Waning of maternal antibody against measles virus in Shufu, China

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ABSTRACT

Background: As measles vaccination coverage has increased, measles infection has shifted to the population of infants. We conducted a follow-up seroepidemiological study among mothers and their infants to evaluate measles seroprevalence and the persistence of maternal measles antibody in Shufu, Kashgar from 2018 to 2020.

Methods: Maternal venous blood and cord blood was obtained among mothers and their infants at 0, 3, 5, 8, 9, and 12 months of age. An enzyme-linked immunosorbent assay was used for quantitative measurement of measles antibodies. We analyzed the correlation between maternal and neonatal measles antibodies, and antibodies persistence after infants were born.

Results: The overall neonatal maternal ratio was 2.38 (95%CI: 2.05–2.71). The measles antibodies for mothers and newborns were 438.93 IU/mL (95%CI: 409.47–470.51 IU/mL) and 440.10 IU/mL (95%CI: 410.82–471.48 IU/mL), respectively. Neonatal measles antibodies were dropping after birth and then beginning to increase starting at 8 months of age.

Conclusions: Infant measles antibody levels progressively declined after birth regardless of maternal measles antibody levels. Efforts should be carried out to eliminate measles.

Introduction

Measles is a highly contagious viral disease caused by the measles virus and occurs seasonally in endemic areas, transmitted by airborne respiratory droplets from infected cases. The basic reproduction rate ($R_0$) of measles has been calculated to be 12–18, indicating 12 to 18 people on average are infected by an initial spreader in a fully susceptible population, which is one of the highest for any human pathogen. 1 Nine out of 10 susceptible people (unvaccinated/have not had measles) who are exposed to measles will get sick. 2 High rates of population immunity are required to interrupt measles virus transmission because of its high infectivity. 3 The measles herd protection threshold was estimated at 85%-94% varies in different settings. 4, 5

Since the development and widespread application of measles vaccines, measles transmission has been effectively controlled. 6 Great progress has made in measles elimination due to global measles elimination efforts. 7 However, eradication of measles still face tough challenges. Measles incidence increased in all World Health Organization regions, and no WHO region has achieved and maintained measles elimination during 2017–2019. 8 Measles reemerged in several countries, even in those effective vaccination programs had been installed for decades. 9 The Measles and rubella initiative indicated that many measles vaccination campaigns scheduled for 2020 have been interrupted or postponed due to the COVID-19 pandemic. As of June 2020, there were over 178 million people at risk of missing out on measles vaccine. 2 The vaccine hesitancy-delay or refusal of measles vaccination globally is one of the reasons. 7 A scholar calculated that a 5% decline in measles, mumps and rubella vaccine (MMR) vaccine coverage in the United States would result in an estimated threefold increase in measles cases for children aged 2–11 years nationally every year, with an additional $2.1 million in public sector costs. 8 Specific subgroups of the population like healthcare workers also play a critical role in nosocomial transmission. 9, 10

In China, two doses of monovalent measles vaccines for children at 8 months and 7 years old, respectively, in planned immunization was carried nationally since 1978, one dose of measles-rubella vaccine for children at 8 months and one dose of MMR for children at 18 months in Expend Programme Immunization was carried nationally since 2007. 11 Two doses of MMR for children (for 8 and 18 months respectively) started from 1 June 2020. Except two doses of MMR in Expend Programme Immunization and post-exposure prophylaxis against measles in susceptible population, no other additional boosters for measles and rubella carried out in children or adults nationwide in China. 11 With supplementary immunization activity and high coverage rates, measles cases in China have fallen since 2014. The incidence of measles in China reached a historic low of .21 cases per million individuals in 2019 (2974 cases). 12

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In Chinese remote areas, due to the shortage of health service personnel, unadvanced facilities, despite declining measles incidence at the national level, measles surveillance in Kashgar, Xinjiang has shown some alarming trends. Kashgar reported the most measles cases in Xinjiang, with measles epidemics occurring once every 3–5 years, and ranked fourth in measles incidence in Xinjiang. 13,14 As vaccination coverage has increased, the population affected by measles infection has shifted to infants and young adults, 12 with cases under 8 months old accounting for 21.81% of infections. 13

To evaluate measles seroprevalence among infants and the persistence of maternal anti-measles antibody, we conducted a seroepidemiological study among mothers and their infants in Shufu, Kashgar from 2018 to 2020.

Methods

Study participants and inclusion criteria

Mothers who delivered babies in Shufu county hospital from January to December 2018 and voluntarily participated in a measles seroprevalence survey were enrolled in our study. The study included women of gestational age ≥35 weeks at Shufu county hospital, Kashgar. All participants were healthy and provided informed consent. Individuals with a family history of immune deficiency, acute infection in the mother, immune deficiency in the newborn, congenital abnormalities, genetic disease, hematological disorders, birth asphyxia, or congenital heart disease of the newborn were excluded from the study. The study was performed in accordance with the principles laid out in the Declaration of Helsinki and was approved by the Ethics Committee of Guangzhou Center for Disease Control and Prevention (identification code: GZCDC-ER[A] 2,016,007).

Maternal venous blood was sampled 2 days prior to delivery and cord blood was obtained from the placenta directly after delivery. Subject demographic and health information, including maternal age, education, history of measles, history of vaccination before pregnancy, previous medical history (hypertension, diabetes, anemia), gestational week, infant gender, and birth weight was collected using a questionnaire administered by nurses. Follow-up appointments and blood collection were performed when the infant reached 3, 5, 8, 9, and 12 months of age.

Blood samples were centrifuged at 3500×g for 15 minutes and sera were transferred into 2 mL cryotubes under sterile conditions. Samples were stored at −20°C for a maximum of 2 weeks. The serum samples were transferred on dry ice to KingMed Diagnostics (Guangzhou, China), a third-party testing agency. Serum samples were stored at −80°C at KingMed Diagnostics. Before testing, sera were let stand for 1 hour and processed when they reached room temperature. An enzyme-linked immunosorbent assay (ELISA; Anti-Measles IgG, Virion/Serion, Würzburg, Germany) was used for quantitative measurement of anti-measles antibodies. The assay was performed according to the manufacturer’s instructions and optical density was measured at a wavelength of 450 nm using a spectrophotometer. Measles antibody levels were recorded as geometric mean concentrations (GMCs). Positive was defined as ≥200 mIU/mL, negative was defined as <200 mIU/mL. Positive GMCs were classified as low (≥200 and < 800 mIU/mL), moderate (≥800 and <3200 mIU/mL) or high (≥3200 mIU/mL). 15,16 The neonatal maternal ratio (NMR), calculated as log (neonatal level)/log (maternal level), 17 was used to evaluate the efficiency of transplacental transfer of maternal anti-measles antibody. The rate of decline in antibody titer in 5 month of age was defined as (GMC of newborn—GMC at 5 month)/5, the rate of increase of antibody titer in 9 month of age was defined as (GMC at 9 month—GMC of newborn)/9. Shufu is a relatively isolated and rural county. It is a part of Kashgar, located southwest of Xingjiang to the east of the Pamir mountains and bordering on Pakistan, Afghanistan, Tajikistan, Kyrgyzstan, Uzbekistan, Kazakhstan and Turkmenistan. The county has a population of approximately 260,000 people. The urban population is only 30,000 individuals, and 97.7% of the population is Uyghur.

Statistical analysis

Statistical analysis was performed using IBM Statistics SPSS version 23 (IBM, Armonk, NY). Values of p < .05 were considered statistically significant. As antibody levels were not normally distributed, antibody data were log transformed and the GMCs and 95% confidence intervals (CIs) of groups were compared.

Differences between groups were assessed using the two-sample independent t test or the chi-square test. Differences among multiple groups were assessed using one-way analysis of variance or non-parametric test. Correlation between the rate of decline/increase in infantile and maternal measles antibody levels were assessed using correlation analysis.

Results

Demographic characteristics

A total of 1015 pairs of mother and infants were enrolled in this study. The mean (± standard deviation) gestational period at enrollment was 39.14 ± 1.49 weeks (range 30–44 weeks), the mean delivery age was 26.53 ± 4.40 years (range 19–45 years), and the mean birth weight was 3.36 ± .47 kg (range 1.50–4.90 kg). Primipara accounted for 32.41% (329/1015) of mothers. Most mothers had completed lower secondary education (75.7%, 764/1009), had four or more family members (78.36%, 793/1012), reported their occupation as homemaker (62.1%, 369/594), and had monthly household incomes of < 2000 yuan per person (70%, 727/1012). Only 15% of mothers (162/1015) had previous medical histories, and 67% (668/997) of infants were second-born children. The sex ratio of infants (M:F) was 94:1. The mean (± standard deviation) APGAR scores of newborns at 1 and 5 minutes were 7.95 ± .74 and 9.02 ± .53, respectively.

NMR

The overall NMR was 2.38 (95%CI: 2.05–2.71). NMR is differed from groups of maternal measles antibody significantly (p < .001), and decreases with increase of maternal antibody level (Table 1).
Measles antibody for puerpera and newborns

The GMCs of measles antibodies for puerpera and newborns were 438.93 IU/mL (95% CI: 409.47–470.51 IU/mL) and 440.10 IU/mL (95% CI: 410.79–471.51 IU/mL), respectively. Overall, 72.7% (738/1015) of puerpera and 73.5% (746/1015) of newborns were positive for measles antibodies. Both the GMCs and positive rate of measles antibodies in newborns were different among groups with different maternal antibody levels (F = 64.91, p < .001).

Correlation between the rate of decline/increase in infantile and maternal measles antibody

The rate of decline in 5 month of age was positively associated with maternal antibodies (r = .386, p < .001), rate of increase in 9 month of age were negatively associated with maternal antibodies (r = .256, p < .001).

Measles antibody persistence

Both GMCs and the positive rate of neonatal measles antibodies were dropping after birth regardless of maternal antibody levels, and then beginning to increase starting at 8 months of age for receiving measles-containing vaccine (MCV). Both the GMCs and the positive rate of measles antibodies for babies at 3,5 months were significantly different from different groups of maternal antibody levels (p all >.001).

Discussion

The major findings of this study were that NMR decreased with increase of maternal antibody levels. Infantile measles antibody levels were dropping after birth regardless of maternal antibody levels. Numerous publications have documented the decreasing presence of neonatal antibody after birth.\(^\text{11,17–20}\) Maternal antibody levels are an established predictor of neonatal antibody levels. However, comparison of antibody levels between studies is difficult owing to the different laboratory tests and standards used. A similar study of maternal antibody was conducted in Guangzhou,\(^\text{17}\) NMR for measles was 1.042, which was much lower than our study’s, indicating that those with lower maternal antibody levels would have higher NMRs as our study’s. Another similar study conducted in Tianjin, China showed a higher measles antibody for puerpera, and a lower maternal antibody in infants than our study.\(^\text{11}\) This result can be explained by the “regression to the mean”,\(^\text{21}\) a statistical phenomenon first proposed by Sir Francis Galton. When the maternal measles antibody concentration was lower than the mean of the population, the neonatal measles antibody concentration was likely to be higher than the mother’s.

A systematic literature review revealed that slower waning of maternal antibody in infants occurred in high disease burden settings than in sustained elimination settings and low burden settings.\(^\text{22}\) Similarly to sustain elimination settings like Ontario, Canada\(^\text{18}\) and Belgium,\(^\text{19}\) a significant loss of measles protection by 3 months of age was observed in the non-elimination settings of Zhejiang,\(^\text{23}\) WuXi,\(^\text{19}\) Tianjin,\(^\text{11}\) Shufu (our study), China. Over decades, China has made great efforts to eliminate measles.\(^\text{24}\) In today’s accelerated measles elimination stage, morbidity continues to decline\(^\text{24}\) and the age distribution of measles has shifted to non-target populations for measles vaccination (children <8 months of age or adults).\(^\text{24,25}\) The waning of maternal antibody in infants will be one of the biggest obstacles to eliminating measles worldwide.

Some research suggests that women of childbearing age should receive measles vaccines before pregnancy to boost antibody levels and improve passive immunization of neonates with maternal measles-specific antibody.\(^\text{15,20,23}\) Infants would be passively immunized by maternal antibody. Antibody levels in infants would waned rapidly as our study documented, irrespective of the maternal antibody level. Higher maternal antibody levels can hamper the neonatal immune response to vaccination.\(^\text{26}\) Our study revealed that higher maternal antibody levels was associated with a faster decline antibody levels in 5 months, and a slower increase in 9 months. However, maternal antibody is still helpful to interrupt early infection for infants. China has no plans for widespread adult
vaccination as part of the national immunization program because of the big cardinal number of population currently. When the costs of adult vaccinations are paid by vaccinees, only a tiny minority may receive the measles vaccine, resulting in low vaccination uptake among women of childbearing age. Thus, the strategy of immunizing women of childbearing age to boost infant’s antibody levels in China is unlikely to succeed. 28

The infantile antibody levels raised since 8 months of age is largely because the measles vaccination. In China, MCV starts at 8 months of age. In some cases, there may have been a delay in receiving the vaccine at 8 months of age for some reason, and would vaccinate at the following feasible month. Therefore, both antibody level and positive rate at 8 or 9 months of age are significantly lower than that at 12 months of age. Sustained high vaccination coverage with two doses of the vaccine is the key preventive measure to successfully eliminating measles. 3 Two doses of MCV in National Immunization Program are free of charge for eligible children and mandatory for enrollment in kindergartens and schools in China, which made China has a highest MCV first–dose and second-dose immunization coverage world widely, 29,30 and a steadily falling in measles cases even during the COVID-19 pandemic. 31 Compare to those Scandinavian countries, opted for recommended vaccination programs, some countries, like France, Italy, and Ukraine adopted mandatory vaccination policies because of vaccine hesitancy. The evidence conclude that the introduction of children routine vaccination mandates increases vaccine coverage and reduces the incidence of vaccine-preventable diseases. 32–34

In pursuing measles elimination era, earlier administration of the initial measles vaccine between 4 and 7 months may be cost-effective and could significantly reduce the burden of measles-related morbidity and mortality in infants in China. 28 Our study had several strengths and limitations. The subjects in our study were followed up from antepartum until 12 months postpartum. We acquired data on measles antibody levels in 1015 pairs of mothers and infants, and documented the progressive decline in infant measles antibody levels. However, we were unable to further analyze the reasons for increasing measles antibody levels in children after 8 months of age and the impact of maternal antibody levels on neonatal immunological responses to vaccination. No measles epidemiological history or the details of measles contain vaccination date and blood collecting date were collected after the infants were born. We measured measles antibody levels using ELISA. Because ELISA sensitivity decreases as antibody concentration decreases, 35 our study may have overestimated susceptibility.

In conclusion, infant measles antibody levels progressively declined after birth regardless of maternal measles antibody levels. Boosting measles antibody levels in women of childbearing age through immunization may not be feasible and cost-effective in China. 11,28 In the approaching measles elimination stage, earlier measles administration in infant may be valid; ensuring sufficient vaccine supply, maintaining high coverage rates of two-dose measles vaccination, continuing to improve laboratory-supported surveillance and outbreak responses, strengthening school vaccination record checking, catch-up vaccination campaign and instituting stricter infection control measures in hospitals will be critically important to measles elimination. 11,25

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Author contributions

Qing He: Writing Original draft, Data analysis; Shujun Fan: data interpretation, Data curation; Zhenxiang Xue: Investigation; Jun Yuan: Resources, Supervision; Yuzhong Wang: Investigation; Zhicong Yang: Resources, Supervision; Ziyang Zhou: Reviewing and Editing; Zhubin Zhang: Conceptualization, Methodology, study design. All authors have read and agreed to the published version of the manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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