Study on factors associated with seroprotection after measles vaccination in children of 6–14 years in Eastern China

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ABSTRACT

Measles cases have occurred in individuals with histories of vaccination against the disease in Zhejiang Province, China. The purposes of this study were to determine the seroprevalence of immunoglobulin G (IgG) measles antibodies in vaccinated individuals, to explore the waning kinetics of measles antibody among children after receipt of a measles-containing vaccine, and to define high-risk groups in the population. A seroprevalence survey of measles antibody was conducted with 1900 randomly selected and age-stratified participants aged 6–14 years in Zhejiang province. In our study, seronegative persons accounted for 7.17% of study participants. A case-control study of participants who had received at least one dose of measles-containing vaccine was conducted, with 123 cases of immune failure and 1593 controls with immune success. Multivariate logistic regression analysis showed that age, and number of doses were the influencing factors for measles immunization failure. The older a participant (odds ratio [OR] = 1.164), the more likely that measles vaccine immunity failed. In addition, immune failure was more likely to occur after one dose of MCV than two doses (OR = 0.008) or three doses and more (OR = 0.047). In a univariate logistic regression analysis, we found that immune failure was more likely to occur with MCV vaccination beginning at 8 months than at 9–11 months (OR = 0.562) and the subjects whose registration residence was in other cities in Zhejiang province (OR = 3.527). However, these differences in seropositivity were not significant in the multivariate logistic regression analysis. The exponential regression equation of the attenuation model after measles immunization was y = 884.64e$^{-0.057x}$ (R^2 = 0.0521, p < 0.001), and results showed that the measles geometric mean concentration of IgG antibodies was approximately 884.64 mIU/ml after the last MCV vaccination and decreased with time since last vaccination.

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1. Introduction

Measles is one of the most infectious diseases in humans. Due to vaccination against the measles virus, there has been a significant decline in the incidence of measles cases and deaths due to the disease [1]. However, measles continues to occur throughout the world despite widespread vaccination—even in countries with high coverage rates [2,3].

Zhejiang, a developed province in China, lies on the east coast of China. In Zhejiang, measles vaccine was introduced in 1967, and routine immunization has been implemented since 1978, with a mandatory 2-dose schedule of vaccines at the age of 8 months and 7 years. Researches on measles vaccination and immunization had been done in Zhuji county, Zhejiang province, in the 1970s and 1980s. The study showed that the immunity induced by successful primary immunization may persist for 15 years [4]. In 2005, the measles immunization program was enhanced by changing the time schedule of the second dose from 7 years to 18–24 months of age. The incidence of measles cases dropped more than 90%, with measles vaccine coverage maintained at >90% in recent decades. However, the presence of measles in recent years has disrupted elimination of the disease in Zhejiang, even though the prevalence of first-dose measles-containing vaccine (MCV) among children at 12 months of age has been above 95% in Zhejiang since 1999 [5,6]. More importantly, there is an increasing percentage of measles cases who have a vaccination history [7], may be caused by such as high coverages of children or other reasons [8,9], but leading to concerns about waning or decay of measles vaccine-induced humoral immunity, despite the reported effectiveness of the vaccine [10,11] (see Figs. 1 and 2).

Like many other places with circulating measles, in addition to insufficient vaccine coverage, both primary and secondary vaccine failures play a role in measles outbreaks in Zhejiang [12,13].

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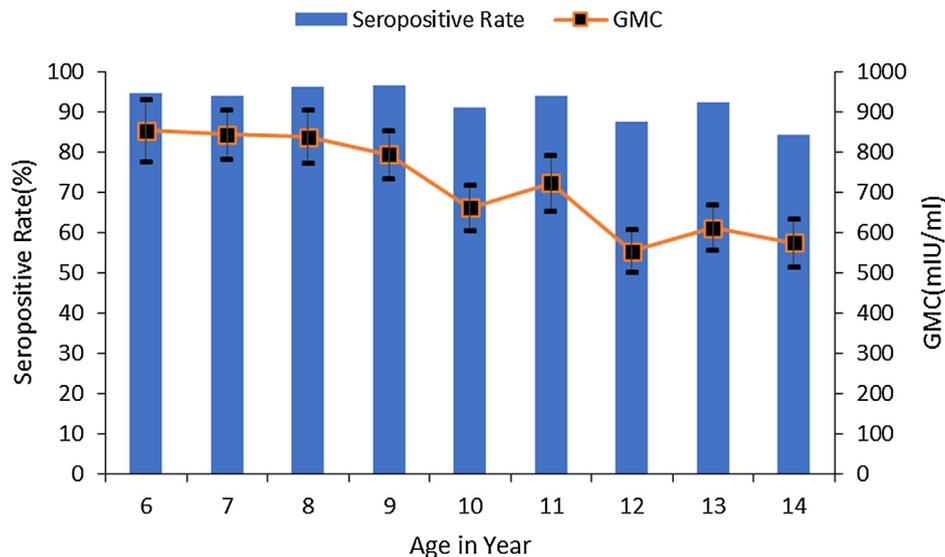 *E-mail address:* hanqinghe@cdc.zj.cn (H. He).

Fig. 1. Age-specific seroprevalence and geometric mean concentrations of antibodies against measles. Error bars represent the 95% confidence interval.
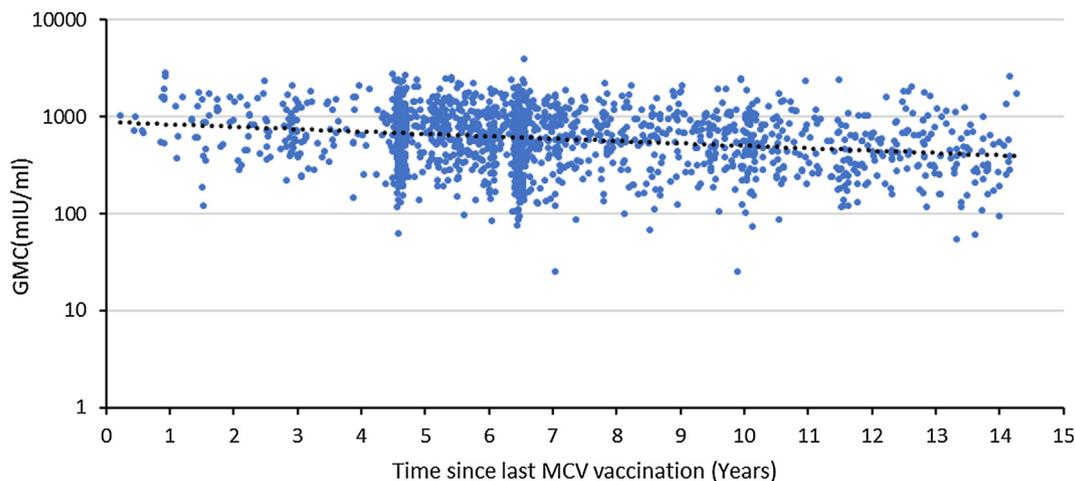

Fig. 2. The geometric mean concentrations of geometric mean concentrations with years since last MCV vaccination.

Waning vaccine-induced immunity may be the main cause of increased serological susceptibility in China [14], with measles outbreaks or epidemics still occurring in communities with high measles vaccine coverage are indirect evidence of this phenomenon [15]. Understanding the factors underlying this susceptibility after vaccination is critical for measles elimination.

Evaluation of measles-specific humoral immunity several years after vaccination and the association of vaccine failure with certain demographic and clinical variables are of considerable interest for measles vaccine-related research. Several factors (including biological sex, heritable genetic factors, and environmental effects) have previously been reported to be associated with waning of measles antibody [16,17]. Research efforts concerning the identification of factors potentially associated with waning of measles vaccine-specific antibody are especially limited in China. Despite public health concerns over the transmission of measles in places with high vaccine coverage in China, the duration and robustness of vaccine immunity has not been clearly characterized. A better understanding of MCV immunity and factors corresponding to its success in children, as well as data to plan appropriate immunization activities to eliminate measles in China, are needed (see Tables 1–4).

The aim of the present study was to determine the seroprevalence of immunoglobulin G (IgG) measles antibodies in 1900 young healthy children and adolescents in Zhejiang. Other objectives were to explore the waning kinetics of measles antibody among children after receipt of an MCV and to define high-risk groups in the population.

2. Methods and materials

2.1. Study subjects

A population-based cross-sectional surveillance study was conducted in healthy populations at two surveillance sites (Wuxing county and Liandu county) in Zhejiang province between May and October 2016, with a total of six schools surveyed in each country. Participants were stratified by age into nine age groups: 6 years old, 7 years old, 8 years old, 9 years old, 10 years old, 11 years old, 12 years old, 13 years old, and 14 years old. When participants were recruiting, they were stratified by age groups, and 150 individuals were required for each age group. Participants were excluded if they had any acute disease or immunodeficiency,

Table 1
Seroprevalence and geometric mean concentrations (GMCs) among subjects with different immunization histories.

Doses of MCV	Total	≥200 mIU/ml		<200 mIU/ml		GMC
		No.	%	No.	%	
Unknown	169	152	89.94	17	10.06	585.44
0 dose	15	12	80.00	3	20.00	541.39
1 dose	275	238	86.55	37	13.45	657.90
2 doses	959	901	93.95	58	6.05	759.21
3 doses and above	482	454	94.19	28	5.81	740.36
Total	1900	1757	92.47	143	7.53	722.58

Table 2
Univariate analysis of categorical variables and their association with measles immunization failure.

Variables	<200 mIU/ml		≥200 mIU/ml		P	OR	95% CI	
	n	%	n	%			Lower	Upper
Sex								
Male (reference)	62	7.22	797	92.78				
Female	61	7.12	796	92.88	0.936	0.985	0.683	1.422
Registration					0.068			
Local county (reference)	91	6.62	1284	93.38				
Other counties in the city	25	9.36	242	90.64	0.111	1.458	0.917	2.317
Other cities in Zhejiang province	4	20.00	16	80.00	0.027	3.527	1.155	10.769
Other provinces	3	5.56	51	94.44	0.758	0.830	0.254	2.711
Low birth weight								
Yes (reference)	2	5.71	33	94.29				
No	121	7.20	1560	92.80	0.737	1.280	0.303	5.397
Starting month of vaccination					0.181			
8 months (reference)	71	8.07	809	91.93				
9–11 months	16	4.95	307	95.05	0.067	0.594	0.340	1.038
12 months	36	7.02	477	92.98	0.478	0.860	0.567	1.304
Father's education					0.583			
Primary school or below (reference)	12	6.63	169	93.37				
Middle school/polytechnic school	100	7.49	1236	92.51	0.680	1.139	0.613	2.118
College or university and above	11	5.53	188	94.47	0.653	0.824	0.354	1.917
Mother's education					0.812			
Primary school or below (reference)	16	7.44	199	92.56				
Middle school/polytechnic school	96	7.28	1222	92.72	0.934	0.977	0.564	1.694
College or university and above	11	6.01	172	93.99	0.572	0.795	0.359	1.760
Measles history								
Yes (reference)	1	4.17	23	95.83				
No	122	7.21	1570	92.79	0.571	1.787	0.239	13.347
Doses					0.000			
1 dose (reference)	37	13.45	238	86.55				
2 doses	58	6.05	901	93.95	0.000	0.414	0.268	0.641
3 doses or more	28	5.81	454	94.19	0.000	0.397	0.237	0.664

Table 3
Univariate analysis of continuous variables and their association with measles immunization failure.

Facts	<200 mIU/ml		≥200 mIU/ml		P	OR	95% CI	
	Mean	Std.	Mean	Std.			Lower	Upper
Age	10.81	2.67	9.77	2.55	0.000	1.203	1.080	1.235
Time since last MCV vaccination (year)	7.71	3.01	6.55	2.94	0.000	1.122	1.063	1.183

Table 4
Multivariate analysis of variables and their association with measles immunization failure.

Variables	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI of Exp(B)	
							Lower	Upper
Age	0.151	0.040	14.360	8	0.000	1.163	1.076	1.257
Doses			9.968	2	0.007			
1 dose (reference)								
2 doses	−0.677	0.227	8.910		0.003	0.508	0.326	0.793
3 doses or more	−0.692	0.274	6.386		0.012	0.501	0.293	0.856

a history of immune disease, or a history of using immunosuppressive agents. Study subjects were also ineligible if they had a received blood products or immunoglobulin during the previous 3 months. Vaccination status was determined by checking the immunization record book for each subject, and disease status was confirmed by laboratory or clinical diagnosis. The ethics committee of Zhejiang Provincial Center for Disease Control and Prevention approved all study materials, including the study protocol and written materials provided to the subjects, parents, and legal guardians. Written informed consent was obtained from parents or guardians of children ≤18 years of age prior to enrollment in the study.

2.2. Laboratory test

A 3–5 ml blood sample was obtained via the median cubital vein, immediately centrifuged, and transferred to a polypropylene tube for storage at −20 °C. Serological tests were performed at the Measles Laboratory of the Department of Expanded Program on Immunization, Zhejiang Provincial Center for Disease Control and Prevention. This laboratory meets the accreditation criteria for WHO National Measles Laboratories. IgG antibodies against measles in the sera were measured by enzyme-linked immunosorbent assay (ELISA) using commercially available kits (Virion/Serion ESR 102M, Germany). Cut-off values and final results were based on the qualitative criteria outlined by the manufacturer, and standard duplicate controls and negative controls were used in every plate. A measles IgG antibody concentration of ≥200 mIU/ml was considered positive, and a concentration of <200 was considered negative [18].

2.3. Statistical analysis

Geometric mean concentrations (GMCs) were calculated using log-transformed titers and were reported as back transformed titers. To obtain an unbiased GMC, values below the measles detection threshold (50 mIU/ml) were assigned half of the threshold value (25 mIU/ml). Immunity failure was defined as a titer of <200 mIU/ml in participants who had received at least one dose of MCV. A fisher's exact test was used to assess the significance of positive seroprevalence proportion between groups with different immunological histories. Kruskal-Wallis H test was used to compare the GMCs among groups. Univariate logistic regression analyses were performed on categorical variables and continuous variables respectively to assess the significance of immunity failure proportion between different groups. A multivariate logistic regression involved all variables was used for backward Wald χ^2 testing, and values with P < 0.05 were retained and P > 0.10 were excluded.

A model of attenuation after measles immunization: A scatter plot was created by using the years since last MCV vaccination as the independent variable and GMC as the dependent variable. After a linear and several curve models were fitted, exponential curve fitting for the largest coefficient of determination was chosen.

All statistical tests were two-sided and considered statistically significant at P < 0.05. Data entry and checks were conducted in EpiData (version 3.1), and the data analysis was performed in Microsoft Office Excel 2017 and SPSS for Windows (version 18.0).

3. Results

3.1. Baseline demographics of subjects

We enrolled 2064 subjects in 2016, of which 1900 (92.05%) had usable serum specimens and full survey, 98(4.75%) refused to take blood samples after completing informed consent and survey, 61 (2.96%) serum samples showed hemolysis or were too little to be detected, and 5 (0.24%) had informed consent and blood samples, but the survey was incomplete.

The overall measles antibody seropositivity was 92.47% (1757/1900). In a comparison of individual age groups, the highest antibody seropositivity (96.62%) was detected in persons aged 9 years, and the lowest seropositivity was recorded in persons aged 14 years (84.33%). The GMCs in these groups were 434.32 mIU/ml and 674.7 mIU/ml, respectively, and the overall GMC of measles was 575.97 mIU/ml (95% CI: 557.83–594.76 IU/ml). GMCs were calculated based on log-transformed titers, and GMCs from some groups were found not to be normally distributed by Kolmogrov-Smirnov normal testing. The results of Kruskal Wallis testing showed that GMCs were statistically different between groups (χ^2 = 129.589, P < 0.001).

One hundred eighty-four subjects had received an unknown or no doses of MCV vaccine, whereas 1716 subjects had received at least one dose of MCV. With an increasing number of vaccine doses, seroprevalence increased. Seroprevalence with unknown immune history, zero, one, two, and three more doses were 89.94%, 80.00%, 86.55%, 93.95%, and 94.19%, respectively. The difference in seropositivity rates among people with different immunological histories was statistically significant (χ^2 = 21.920, P < 0.001).

3.2. Factors associated with measles immunity failure

In participants who received at least one dose of MCV, we defined a GMC < 200 mIU/ml as immune failure and a GMC ≥ 200 mIU/ml as immune success. In our study, the rate of seropositive was 92.83% in the previously vaccinated individuals, and seronegative persons accounted for 7.17%. A case-control study of 123 cases of immune failure and 1593 controls with immune success was conducted. A univariate logistic regression analysis included the following categorical variables: sex, place of residence registration, low birth weight, starting month of vaccination, father's education, mother's education, measles history, number of doses, and vaccine type.

The results showed that residence registration, and number of doses were associated with measles immunity failure (P < 0.05).

Immune failure was more likely to occur with residence registrations in other cities in the province (odds ratio [OR] = 3.527, 95% CI: 1.155–10.769). One dose of MCV vaccination was more likely to lead to immune failure than two doses (OR = 0.414, 95% CI: 0.268–0.641) or 3 doses or more (OR = 0.397, 95% CI: 0.237–0.664). In addition, immune failure was more likely to occur with MCV vaccination beginning at 8 months than at 9–11 months (OR = 0.595, 95% CI: 0.340–1.038).

A univariate logistic regression analysis was also performed on continuous variables, and the results showed that age and time since last MCV vaccination were associated with the occurrence of measles immunization failure. As age increased, measles immunity failure was more likely to occur (OR = 1.203, 95% CI: 1.080–1.235). Similarly, the greater the number of years since the last MCV vaccination, the more likely measles immunity failure was to occur (OR = 1.122, 95% CI: 1.063–1.183).

After univariate logistic regression screening, all variables were included in a multivariate analysis. The analysis indicated that age, and number of doses were factors associated with failure of measles immunity. The older a participant (OR = 1.163), the more likely measles vaccine immunity failed. One dose of MCV was more likely to result in immune failure than two doses (OR = 0.508, 95% CI:0.326–0.793) or three doses and more (OR = 0.501, 95% CI:0.293–0.856).

3.3. Model of attenuation after measles immunization

We collected information on measles vaccination history from each subject and calculated the time interval between the dates of final MCV vaccination and blood sampling. The persistence of measles antibody and attenuation of antibody protection is reflected in the exponential curve fitting. The exponential regression equation was $y = 884.64e^{-0.057x}$ ($R^2 = 0.0521$, $P < 0.001$), which showed that measles antibody GMCs were approximately 884.64 mIU/ml after the last MCV vaccination, and GMCs decreased over time.

4. Discussion

Measles is still a major cause of death among vaccine-preventable viral diseases [19]. We previously showed waning immunity to measles vaccine in young adults and demonstrated the effects of revaccination in secondary school students (14 years old) [20]. In the present study, we further explored humoral immunity after vaccination in children 6–14 years old.

The results of our study showed a total seropositivity of 92.47% in children aged 6–14 years in Zhejiang. Due to the high transmissibility of measles virus, a herd-immunity level of 96–98% vaccination is estimated to be necessary to protect populations from measles outbreaks [21]. Our results suggest that immunity in this highly vaccinated population is insufficient to provide this protection [18]. There was a decline in seropositivity with age from about 95% at 6–9 years to less than 90% at 12–14 years, and the lowest seropositivity in our study was detected in 14 year olds (84.33%). Similarly, GMC declined gradually with age. These results indicated primary or secondary vaccine failure and waning immunity after vaccination, despite the high immunogenicity of measles vaccines.

In this study, to determine the measles immunity profiles of vaccinated children, we divided the whole population into five groups based on differences in the number of doses of MCV. Our results suggest that seroprevalence increased with doses, and significantly higher concentrations of antibodies were detected in people who had two or more doses. The effectiveness of a single dose of MCV was previously reported to be less than 90%, based on measles surveillance data in Guangzhou [22]. Therefore, one dose of MCV may not effectively elicit an immune response, and the apparent immunity gap in Zhejiang may be relieved with additional doses of MCV vaccine. Another finding of this survey was that although the GMC after two doses of MCV was significantly higher than that after one dose, the seroprevalence following two doses of MCV was similar to that after three or more doses of MCV (93.95% vs. 94.19%). Therefore, children and young adults may not obtain additional benefit from more than two doses of MCV.

Our study failed to reveal any significant associations between seroprevalence and demographic variables, which is consistent with results in another recent study [23]. However, associations between biological sex and either humoral or cellular immunity to measles vaccine have been found elsewhere [24]. This inconsistency may be explained partly by the difference in natural measles infection and vaccination in different studies [25,26], suggesting that further research is warranted to confirm or refute differential responses to measles vaccination and demographic and clinical variables in China.

We found higher measles antibody seropositivity in subjects first vaccinated with MCV at 9–11 months than in those first vaccinated at 8 months (91.93% vs. 95.05%). However, our study did not have enough statistical precision to show a statistical difference between the two groups. Early administration of the first MCV dose has been reported to reduce vaccine immunogenicity

or measles antibody persistence [27,28]. Previous studies have shown similar immunogenicity of MMR vaccine administered at the ages of 8 months and 12 months [29], but shorter long-term persistence in those children that were immunized early [30,31]. Therefore, we suggest that administration of the first dose be delayed to 12 months during periods of low measles risk.

This study also demonstrated waning of measles-specific antibody titers over time, with a statistically significant association between antibody levels and time since last immunization ($P < 0.001$). Among 1716 subjects who had at least one dose of MCV, we found 123 seronegative individuals, which is consistent with the measles seropositivity observed in children in this study [31]. In our study, measles GMC was approximately 884.64 mIU/ml after the last MCV vaccination, and, at about 25.27 years after the last MCV vaccination, GMCs are expected to decrease to 200 mIU/ml. and that at about 25.27 years after the last MCV vaccination, these GMCs were expected to decrease to 200 mIU/ml, and that at about 30.32 years after the last MCV vaccination, these GMCs were expected to decrease to 150 mIU/ml.

It is well understood that antibody titers after vaccination are lower (or antibody loss more rapid) than that after natural infection [32]. This is especially relevant with high measles vaccine coverage rates in a population, which usually results in lower disease incidence and fewer natural infections. With a low measles incidence, people who are vaccinated have less of a chance for immune enhancement after natural exposure to measles virus, and waning of vaccine immunity may have contributed to the increase in measles susceptibility observed in adolescents and young adults [33].

An increase in the number of susceptible individuals decreases herd protection, resulting in a gap in protection of the population against measles. Therefore, to close the immunity gap in the absence of natural contact with measles virus, it is necessary to continue to administer vaccines to susceptible adolescents [34]. As we suggested previously, the revaccination program in secondary school students (15 year olds) should continue [19].

5. Conclusions

Our results confirm that measles virus antibody seropositivity decreases over time after vaccination, leading to a gap in protection of the population against measles. Further, levels of measles-specific antibodies in persons who received a greater number of doses were higher than those who received only one dose. Our study indicates that a possible immunity gap may occur 26 years after vaccination with the last dose of MCV during eras of low measles incidence, and we suggest that additional vaccinations may still be needed in these vaccinated adolescents. In addition, we suggest that administration of the first dose of MCV be delayed to 12 months during eras of low measles risk.

Limitations

There are some limitations to this study. The neutralization test (NT) is regarded as the gold standard method for assessing measles immunity, but ELISAs are more convenient and have been used widely, especially in large-scale serological surveys. There is good agreement between NT and ELISA for seropositive specimens, and the measles IgG ELISA is adequate for immunity testing [34,35]. Regardless, the results of our present study provide a valuable estimate of the gap in immunity against measles in Zhejiang province. Another limitation was that we could not obtain antibody levels prior to immunization, nor could we continuously monitor antibody titers in subjects due to feasibility and budget limitations. However, the measles antibody prevalence in different

age groups was determined, and these results suggest waning immunity over time in this population. A cohort study is needed to better define the demographic factors associated with measles vaccine responses.

Acknowledgments

Declaration of Competing Interest

The authors declare no conflicts of interest.

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