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Factors associated with delayed measles vaccination among children in Shenzhen, China: A case-control study

Weiyan Lin[1], Yongzhen Xiong[2], Hao Tang[1], Baoli Chen[1], and Jindong Ni[1,*]

[1]Department of Epidemiology and Biostatistics; Dongguan, China; [2]School Clinic; Guangdong Medical College; Dongguan, China

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Abbreviations: MCV, measles-containing vaccine; EPD, Expanded Programs on Immunization; MMR, measles-mups -rubella; MR, measles-rubella; VIF, variance inflation factor; OR, odds ratios

A delay in the first dose of measles-containing vaccine (MCV1) may contribute to outbreaks of measles, resulting in a high age-specific incidence in infants <1 y of age. To determine the factors associated with delayed MCV1 vaccinations, we used data from the China Information Management System for Immunization Programming. Additionally, the parents/guardians of 430 children whose MCV1 vaccinations were delayed, as well as the parents/guardians of 424 children who received timely vaccinations, were surveyed by telephone. Children were less likely to receive timely MCV1 vaccinations if they belonged to an immigrant group, were male, had poor health status, had a father whose occupation e.g., a manager, had a history of delays in other Expanded Programs on Immunization (EPI) vaccinations, had parents who did not believe vaccinations were important for their children, and experienced shorter travel times to and longer waiting times in EPI clinics. The children of mothers whose occupational status (technician) were more likely to receive timely MCV1 vaccinations. The timeliness of MCV1 vaccinations should be considered as an additional indicator of the quality of vaccination programs.

Introduction

Measles is a highly contagious disease that caused serious illness and many deaths during early childhood in the pre-immunization era. The widespread use of measles vaccines for over 30 y, as well as the implementation of measles control programs, has led to a substantial decline in global measles morbidity and mortality, and many countries have now moved from a control to an elimination phase.[1] Measles elimination is defined as the absence of endemic measles transmission in a defined geographical area for >12 months in the presence of a well-performing surveillance system.

Between 1956 and 1965, prior to the current measles vaccination program in China, the overall annual incidence of measles was 772.4 per 100,000 population.[2] The measles vaccine was introduced in China in 1967 and routine administration, corresponding to the World Health Organization (WHO) Expanded Program on Immunization (EPI), began in 1981–1984. A vaccination regimen in which children receive 2 doses of the measles vaccine, the first at 8 months and the second at 7 y, was introduced in 1985.[3] The age for the second dose [measles-containing vaccine (MCV2)], which includes the measles–mumps–rubella (MMR) vaccine and the measles–rubella (MR) vaccine, was lowered to 4 y in 2000 and to 18–24 months in 2006.[4]

The incidence of measles in China decreased substantially since the 2-dose MCV program was implemented. Since the 1990s, the annual incidence of measles has declined to a low level, about 10 per 100,000 population.[5] Sustaining high coverage of the MCV vaccines was regarded as being necessary to eliminate the disease. However, in recent years, even in communities with high MCV vaccine coverage, outbreaks still occur[6,7] The increase in measles incidence has been accompanied by significant changes in the age distribution of infections. Infants <1 y have become the most vulnerable population.[8,9] In China, the first dose of MCV is administrated at 8 months of age, and standard estimates of vaccination coverage are based on the vaccination status at 12 to 23 months of age. In such a situation, even if the MCV vaccination coverage was reasonably high, there may be many children who are left unprotected for several months because of delayed MCV vaccination. This may explain the high incidence of measles in children aged 8–11 months that was observed in our previous study.[10] The timeliness of vaccine administration has received increasing attention in many countries, especially when the level of vaccination coverage is close to that needed for protective herd immunity.[11-13]

Therefore, more attention should be paid to the timeliness of MCV vaccination, which is very important if measles is to be eliminated. The aims of the current study were to identify

*Correspondence to: Jindong Ni; Email: david3847@sina.com
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possible risk factors related to delays in the first dose of the measles vaccine in Shenzhen, China.

Results

Participation

Surveys were returned by 430 of the 805 (53.4%) parents/guardians of children who MCV1 vaccinations were delayed and 424 of the 825 (51.4%) parents/guardians of children who received timely MCV1 vaccinations, which resulted in an overall response rate of 56.1% (state range: 50.2–64.1%). A total of 854 children, 457 boys (53.5%) and 397 girls (46.5%), in Shenzhen aged 9–24 months were enrolled in the telephone survey. There were 414 (48.5%) local residents and 440 (51.5%) immigrants. Four hundred and eighty (56.2%) of the surveys were completed by mothers, 351 (41.1%) by fathers, and 23 (2.7%) by other caregivers, including grandparents, babysitters and legal guardians. There was no significant difference in the responders between the timely measles vaccination group and the delayed vaccination group ($P > 0.05$).

Univariate association analyses of possible factors for delayed measles vaccination

The risk of delayed MCV1 vaccination was higher among boys than girls ($P = 0.029$). Delayed MCV1 vaccination was more likely to occur in children with poor health status than in healthy children ($P = 0.009$). Households with a higher number of children were associated with delayed MCV1 vaccination ($\chi^2_{linear} = 7.51$, $P = 0.006$).

There were 809 (94.7%) of the fathers and 785 (91.9%) of the mothers had secondary school or higher education. The education levels of the fathers and mothers were not significantly associated with the delayed MCV1 vaccination ($P > 0.05$). There were no significant differences in the ages of the parents between the timely MCV1 vaccination group and the delayed vaccination group (fathers: 30.86 vs. 31.04 y, respectively, $Z = 0.223$, $P = 0.824$; mothers: 28.79 vs. 28.89 y, respectively, $Z = 0.839$, $P = 0.402$).

In the delayed MCV1 vaccination group, 203 (47.2%) respondents reported that their children had a history of delays in other EPI vaccinations, which was significantly associated with delayed MCV1 vaccination ($P < 0.001$). Individuals who spent less time in traffic were more likely to be in the delayed MCV1 vaccination group ($\chi^2_{linear} = 32.05$, $P < 0.001$).

Among the 480 mothers, 358 (74.6%) indicated that EPI vaccinations were "Important" for their children, which was similar to that of the other respondents (79.9%) ($\chi^2 = 3.41$, $P = 0.065$). Three hundred and six (63.8%) mothers and 248 (66.3%) of the other respondents indicated that timely vaccinations, according to the recommended schedules, were a "necessity" for their children; there was not a significant difference between the mothers and the other respondents ($\chi^2 = 0.61$, $P = 0.437$).Overall, 76.9% of the respondents indicated that EPI vaccinations were "important" for their children, and 64.9% of the respondents indicated that timely vaccinations according to the recommended schedules were a "necessity" for their children. Both the respondents' beliefs concerning the "important" health effects of vaccination and the "necessity" for timely vaccination were associated with timely MCV1 vaccination ($P < 0.001$).

Six hundred and twenty-nine (73.7%) of the respondents reported that it took <10 min to travel to the EPI clinic, which was significantly related to timely MCV1 vaccinations ($P < 0.001$). Five hundred and thirteen (60.1%) of the respondents reported that the waiting time in the EPI clinic was <20 min, which was inversely related to timely MCV1 vaccinations ($\chi^2_{linear} = 41.63$, $P < 0.001$).

Three hundred and eleven (64.8%) mothers and 240 (64.2%) of the other respondents were satisfied with the immunization practices. There was no significant difference in this answer between the mothers and the other respondents ($\chi^2 = 0.35$, $P = 0.851$). Two hundred and seventy-nine (58.1%) mothers were satisfied with the immunization practices and behaviors of the healthcare providers. The satisfactory rate was 62.8% for the other respondents, which was not significantly different from that of the mothers respond ($\chi^2 = 1.95$, $P = 0.163$). In all, 551 (64.5%) of the respondents were satisfied with the immunization practices, and 514 (60.2%) of the respondents were satisfied with the behaviors of the healthcare providers. Parents who were satisfied with the immunization practices and behaviors of the providers were associated with delays in MCV1 vaccinations ($P < 0.001$) (**Table 2**).

Multivariate association analysis of possible factors for delayed measles vaccination

Multiple logistic regression models were used to control potential confounding variables. The factors associated with delayed MCV1 vaccination, as compared with the reference group of timely vaccinated children, are presented in **Table 2**. There were 13 variables that met the criteria for entry in the initial logistic regression models. In the final logistic regression model, factors remaining as independent predictors of delayed MCV1 vaccination were boys, immigrants, children who had a history of delays in other EPI vaccination, children with poor health status, perception of a long travel time to the EPI clinic, parents who did not believe that EPI vaccinations were "Important" for their children, and perception of a long waiting time in the EPI clinic. Compared with unemployed and other occupations, children whose mother's occupation was a "technician" was at less risk of delayed MCV1 vaccinations (OR = 0.29, 95%CI: 0.13, 0.63). Additionally, children whose father's occupation was a "manager" was more likely to have delayed MCV1 vaccinations (OR = 4.29, 95%CI: 2.15, 8.58). VIF was used to check for multi-colinearity. None of the VIF values was up to 5, which meant there was no colinearity in the model (**Tables 1, 2**).

Discussion

This study examined the factors influencing timely measles vaccinations, defined as those infants who received the MCV1 vaccine within 1 month of the first day of the eighth month of

Table 1. Demographic characteristics of the children with delayed MCV1 vaccinations

Classification	Timely vaccination	Delayed vaccination	Unadjusted OR (95%CI)	Adjusted OR (95%CI)	VIF
Gender					0.197
Boy	211	246	1.17 (1.02, 1.36)	1.46 (1.05, 2.04)	
Girl*	213	184	1	1	
Residential status					0.318
Local residents*	285	129	1	1	
Immigrants	139	301	4.78 (3.58, 6.39)	3.70 (2.65, 5.16)	
Health status of child					
Good*	346	319	1	1	0.536
Poor	78	111	1.54 (1.11, 2.14)	1.73 (1.15, 2.59)	
Number of children in household					
1 child*	283	250	1		
2 children	124	152	1.39 (1.04, 1.86)		
≥3 children	17	28	1.86(1.00, 3.49)		
Occupation of mother					0.681
Worker	25	23	0.77 (0.43,1.40)	0.79 (0.35, 1.75)	
Self-employed staff	82	56	0.57 (0.39, 0.84)	0.66 (0.38, 1.14)	
Manager	16	38	2.00 (1.08, 3.68)	1.34 (0.62, 2.91)	
Technician	35	14	0.34 (0.18, 0.64)	0.29 (0.13, 0.63)	
Service staff	55	48	0.73 (0.48, 1.13)	0.69 (0.39, 1.22)	
Other*	211	251	1	1	
Occupation of father					0.686
Worker	41	58	2.43 (1.42, 4.17)	1.44 (0.71, 2.95)	
Self-employed staff	146	100	1.18 (0.76, 1.83)	1.17 (0.65, 2.10)	
Manager	30	73	4.18 (2.39, 7.31)	4.29 (2.15, 8.58)	
Technician	68	64	1.62 (0.98, 2.66)	1.67 (0.88, 3.17)	
Service staff	60	89	2.55 (1.56, 4.16)	1.82 (0.99, 3.36)	
Other*	79	46	1	1	

*Reference category.

Table 2. Factors of children's preventive vaccination related to delays in MCV1 vaccination

Classification	Timely vaccination	Delayed vaccination	Unadjusted OR (95%CI)	Adjusted OR (95%CI)	VIF
History of delay in other EPI vaccinations					0.276
Yes	140	203	1.27 (1.14, 1.42)	1.64 (1.16, 2.30)	
No*	284	227	1	1	
Awareness of importance of immunization					<0.001
Yes*	373	284	1	1	
No	51	146	3.76 (2.64, 5.36)	2.89 (1.76, 4.76)	
Awareness of necessity of timely vaccinations					
Yes	311	243	2.12 (1.59, 2.82)		
No*	113	187	1		
Travel time (min)					0.586
0～	119	195	2.70 (1.90, 3.84)	3.38 (2.18, 5.24)	
5～	165	150	1.50 (1.06, 2.13)	1.76 (1.14, 2.69)	
10～*	140	85	1	1	
Waiting time in EPI clinic (min)					0.161
0～*	190	120	1	1	
10～	105	92	1.43 (1.00, 2.05)	1.54 (0.99, 2.37)	
20～	123	218	2.90 (2.11, 3.97)	2.60 (1.77, 3.80)	
Satisfaction with immunization practice of the providers					
Yes*	240	311	1		
No	184	119	0.50 (0.38, 0.66)		
Satisfaction with behavior of the providers					
Yes*	225	289	1		
No	199	141	0.55 (0.42, 0.73)		

*Reference category.

life, using an EPI vaccination coverage survey in Shenzhen, China. The results showed that the rate of timely MCV1 vaccinations was 86.5 percent in local children and 80.0 percent in immigrant children.[14] Based on the data from China Information Management System for Immunization Programming, there were 41.0% of the children born in 2012 received delayed MCV1 vaccinations in Shenzhen, China. Delayed MCV1 vaccination enlarges the gap between the loss of protection from maternal antibodies and full protection acquired from vaccine-induced immunity.[15] Infants that received delayed MCV1 vaccinations are more susceptibility to measles. Delay in vaccination was recognized as the primary cause of a large measles epidemic in the USA in 1989–1991.[11] In our previous study, we found that the measles incidence increased sharply once the infants reached 5 months of age. Although the incidence decreased after the infants reached 8 months of age, it was still maintained at a relatively high level. In China, the first dose of MCV is administrated at 8 months of age. Thus, the decrease in the measles incidence after 8 months may be due to the measles vaccine. Delayed vaccination may contribute to the high incidence of measles in infants 8–11 months of age.[10] Therefore, an investigation of the reasons for untimely vaccination is of critical importance to eliminate measles.

Our study identified several independent determinants of delays in MCV1 vaccinations among 9–23-month-old children in Shenzhen, China. Girls were more likely to receive timely MCV1 vaccinations than boys. Other studies have shown that gender of children did not significantly influence delay vaccination.[16,17] Parental occupations were significantly associated with delayed MCV1 vaccination; we assume that the free time of parents in different occupations is variable, which results in some parents having less time to spare for their child's vaccination. Mother's education has shown the positive association with timely vaccination in studies in Uganda and in the USA.[18,19] However, similar to the study in Belgium,[16] mother's level of education was not an independent predictor for timely vaccination in this study.

The risk of delayed MCV1 vaccination for migrant children was more than 3 times higher than that for local children. The migration of children is often associated with lower vaccination coverage in China, mainly as a result of migrants' high mobility, low socioeconomic status, lower level of knowledge and awareness about vaccination, and insufficient access to vaccination services in receiving areas.[20] These reasons may partly explain the higher risk of delayed MCV1 vaccinations of migrant children. Children with poor health were associated with delayed MCV1 vaccination. This might be partially caused by the child being sick during the recommended immunization period.[21] The number of children in households did not affect the risk of delayed vaccination in our study, which is different from studies in 4 developing countries, in 31 low and middle income countries.[12,22] This difference may be explained by the fact that family planning policy was implemented in China and most families (more than 60%) in our study have 1 child.

Most of the previous studies on timely vaccinations focused on societal factors.[17,20-23] In our study, we paid more attention to the factors related to children's preventive vaccination and identified some factors that were significantly associated with delayed MCV1 vaccination, which were rarely reported before. Additionally, these factors may be more practical to address in the future. The results show that children who had a history of delays in other EPI vaccinations were at significantly increased odds of experiencing MCV1 vaccination delays. Parental awareness of the importance of vaccination had a stronger effect on their children's timely vaccination uptake. Additionally, longer waiting time in EPI clinics were significantly more likely to result in delayed MCV1 vaccination. This suggests that some interventions should be implemented by the EPI clinics to perform follow-ups of these children to improve parental knowledge about the necessity of timely vaccination, to improve the service quality of the EPI clinics and to limit the waiting time, and more attention should be paid to children with a history of delays in EPI vaccinations.

To our surprise, travel time to EPI clinics was inversely related to delayed MCV1 vaccinations. A possible explanation was that the children received EPI vaccinations in local community health centers in Shenzhen, and most of them (73.7%) can reach the EPI clinics in a relatively short time (<10 min). Thus, the travel time was not sufficiently long to impact the children's timely vaccinations. A previous study reported that the distance from the nearest health center was not correlated with the delayed vaccinations.[17] Therefore, there may be some other reason why the travel time had an effect on the delay in MCV1 vaccinations.

Some limitations of this study also needed to be noted. First, the study population was sampled from the China Information Management System for Immunization Programming. Children who had not registered in this system were excluded from the study. This may potentially bias the sample and, thus, impact the results. Second, the health status of the children was a subjective judgment by the parents or guardians. We have not defined "good health status" and "poor health status" in this study. This may negate our result regarding the effect of poor health status on MCV1 vaccinations. However, because postponing the vaccination was a voluntary decision made by the caregiver, not the doctor, the subjective judgment of the parents or guardians may directly impact vaccination timeliness, especially if the child had minor health problems during the recommended immunization period. Third, in previous studies, the economic status of the family was regarded as an effect factor related to EPI vaccination coverage and age-appropriate immunization status.[23,24] However, most of the children's parents or guardians refused to answer the question about the income of the family in our pilot survey, and the question was not included in the final questionnaire.

In conclusion, to eliminate measles, it is necessary to maintain timely MCV1 vaccinations, even though the routine vaccination coverage is high. This study showed the effect of some factors on delayed MCV1 vaccinations. Additionally, the timeliness of MCV1 vaccinations could be further improved further by strengthening EPI clinics services, improving health education to increase the level of knowledge about EPI vaccination, and targeting vaccination to children who are immigrants or who have a

history of delays in EPI vaccinations. The risk factors contributing to a delay in MCV1 vaccination, as well as possible measures to improve the timeliness of vaccination, that were identified in this study may also apply to similar settings in China. The timeliness of vaccination should be considered as an additional indicator of the quality of vaccination programs whenever possible.

Methods

Data collection study population and sample

The retrospective, cross-sectional telephone survey was conducted between May 2013 and October 2013 in Shenzhen, which is located in southern China and has a population greater than 10 million. Information regarding the MCV vaccination of the infants was collected from the China Information Management System for Immunization Programming. In the 2012 birth cohort, there were 217172 eligible children for the MCV1 vaccination and the coverage rate was 99.5%. The schedule time of measles vaccination in China is at 8 months. The timely measles vaccination was defined as the MCV1 vaccine (including measles or measles-rubella combined live attenuated vaccine) conducted within one month of the first day of the eighth month of life.[21,23] There were 127045 (58.5%) eligible children received the MCV1 vaccine timely; 89040 (41.0%) children received delayed MCV1 vaccinations.

The target populations were infants aged 9 months to 2 y and was divided into 2 groups: the timely measles vaccination group and the delayed measles vaccination group. The formula $n_1 = n_2 \frac{1}{2} \left(\frac{z_\alpha + z_\beta}{sin^{-1}\sqrt{p_1} - sin^{-1}\sqrt{p_2}} \right)^2$ was used for the sample size calculation, with the following assumptions: a 2-sided test, with a precision of 0.05, 80% power, would detect a 10% difference in the proportions of the possible risk factors between the timely vaccination group and the delayed vaccination group. Using this formula, we obtained $n_1 = n_2 = 392$, therefore, recruitment continued until at least 400 participants were selected for each group.

Participants in the study were randomly selected from the lists of names of the infants in the 2 groups. The parents or legal guardians were interviewed by telephone by well-trained interviewers. To reduce refusals, the sampled child was called 3 times (if busy or if no response) before being considered invalid, and, thus, excluded from the study.

Recruitment continued until at least 400 participants in each group were selected. A questionnaire was used for the data collection. Data on children's birth date, gender, type of residence, and date of previous vaccinations were also extracted from the China Information Management System for Immunization Programming. Possible risk factors related to the delay in vaccination that were listed in the questionnaire included information pertaining to the demographic characteristics of the parents, including the education level of the father and mother, occupation of the father and mother, the number of children in the household, perceived perception of the importance of EPI vaccination for the child (The responses were based on multiple choices: "important," "moderately important or hard to rate the importance," "not important") and the necessity of timely MCV vaccination for the child (The responses were based on multiple choices: "necessary," "moderately necessary or hard to rate the necessary," "not necessary"), health status of the child (The health status of the children was a subjective judgment by the parents or guardians based on: "good health status" or "poor health status"), any history of delays in other EPI vaccination of the child(delayed vaccination was defined as vaccination one month after the age specified in the national immunization schedules),[21,23] the travel time to the EPI clinic, the waiting time in the EPI clinic, and the immunization practices and behaviors of the providers.

Analysis

Possible determinants of delays in MCV1 vaccination uptake were investigated using univariate and multivariate logistic regression. The trend in delayed MCV1 vaccination and travel time and waiting time were compared using the Mantel–Haenszel method (linear-by-linear association). Pearson's χ^2 test was used to compare the qualitative data from the mothers with that of the other respondents. Variance inflation factor (VIF) was used to check for multi-colinearity. A two-sided p value <0.05 was considered to be statistically significant. Odds ratios (ORs), adjusted ORs and 95% confidence intervals (95% CI) are presented for the main findings. Only statistically significant variables ($P < 0.05$) are listed.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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