (Jiangsu Provincial Bureau of Statistics, n.d.) (Appendix Table S2). The age-specific sero-prevalence data during 2009–2015 in Jiangsu Province were obtained from the published literature (Hu et al., 2018).

2.2. Model formulation

An age- and time-dependent discrete compartmental model is proposed to simulate the transmission of measles based on the natural history of measles infection and the vaccination history of routine vaccination and SIAs. The total population $N(a,t)$ is divided into three compartments (Fig. 1): susceptible $S(a,t)$, infected $I(a,t)$, and immunized due to vaccination or recovery from measles infection $R(a,t)$, in which a denotes age and t denotes the time. $\lambda(a,t)=\beta(a,a^{'},t)\frac{I(a,t)}{N(a,t)}$ is age- and time-dependent force of measles infection based on 'who acquires infection from whom' (WAIFW) matrix (Bolker and Grenfell, 1993; Gay et al., 1995; Keeling and Grenfell, 1997; Edmunds et al., 2000) and $\beta(a,a^{'},t)$ denotes the transmission rate between susceptible $S(a^{'},t)$ in age group $a^{'}$ and infectious individuals $I(a,t)$ in age group a at time t (see Appendix for details). Denote $b(t)$ as the number of new births at time t, and $d(a,t)$ as age- and time-dependent natural death rate among the general population. $v(a)$ is the routine vaccination coverage rate of children aged 8–23 months (the first dose for children aged 8–17 months and the second dose for children aged 18–23 months (Ma et al., 2014); and $\theta(a,t)$ is the mandatory catch-up vaccination coverage rate in SIAs during 2009–2012 among children aged 8 months-14 years regardless of previous vaccination history. Denote $p(a)$ as the age-dependent vaccination protection rate for the first and second dose, γ as the recovery rate, and $\delta(a)$ as the immunity waning rate. The measles-induced death rate is as low as 0.025%-0.087% per year in China (Ma et al., 2019) and is not considered in the model.

To account for the transmission dynamics of children aged 0–7 months and 8 months-23 months accurately, we used one month as a running time unit so that if the time increases one month from time t to $t+1$, then the age of people increases one month. We assume that all newborns ($a=0$) are susceptible and the maximum age of people is 99 years old so the population is divided into 1200 age groups, from aged 0 to 1199 months. The age-structured discrete difference equations (see Appendix for the full model with seasonality and initial age distribution) are shown below:

$$\begin{cases} S(a+1,t+1)=S(a,t)-(v(a)p(a)+\theta(a,t)p(a)+d(a,t))S(a,t)-\beta(a,a^{'},t)\dfrac{I(a,t)}{N(a,t)}S(a,t)+\delta(a)R(a,t), \\ I(a+1,t+1)=I(a,t)+\beta(a,a^{'},t)\dfrac{I(a,t)}{N(a,t)}S(a,t)-(\gamma+d(a,t))I(a,t), \\ R(a+1,t+1)=R(a,t)+(v(a)p(a)+\theta(a,t)p(a))S(a,t)+\gamma I(a,t)-(d(a,t)+\delta(a))R(a,t), \end{cases} \tag{1}$$

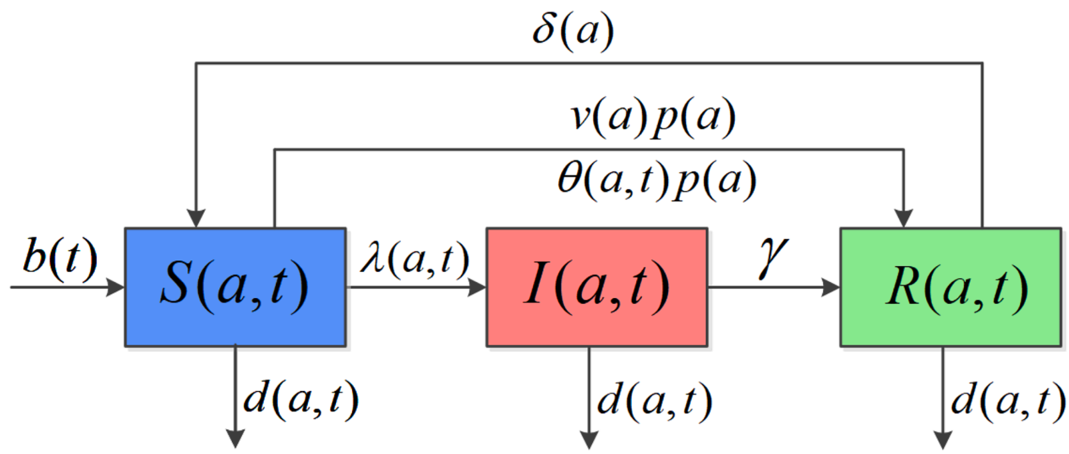

Fig. 1. A compartmental model of measles transmission. $S(a,t)$, $I(a,t)$, and $R(a,t)$ denote the susceptible, infected and immunized individuals at age a and time t. $N(a,t) = S(a,t) + I(a,t) + R(a,t)$, the total population at age a and time t;$\lambda(a,t)$, age- and time-dependent force of measles infection; $b(t)$, the number of new births at time t; $d(a,t)$, age- and time-dependent natural death rate among general population; $v(a)$, routine vaccination coverage rate of children aged 8–23 months;$\theta(a,t)$, catch-up vaccination coverage rate in supplementary immunization activities (SIAs) during 2009–2012 among children aged 8 months-14 years; $p(a)$, age-dependent vaccination protection rate;γ, the recovery rate;$\delta(a)$, the immunity waning rate.

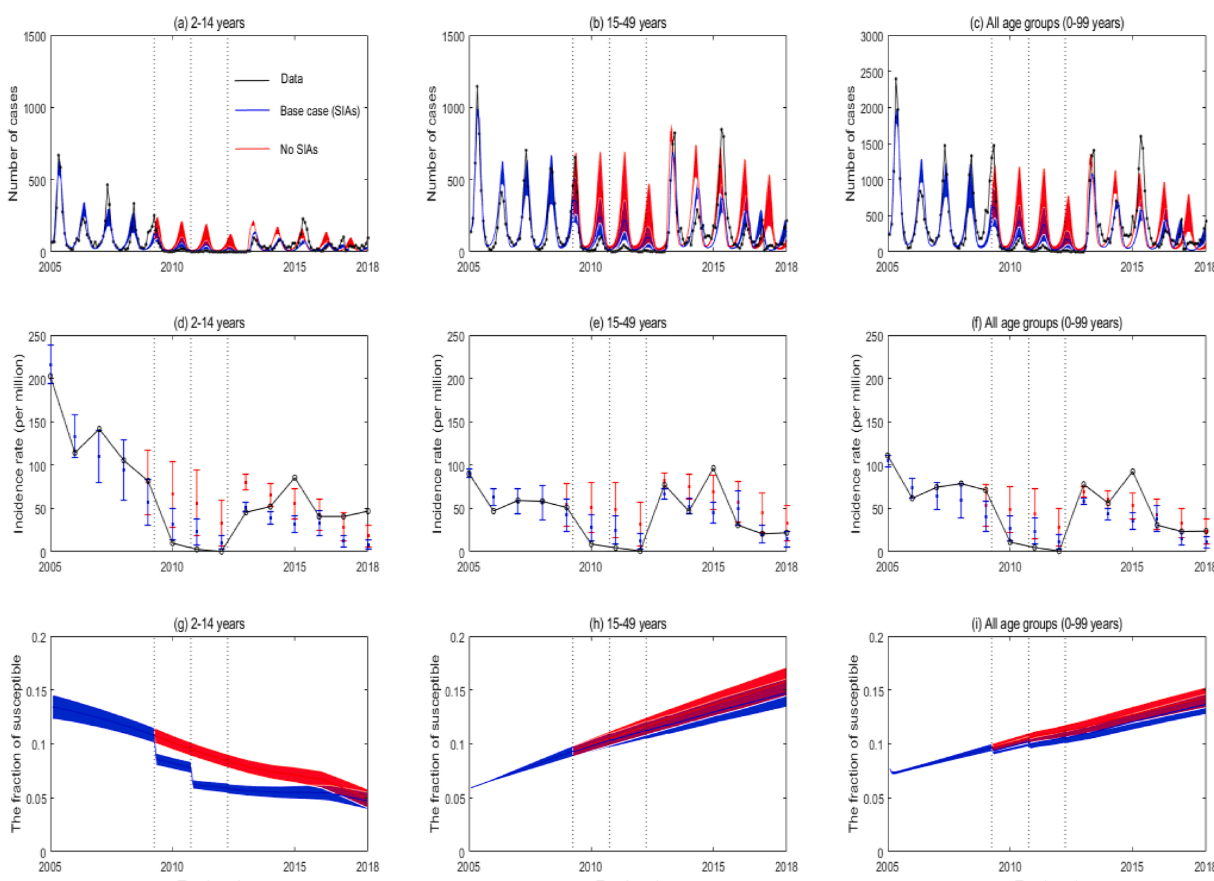

Fig. 2. (a)-(c) Model fit (blue lines) to the monthly number of new measles cases (black dots) aged 2–14 years, 15–49 years, and all age groups (0–99 years). Dashed vertical black lines show three-time SIAs in March 2009, September 2010, and March 2012. The blue and red areas show a 95% confidence interval (CI) in the base case with SIAs and counterfactual scenario without SIAs, respectively. (d)-(f) Observed annual measles incidence rate (black circles) and model fit with (blue, and error bar denotes 95% CI) and without (red) SIAs. (g)-(i) Estimated age-specific fraction of susceptibles with (blue) and without (red) SIAs. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and the new newborns satisfy the following equation:

$$\begin{cases} S(0,t) = b(t), \\ I(0,t) = 0, \\ R(0,t) = 0. \end{cases} \quad (2)$$

2.3. Model calibration

We estimated some of the model parameters (including the age-dependent transmission rates, initial immunity fractions aged 8 months-15 years in 2005 and immunity waning rates) using the nonlinear least-squares method by calibrating the model using the monthly number of new measles cases for different age groups from 2005 to 2018 (Fig. 2a–c) in Jiangsu Province, China. Detailed data fitting for all age groups was shown in Appendix Fig. S1 and the estimated parameter values were listed in Appendix Table S3. The other model parameters were obtained from the published literature or the database from Jiangsu CDC (see Appendix). We used the annual incidence rate data (Fig. 2d–f, Appendix Fig. S2) and sero-prevalence data aged 5–49 years during 2009–2015 (Hu et al., 2018) (Appendix Fig. S3) for model validation. In each simulation, we calculated the sum of square errors between the model output and data and selected the top 10% with the least square errors to generate 95% confidence intervals (CI) (Toni et al., 2009). We also performed a sensitivity analysis to account for the underreporting of case data (Appendix Figs. S5-S8), increasing the number of samples and density in the Appendix. The detailed calibration procedure for parameter and initial age distribution of population size are described in the Appendix. All analyses and simulations were performed in MATLAB R2019b.

2.4. Evaluation and prediction analysis

We evaluated the impact of SIAs during 2009–2012 on the new measles cases (Fig. 2a–c, Appendix Fig. S1), the incidence rate (Fig. 2d–f, Appendix Fig. S2), the immunity fraction (Appendix Fig. S3) and the fraction of susceptibles (Fig. 2g–i, Appendix Fig. S4), compared with no SIAs. The World Health Organization (WHO) defines measles elimination as “the absence of endemic measles virus transmission in a defined geographical area for at least 12 months in the presence of a surveillance system that has been verified to be performing well” (Papania and Orenstein, 2004; Ma et al., 2011; World Health Organization Regional Office for South-East Asia, 2015). Here in our model simulation, we set the threshold of the incidence rate to be <1 per million, which might serve as a good indicator of approaching the elimination goal (Papania and Orenstein, 2004; Ma et al., 2011; World Health Organization Regional Office for South-East Asia, 2015). We predicted whether and when the measles elimination goal would be reached and the impact of additional SIAs (for children aged 8–23 months as before, 6 years at primary school entry, and young adolescents aged 15–19 years (Hao et al., 2019) implemented in September 2022 on accelerating its elimination (Fig. 3; Appendix Fig. S9, Tables S4-S6). We calculated the effective reproduction number $R_e(t)$ (see Appendix) (Yang et al., 2019; Yang, 2020; Keeling and Rohani, 2008) and predicted the outbreak risk $Prob_{outbreak}$ (i.e., outbreak probability) (Lastname, et al., 2019; Béraud et al., 2018) when n infections aged 0–99 years are reintroduced, regardless of whether reintroductions occur as separated events (imported cases) or not (Fig. 4), as follows:

$$Prob_{outbreak} = \begin{cases} 0, & R_e(t) \leqslant 1, \\ 1 - \left(\frac{1}{R_e(t)}\right)^n, & R_e(t) > 1. \end{cases} \quad (3)$$

We also predicted the outbreak risk $Prob_{outbreak}$ for different reintroduced infections ($n = 1,5,10$) with different dispersion parameter k (Appendix Fig. S10) (Lloyd-Smith et al., 2005).

3. Results

3.1. Impact of SIAs on new measles cases and the incidence rate

SIAs have greatly decreased new measles cases and the incidence rate. In the base case with three-time SIAs in March 2009, September 2010 and March 2012 (blue areas in Fig. 2a–c), we estimated the cumulative numbers of new measles cases for all age groups (0–99 years) from March 2009 to December 2012 (in the short run) and to December 2018 (in the long run) are 6,699 (95% CI: 2,928–10,469), and 22,411 (15,146–29,675), which are close to the reported data 5,214 and 28,937, respectively. If SIAs were not implemented (red areas in Fig. 2a–c), these two numbers would become 12,226 (4,916–19,537) and 34,274 (21,350–47,199), respectively. This indicates that three-time SIAs may have averted 45.0% (42.9%-47.0%) and 34.3% (30.7%-37.9%) of new measles cases in the short and long run, respectively.

The incidence rate for all age groups has decreased from 40.8 (22.9–58.7) per million in 2009 to 11.3 (3.0–19.6) per million in 2012 after three-time SIAs in the base case (blue bar in Fig. 2d–f), while it would decrease from 53.6 (29.6–77.5) per million in 2009 to 28.2 (6.4–50.0) per million in 2012 without SIAs (red bar in Fig. 2d–f). The incidence rate was estimated to be 10.8 (4.1–17.5) and 23.6 (9.1–38.2)

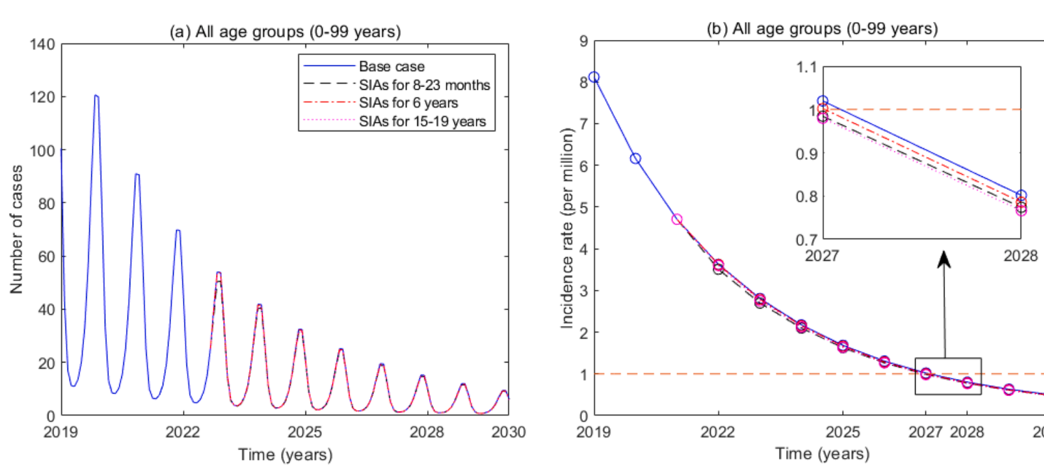

Fig. 3. Projections of monthly measles cases (a) and the yearly incidence rate (b) for all age groups in four scenarios: the base case (blue line), SIAs in September 2022 for children aged 8–23 months (black line), 6 years at primary school entry (red line), and young adolescents aged 15–19 years (green line). The orange horizontal line in (b) denotes the elimination goal, i.e., one case per million, and the inset shows zoomed incidence rate for a slice of the time-series near the elimination goal. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

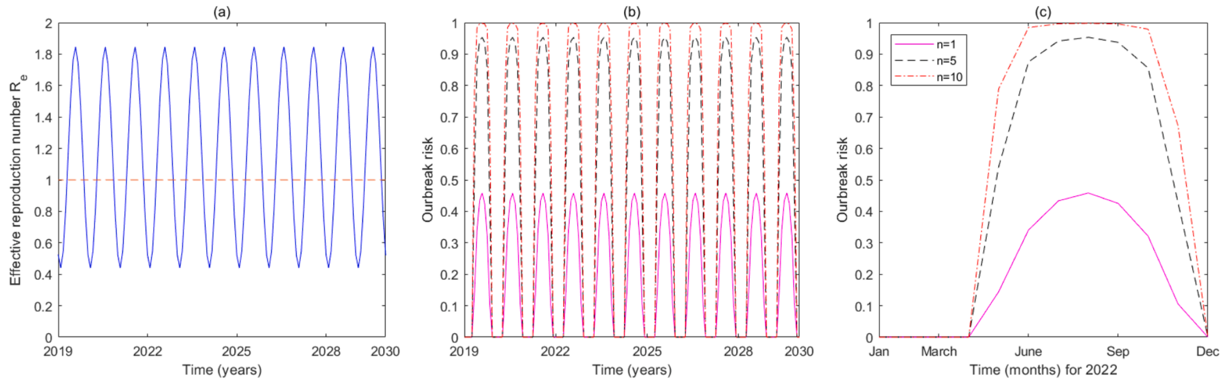

Fig. 4. The effective reproductive number R_e (a) and the outbreak risk (outbreak probability) given a different number of monthly imported cases (n = 1, 5, 10) during 2019–2030 (b) and for 2022 (c) as an example.

per million with and without SIAs in 2018. This indicates that SIAs reduced the incidence rate by 23.8% (23.1%-24.5%), 59.8% (57.4%-62.2%), and 54.2% (50.6%-57.9%) in 2009, 2012, and 2018, respectively.

3.2. Impact of SIAs on the immunity fraction and the fraction of susceptibles

SIAs have increased the immunity fraction and decreased the fraction of susceptibles for these children with catch-up vaccination. This can be seen from Appendix Fig. S3 that the immunity fraction increases from 91.7% in March 2009 to 94.2% in April 2012 for children aged 8–23 months after three-time SIAs. Similarly, the immunity fraction increases from 98.9% to 99.2% for children aged 2–4 years, and from 85.9% to 92.4% for children aged 5–14 years after three-time SIA, respectively. However, the immunity fraction for the population aged 15–49 years continues to decrease from 90.8% in January 2009 to 86.5% in December 2015 due to the waning immunity, which is in accordance with the reported data for the population aged 5–14 and 15–49 years during 2009–2015 in Jiangsu Province (Hu et al., 2018) (Appendix Fig. S3). We estimated that the immunity fraction for the population aged >=50 years decreased from 92.8% in 2009 to 87.2% in 2015.

The fraction of susceptibles decreases from 8.3% in March 2009 to 5.8% in April 2012 for children aged 8–23 months (Appendix Fig. S4), and from 10.8% to 5.8% for children aged 2–14 years (Fig. 2g) after three-time SIAs, respectively. SIAs also have indirect long-term benefits in decreasing the fraction of susceptibles aged above 15 years when the children aged 2–14 years with SIAs grow up. This can be seen from Fig. 2h and Appendix Fig. S4 that the fraction of susceptibles for the population aged 15–49 years and above 50 years in December 2018 (after implementing SIA 9 years) are estimated to be 15.2% and 15.4%, respectively, lower than 16.3% and 15.6% in the absence of SIAs. However, the fraction of susceptibles aged 15–49 years and above 50 years may have increased gradually to 15%-16% in 2018 irrespective of SIAs due to the waning immunity.

3.3. Impact of SIAs on measles elimination

Under the current interventions, we predicted the monthly measles cases and the incidence rate would decrease steadily from 2019 to 2030 and it would reach the measles elimination goal in 2028 (Fig. 3). Administrating non-selective SIAs to children aged 8–23 months, or young adolescents aged 15–19 years separately in September 2022 would accelerate the elimination one year earlier (in 2027), but SIAs for children 6 years at primary school entry would still reach the elimination goal in 2028. This may be because the number of susceptible population aged 6 years is less than the number for the population aged 8–23 months and 15–19 years.

3.4. Predicting the outbreak risk

We estimated the effective reproduction number as 0.44–1.85 in 2019 in the presence of routine vaccination (Fig. 4a). This number from 2020 to 2030 would follow a similar periodic pattern and range, predicting the outbreak risk for different imported cases (Fig. 4b). For example, in 2022 (Fig. 4c), if the monthly imported measles case is 1, the estimated outbreak risk will be 0.11–0.46 during May-November and the risk is highest at 0.46 in August. If the monthly imported measles cases increase to 5, the outbreak risk will increase to 0.43–0.95 and the highest risk will reach 0.95. If the monthly imported measles cases continue increasing to 10, the outbreak risk will reach as high as 0.67–0.998 and the highest risk will reach 0.998.

4. Discussion

In this study, we have developed a comprehensive measles transmission dynamic model taking into account population demographics, age-specific contact patterns, seasonality, routine vaccination, and SIAs based on multi-source data (age-specific monthly cases and seroprevalence). We found that three-time SIAs during 2009–2012 (Fig. 2) may have reduced by 31%-47% of the measles cases, 51%-62% of the incidence rate, and 30%-46% of the fraction of susceptibles aged 8 months-14 years. We predicted that the measles elimination goal may be reached in 2028 and additional SIAs for the population aged 8–23 months and 15–19 years may accelerate the elimination one year earlier (Fig. 3). We also found that the outbreak risk may be greater than 70% once the monthly imported measles cases exceed ten (Fig. 4).

Our study shows that the impact of SIAs may gradually decline over time. Three-time SIAs can avert 45% of measles cases in the short run but this fraction will reduce by 10% if the study period becomes six years longer when calculating the number of cumulative measles cases (Fig. 2). Moreover, the fraction of susceptibles aged 2–14 years in 2009 and 2012 is 8.6% and 5.8% in the base case, obviously lower than 10.8% and 8.5% without SIAs, respectively, but this fraction becomes 4.7% in 2018, very close to 4.9% without SIAs. This indicates that SIAs can bring more short-term benefit but this benefit wanes because the main source that decreases the fraction of susceptibles and increases the immunity rate is routine vaccination. It is worth noting that these quantitative results on the effect of essential SIAs and its decline have not been investigated in previous SIAs studies (Wagner et al., 2016; Li et al., 2017; Chong et al., 2018; Hao et al., 2019; Trentini et al., 2017; Yang et al., 2019).

Our finding demonstrates that additional SIAs are beneficial to accelerating measles elimination. SIAs for children aged 8–23 months and young adolescents aged 15–19 years can reach the elimination goal earlier from 2028 to 2027, compared with no additional SIAs, while SIAs for children aged 6 years at primary school entry may have little impact due to the lower population size of susceptible (Fig. 3). Previous SIAs are mainly for children aged 8 months-14 years, which did not involve young adolescents aged 15–19 years. Our model shows that adolescent SIAs through school-based catch-up campaigns are beneficial to the control of measles transmission. This is consistent with a previous study (Hao et al., 2019) which also suggested that adolescent SIAs would accelerate elimination.

Our results demonstrate the outbreak risk increases sharply as the monthly imported measles cases increase. The maximal outbreak risk would increase from 0.46 to 0.95 or 0.998 when the number of monthly imported measles cases increases from 1 to 5 or 10 (Fig. 4). Maintaining high levels of population immunity among the population living in these almost measles-free areas is very important to reduce the risk of spread following an importation. Moreover, the maintenance of a sensitive surveillance system is essential so that any imported measles cases can be detected early and health authorities can respond quickly to effectively control the possible outbreak.

Our study has several limitations. First, the measles cases data used to calibrate the model are from the CDC surveillance system, which may be underreported. We also assumed the reporting rate of these cases is the same for all age groups. The reporting rates may be higher for infants and young children than for older age groups. Sensitivity analysis showed that involving lower reporting rates may have little impact on the effectiveness of SIAs. Second, the incidence rate of <1 per million, used to calculate the time when measles will be eliminated, is just an indicator of approaching the measles elimination goal, rather than the exact criterion of measles elimination. Third, with the available data, we did not consider the potential difference between these vaccinated individuals with secondary failure and those who were susceptible all the time. Moreover, we did not consider the possible immunity difference between the vaccinated and recovered individuals after natural infection (Bianchi et al., 2021) because the immunity derived from natural infection (including subclinical infection) is very low ($<0.1\%$) in our case study and the sero-prevalence survey data cannot differentiate them (Winter et al., 2018; Glass and Grenfell, 2004). Fourth, we did not consider potential geographical heterogeneities in the incidence and immunity levels at the city scale. Moreover, we did not consider whether the measles cases are migrant population or permanent residents. Migrant workers and their children may have lower immunity levels and be the main source of measles cases. Fifth, we assumed that all the new births aged 0–7 months are susceptible which may underestimate the protective level of maternal immunity. Lastly, the impact of non-pharmacological interventions (e.g., social distancing, face mask, city lockdown) due to the COVID-19 epidemic on the contact rate of measles transmission and measles vaccination rate remains unclear (Durrheim et al., 2022), which may affect the prediction results.

In conclusion, SIAs have greatly reduced the measles incidence and the fraction of susceptibles, but the benefit may wane over time. Additional SIAs for children aged 8–23 months and young adolescents aged 15–19 years would accelerate the measles elimination.

5. Declarations

Availability of data and materials: The data utilized in this study are referenced in the article and included in its supplementary information files.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data is in the Appendix.

Acknowledgments

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Authors' contributions

M.S., Y.X., and Z.P. conceived and designed the study. X.S., Y.L., C. W., Z.W. extracted the measles data from Jiangsu CDC. M.S. analyzed the data, carried out the analysis and performed numerical simulations. M.S. wrote the first draft of the manuscript, and L.R., Y.X., and Z.P. made the important revision. All the authors contributed to writing the paper and agreed with the manuscript results and conclusions.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtbi.2022.111242.

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