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# Risk factors for measles virus infection and susceptibility in persons aged 15 years and older in China: A multi-site case-control study, 2012–2013

**Chao Ma**[a], **Lixin Hao**[a,*], **Lance Rodewald**[b], **Qian An**[c], **Kathleen A. Wannemuehler**[c], **Qiru Su**[a], **Zhijie An**[a], **Linda Quick**[c], **Yuanbao Liu**[d], **Rui Yan**[e], **Xiaodong Liu**[f], **Yanyang Zhang**[g], **Wen Yu**[h], **Xiaoshu Zhang**[i], **Huaqing Wang**[a], **Lisa Cairns**[c], **Huiming Luo**[a], **Christopher J. Gregory**[c]

[a]National Immunization Program, Chinese Center for Disease Control and Prevention, Beijing, China

[b]Expanded Program on Immunization, World Health Organization Office in China, Beijing, China

[c]Global Immunization Division, Centers for Disease Control and Prevention, United States

[d]Division of Expanded Program on Immunization, Jiangsu Provincial CDC, Nanjing, China

[e]Division of Expanded Program on Immunization, Zhejiang Provincial CDC, Hangzhou, China

[f]Division of Expanded Program on Immunization, Shandong Provincial CDC, Jinan, China

[g]Division of Expanded Program on Immunization, Henan Provincial CDC, Zhengzhou, China

[h]Division of Expanded Program on Immunization, Yunnan Provincial CDC, Kunming, China

[i]Division of Expanded Program on Immunization, Gansu Provincial CDC, Lanzhou, China

## Abstract

**Introduction:** Endemic measles persists in China, despite >95% reported coverage of two measles-containing vaccine doses and nationwide campaign that vaccinated >100 million children in 2010. An increasing proportion of infections now occur among adults and there is concern that

* Corresponding author. Haolx@chinacdc.cn (L. Hao).

Authors' contributions

Chao Ma,. Christopher J Gregory, Lixin Hao, and Huiming Luo designed the study and directed its implementation, including quality assurance and control. Chao Ma, Qian An, Kathleen A. Wannemuehler, Qiru Su, and Zhijie An designed and implemented the study's analytic strategy. Huaqing Wang and Linda Quick helped supervise the field activities. Yuanbao Liu, Rui Yan, Xiaodong Liu, Yanyang Zhang,Yi Kong, Xiaoshu Zhang led their field investigation in the six study sites. Lisa Cairns and. Lance Rodewald helped conduct the literature review and prepare the Methods and the Discussion sections of the text.

Competing interests

The authors declare that they have no competing interests.

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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.

Disclaimers

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. Use of trade names and commercial sources are for identification purposes only and does not imply endorsement by the Public Health Service or the US Department of Health and Human Services.

persistent susceptibility in adults is an obstacle to measles elimination in China. We performed a case-control study in six Chinese provinces between January 2012 to June 2013 to identify risk factors for measles virus infection and susceptibility among adults.

**Methods:** Persons ≥15 years old with laboratory-confirmed measles were age and neighborhood matched with three controls. Controls had blood specimens collected to determine their measles IgG serostatus. We interviewed case-patients and controls about potential risk factors for measles virus infection and susceptibility. Unadjusted and adjusted matched odds ratios and 95% confidence intervals (CIs) were calculated via conditional logistic regression. We calculated attributable fractions for infection for risk factors that could be interpreted as causal.

**Results:** 899 cases and 2498 controls were enrolled. Among controls, 165 (6.6%) were seronegative for measles IgG indicating persistent susceptibility to infection. In multivariable analysis, hospital visit and travel outside the prefecture in the prior 1–3 weeks were significant risk factors for measles virus infection. Occupation and reluctance to accept measles vaccination were significant risk factors for measles susceptibility. The calculated attributable fraction of measles cases from hospital visitation was 28.6% (95% CI: 20.6–38.8%).

**Conclusions:** Exposure to a healthcare facility was the largest risk factor for measles virus infection in adults in China. Improved adherence to hospital infection control practices could reduce risk of ongoing measles virus transmission and increase the likelihood of achieving and sustaining measles elimination in China. The use of control groups stratified by serological status identified distinct risk factors for measles virus infection and susceptibility among adults.

### Keywords

Measles elimination; China; Nosocomial transmission; Adults

## 1. Introduction

The presence of a safe and effective vaccine for measles has allowed many countries to successfully control the disease and reduce the global burden of disease substantially. All six World Health Organization (WHO) regions now have measles elimination goals, but no other region has yet been able to replicate the previous success of the WHO Region of the Americas [1]. In 2006, China endorsed an action plan for measles elimination by 2012 [2]. This plan was modeled on the successful elimination plan in the Americas, including a 2-dose routine measles-containing vaccine (MCV) schedule with > 95% coverage and use of supplementary immunization activities (SIAs) [3]. In September 2010, China conducted a synchronized nationwide SIA and vaccinated>100 million children aged 8 months–14 years [4] (Fig. 1).

In 2012, the WHO Western Pacific Region, including China, recorded its lowest-ever measles incidence (5.9 per million population) [5], and appeared to be approaching elimination. However, endemic measles virus transmission in China has not been interrupted [6,7], and a large resurgence in measles cases was seen in 2014 and 2015[8]. The resurgence revealed ongoing and emerging challenges; these include changing measles epidemiology, with increased measles incidence occurring among young adults and infants too young to be vaccinated, as well as heterogeneity of measles epidemiology among subnational areas and specific populations [8]. During 2014 through 2016, among all cases reported in China, over 40% were among adults of 20 years or above [9,10], and sustained measles virus transmission among adults was documented in a community setting [11].

The low measles incidence after the nationwide measles SIA in 2010 provided an opportunity to assess the impact and limitations of a vaccination strategy targeting children in epidemiological situations where adults make up a large percentage of measles case-patients [6]. We conducted an all-age case-control study during 2012–2013 to understand remaining barriers to measles elimination in China and guide further targeted efforts to reach this goal. Results for infants and children have already been published [12,13]; in this paper, we summarize results for persons aged ≥ 15 years. The specific objectives of this analysis were to identify risk factors for measles virus infection and susceptibility in adults following a nationwide measles vaccination campaign targeting children up to age 14 years.

## 2. Methods

### 2.1. Study location and time

Since 1986, China's 31 mainland provinces have been divided into three groups according to economic and social development: eastern, central, and western regions [14,15]. We selected six provinces for the study based on geography and measles epidemiology as described in detail previously [12]. Jiangsu, Zhejiang, and Shandong were selected from the more developed eastern region, and Henan, Gansu, and Yunnan from the less developed central and western regions. We combined the central and western regions because of overall similar demographics and measles epidemiology. These six provinces have a total population of around 406.8 million, 29.3% of the total population of China in 2017 [16]. The study sought to investigate all laboratory-confirmed measles cases reported from these provinces from January to December 2012. Because the number of reported cases did not meet the estimated sample size requirement by the end of 2012 (see below), we extended the study for 6 more months to cover the 2013 peak measles season.

### 2.2. Sample size

We powered the study for separate analysis of the eastern and central/western regions. Assuming a risk factor prevalence in controls of 30%, and a population seroprevalence of 85% (based on assessment of provincial measles serosurveys), 250 adult cases with three age and neighborhood matched controls in each of the eastern and central/western regions would provide a 90% power to detect a 20% difference in exposure prevalences.

### 2.3. Measles surveillance and case selection

A case-based, laboratory-supported measles surveillance system (MSS) was established in China in 1997, initially in selected provinces, and implemented nationwide in 2009 [17]. Every suspected measles case seeking healthcare in a hospital or identified by county level CDC staff during an outbreak investigation will be reported to the system after investigation by county-level CDC staff using a standardized, in-person questionnaire. China's Measles Laboratory Network consists of over 330 prefecture-level laboratories, 31 provincial laboratories, and one national laboratory that has been accredited by WHO as a

Regional Reference Laboratory continuously since 2003. We used this measles surveillance system to identify cases for the study.

Once a suspected measles case-patient seeks health care, the healthcare provider is expected to report the case within 24 h. Suspected measles cases are confirmed based on laboratory findings, an epidemiologic link, or clinical criteria. For this study, only case-patients confirmed by positive IgM enzyme-linked immunosorbent assay (SERION ELISA anti-measles virus IgM, Institut Virion\Serion GmbH) or isolation of measles virus in a WHO Global Measles and Rubella Laboratory Network accredited laboratory were enrolled. Reported cases were enrolled sequentially up to the desired sample size. Case-patients were excluded if they received MCV 7–14 days before rash onset [18] or declined to participate in the study. Case-patients were enrolled through June 2013 in each province until the calculated sample size was reached for each age group.

### 2.4. Control selection

We enrolled three neighborhood controls matched to case-patients within the following age strata: 15–24 years, 25–34 years, and ≥ 35 years. Controls were selected starting with the household closest to that of the case-patient. If more than one age eligible individual lived in the household, we selected the one closest in age to the case-patient. Subsequent households were visited until three eligible controls were found and enrolled. Potential controls were excluded if they refused consent for study participation or if they had a history of fever and rash in the previous 3 months, to ensure that they were unlikely to be undiagnosed measles cases.

### 2.5. Laboratory testing

IgM testing of suspected cases was performed per the established laboratory testing protocols of China Centers for Disease Control and Prevention (CDC)/provincial CDCs. For controls, 3 ml of blood was collected at the time of interview after informed consent was obtained. Serum separated samples were transported under cold storage to the provincial CDC and stored at −20 °C until testing. ELISA testing of serum samples for measles IgG using the Verion kit was performed at National Measles and Rubella Laboratory in China CDC, which was Regional Reference Laboratory for Measles in WHO’s Western Pacific Region. IgG titers were considered positive if ≥ 200 IU/ml, negative if < 200 IU/ml. IgG negative individuals were assumed to be susceptible to measles infection. We therefore had three control groups in our analysis: all controls regardless of serostatus, IgG positive controls and IgG negative controls.

### 2.6. Data collection

Trained investigators conducted in-house face-to-face interviews with case-patients and controls using a standard questionnaire. Variables collected included demographic characteristics, vaccination history, hospital exposure, health care service utilization and access, occupation, education level, details of daily commute, recent travel in the past three weeks and migration status. Migration status was defined by either a history of having at least one previous residence outside of the current county of residence or a history of ever having migrated from a different county, prefecture, or province to the current place of residence.

### 2.7. Data analysis

A summary description of demographic variables and risk factors of interest was completed for all case-patients and controls by region. To analyze variables potentially associated with susceptibility to measles in adults, seropositive controls (indicating individuals with immunity to measles) were compared to a combined group of seronegative controls (still susceptible to infection) and case-patients (who were susceptible before their recent infection). Matched odds ratios (mORs) and 95% confidence intervals (CIs) for risk factors were calculated via conditional logistic regression. Adjusted matched odds ratios (amORs) were obtained from a multivariable conditional logistic regression. Model building sequentially assessed each factor's significance, then significant factors were further assessed adjusted for other variables for the most parsimonious multivariable model. To analyze variables potentially associated with measles infection in adults, cases-patients were compared to seronegative controls using mORs and amORs via conditional logistic regression. Attributable fractions (AF) were calculated for those exposure risk factors that could be interpreted as causal, using the formula: $AF = P[E \mid D] * (1 - \frac{1}{mOR})$; where P[E | D] is the observed prevalence of the exposure among cases. We used bootstrapping to calculate a 95% CI for the AF by repeatedly sampling with replacement n matched sets, where n is the total number of matched sets available in the analysis [19]. The 2.5th and 97.5th percentiles of 500 estimated AFs define the 95% CI.

### 2.8. Ethical considerations

We obtained written informed consent from participants over the age of 18, and from parents or guardians of children under 18 years old. Verbal assent for participation was also obtained from children aged 15–18 years old for blood specimen collection. The study protocol was reviewed and approved by the Ethics Review Committee of the WHO Regional office for Western Pacific Region (Unique ID Number: 2011.24.CHN.05.EPI), and the Ethical Review Committee of China CDC(Unique ID: 201117). The protocol was reviewed in accordance with CDC human research protection procedures and determined to not be human subjects research requiring institutional review board review.

## 3. Results

From January 2012 through June 2013, the six study provinces reported 30,249 suspected measles cases (32% of the national total), of which 5978 (20%) were eventually classified as measles. Among these 5978 case-patients, 5876 (98%) were laboratory confirmed, six were epidemiologically confirmed and 96 were clinically compatible. Among the laboratory confirmed cases, 1982 (34%) were in adults aged ≥ 15 years. The percentage of measles cases in adults aged ≥ 15 years ranged from 14% in Henan Province to 57% in Zhejiang Province. For this study, 899 (45.4%) case-patients aged ≥ 15 years were enrolled: 591 from the eastern region and 308 from central/western region. Zhejiang contributed the largest number of case-patients (282), followed by Shandong (242), Yunnan (167), Jiangsu (72), Henan (70), and Gansu (66). Enrolled and non-enrolled case-patients did not significantly differ by age group ($\chi^2$ = 1.81, p = 0.40) or sex ($\chi^2$ = 0.25, p = 0.61). In total, 5994 households were visited, and 2756 potential controls were approached. Among them, 2498 controls were enrolled, 258 were excluded for either refusing consent for participation, refusal for blood sample, or having a history of fever and rash in the past 3 months.

A total of 899 case-patients, 2333 seropositive controls and 165 seronegative controls were included in the analysis (Table 1). Case-patients did not differ from controls by sex or age-group. Among enrolled case-patients, 58% were female, and the percentage was similar between the eastern and central/western regions. Over 40% of case-patients were in the 25–34 year-old age group in both regions, but case-patients in the central/western region were younger than in the eastern region (p = 0.0002). Among controls, overall 93.4% were seropositive (n = 2333) for measles IgG, and seropositivity varied little by age-group and region: seropositivity ranged from 91% in Gansu and Jiangsu to 95% in Shandong (data not shown). Case-patients and controls had different rates of visit to a hospital or clinic for any reason at least once in the 8–21 days before rash onset or interview: 32% of case-patients, 4% of seropositive controls, and 5% of seronegative controls. Reasons for visits included fever and cough (14% case-patients, 1% controls), other illness (5% case-patients, 1% controls) and other non-illness visits (14% case-patients, 3% controls). Visits were further classified as inpatient (10% case-patients, 0.4% controls) and non-inpatient (21% case-patients, 4% controls).

On univariate analysis, measles immune individuals (seropositive controls) were more likely than measles susceptible individuals (seronegative controls and case-patients) to have a college education, work in a college setting or as a healthcare worker rather than a factory setting, have had a measles vaccination, or report being willing to receive measles vaccination (Table 2). Since only 44% of case-patients and 62% of controls were aware of their vaccination status, vaccination history was excluded from the multivariable analysis. The multivariable analysis indicated that immune adults were more likely to work in a college [amOR 5.11 (95% CI: 2.81, 9.30)] or health care setting [amOR 7.3 (95% CI: 3.85, 13.83)], and were more likely to report a willingness to receive measles vaccination [amOR 1.79 (1.21, 2.65)].

From univariate and multivariable conditional logistic regressions, case-patients were more likely than seronegative controls to have visited the hospital for a reason other than vaccination in the 8–21 days before rash onset or investigation date [amOR 13.86 (95% CI: 3.26, 58.96)]; and they were more likely to have traveled outside the prefecture in the prior 1–3 weeks [amOR 4.27 (95% CI: 1.07, 16.98)] (Table 3). The attributable fraction for any non-vaccine hospital visit and for travel outside the prefecture in the prior 1–3 weeks was 28.6% (95% CI: 20.6–38.8%) and 14.3% (95% CI: 4.3–24.4%), respectively.

## 4. Discussion

Our case-control study of adult measles in 6 provinces of China has shown that: (1) immunity among controls was very high (>90%), and associated with working in a college environment or in the health care system; (2) independent attributable fractions of an adult acquiring measles virus infection were 28% for visiting a hospital and 14% for traveling outside of the prefecture one to three weeks prior to measles onset; and (3) no other risk factor examined was able to explain a programmatically-meaningful amount of measles virus transmission to adults. Among controls, over 90% stated willingness to receive measles vaccination. The implication of these findings is that no single programmatic action will be able directly to eliminate measles among adults in China; rather, a combination of programmatic actions including strengthening of infection control procedures in hospitals and carefully targeted vaccine campaigns against groups with expected lower immunity levels is likely to be needed.

### 4.1. Strengths and Weaknesses

Strengths of the study include that (1) measles case identification and verification was conducted by a real-time, national measles and rubella surveillance system that has met WHO quality and sensitivity standards continuously since 2011; (2) all of the measles cases were laboratory confirmed and laboratory testing of cases and controls was performed by the National Measles and Rubella Laboratory network, which consists of WHO-verified reference laboratories for the WHO Western Pacific Region; (3) measles immunity was measured directly among controls to provide an objective assessment of immunity, (4) three controls were matched per case to provide additional sample size for analyses of controls' factors associated with immunity or susceptibility to measles. This study was part of a full-age measles case control study. Therefore, published findings from the other age groups [12,13], can be compared with these finding for a broader understanding of measles virus transmission in China.

Weaknesses of the study include that only six of China's 31 provinces were studied, limiting generalization to the entire country. Countering this limitation is that the six provinces were selected to be representative of the three different regions of China based on social developmental status - east, middle, and western China. Even though the national measles surveillance system met and continues to meet WHO quality criteria, it is highly unlikely that all measles cases were reported, especially milder cases and those not medically-attended. Therefore, the cases cannot be said to represent all measles cases in the study provinces. Few case-patients or controls knew their measles vaccination status or had access to their measles vaccination history. Recall of measles vaccination status is unreliable and subject to recall bias, especially for adults who would have been vaccinated years to decades earlier. That few adults know their measles vaccination status was understood before the study was conducted, and it was for this reason that we measured the controls' immunity to measles. Exclusion of fever-rash cases from the control group may have caused an upward bias of the risk factor 'visiting a hospital'. However, because<10% of potential controls were excluded for any reason, we believe that any upward bias will be small.

### 4.2. Study in the context of the scientific literature

High population immunity is known to be necessary to eliminate measles; however, an open question is how high immunity must be among adults for successful elimination of measles. A 2016 symposium about closing measles and rubella immunity gaps among adults and adolescents stated that "evidence that susceptible adult populations can maintain virus transmission in the absence of susceptible childhood populations is, so far, inconclusive," and that the "level of priority that should be given to addressing immunity gaps in adolescents and young adults remains unclear" [20]. Our study did not answer the question of the necessity of closing an immunity gap among adults, but rather provided evidence as to where transmission was occurring, although less than a third of transmission could be attributed to a single risk factor. However, although not representative of the population due to the neighborhood matching approach to control enrollment, our study did show that among controls, immunity was high -- at the same level as that seen in the United States among adults as shown by Lebo and colleagues [21].

Nosocomial transmission of measles virus is a well-described phenomenon, as hospitals and other healthcare settings emerge as a significant place of transmission when a country is at or near the elimination of measles [22]. Health care personnel are at a 2- to 19-fold increased risk of occupational exposure to measles virus, and health care personnel are known to participate in chains of measles virus transmission. It is for this reason that some countries have implemented requirements to demonstrate proof of measles immunity among health care workers [23]. Hospital-based measles outbreaks have been documented in China, as shown by Jia and colleagues [24]. Our study of adults is consistent with the current belief that nosocomial transmission of measles virus is important, and is also consistent with findings from this study's companion case-control studies. The risk of measles in these six provinces attributable to visiting the hospital was 43% among children < 8 months (too young to vaccinate in China) and 32% among children 8 months to 14 years of age [12,13]. Another case-control study conducted in China showed visiting a hospital to be a significant risk factor, and demonstrated nosocomial transmission in an intravenous drip treatment room [25].

Travel and migration are also well known risk factors for acquisition of measles virus. Internal travel and migration in China is very high; travel during the Chinese Spring Festival is the largest annual movement of humans in the world, with an estimated 3 billion individual trips taking during the 40 days around Spring Festival [26]. In China, travel is believed to be a risk factor for acquiring measles among susceptible persons, although not all studies found an association with travel. For example, Wagner and colleagues found inter-city travel to be protective against measles in Tianjin, although they believed that travel may have been confounded by correlation with socioeconomic status [27]. Our study's two companion case control studies both found travel to be a significant risk factor. Travel is different than migration, in which families move from one place to another, often in job-related moves. China has large internal migration, and a previous analysis of measles surveillance data by Ma and colleagues showed that nearly 50% of reported measles cases in China were among individuals living in a different county than that in which they were born [6].

### 4.3. Implications for the program

It was reassuring to see a high level of immunity among controls, and that health care workers were more likely to be immune to measles than adults of other occupations. However, we found that the single largest risk factor for a susceptible adult acquiring measles was a recent visit to a hospital. Considering that visiting a hospital was the largest risk factor in the companion case-control studies implies that regardless of age, visiting a hospital is associated with a significant risk of exposure to measles. Furthermore, nosocomial transmission will remain important even after endemic transmission is interrupted. For example, the experience in the United States is that hospitals remain as potential sites of transmission following measles virus introduction, and that responding to hospital-based measles outbreaks is very expensive [28]. Reducing measles virus transmission in hospitals in China is likely to help reduce transmission of measles virus in the country overall.

Our finding that immunity among control subjects to measles virus was above 90% and that few adults knew or had access to their immunization records, coupled with the very large size of the adult population (>500 million adults in the study age group), implies that campaigns to close a relatively small immunity gap among adults would be difficult or inefficient. If all adults are targeted, the vast majority of those targeted for vaccination will be immune already. A selective campaign targeting those who cannot show a history of being vaccinated or having had measles will be challenged by the small percent of adults with vaccination records. Our finding that travel poses a risk of measles is not a programmatically actionable finding. With the development of a highly efficient travel infrastructure, travel within China is increasing, which is simply part of the environment in which measles elimination must occur.

### 4.4. Recommendations

This study and its companion studies support several recommendations. First, high quality measles surveillance must continue, with careful observation of the incidence among different age groups. Surveillance can provide useful information on direct and indirect protection against measles and will help determine whether adult transmission will hinder elimination of measles.

Second, effort should be directed to make hospitals and health care facilities safer from measles, including vaccination strategy for health care workers. We believe that government and professional health care organizations, especially those involved with hospital infection control, should establish guidelines for prevention of nosocomial measles and hospital control measures after contact with a measles case-patient, along the lines of recommendations of Botelho-Nevers and colleagues [22].

Third, studies, including mathematical modeling studies, should be used to identify high-value targets for vaccination that can accelerate elimination of measles in China. These target groups may be subsets of adults (e.g., health care workers and college students) or they may be older children, as has been identified by Hao and colleagues in a recently-published modeling study that was based on a national serological survey [29].

## 5. Conclusion

As China is nearing the elimination of measles, the epidemiology of measles has been changing. The incidence of adult measles is decreasing, but the proportion of measles among adults is increasing. Our study and its companion studies identified visiting a hospital as a significant risk factor for acquiring measles. Mitigating this risk factor will be important during and after elimination of measles in China.

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## References

[1]. Global WHO. control and regional elimination of measles, 2000–2012. Wkly Epidemiol Rec. 2014;89:45–52. [PubMed: 24524163]

[2]. MOH. 2006. National Plan of Measles Elimination in China 2006–2012. http://www.moh.gov.cn/jkj/s3581/200804/361e2acfadcc4e93bcac60235d307a48.shtml. 2006.

[3]. Castillo-Solorzano CC, Matus CR, Flannery B, Marsigli C, Tambini G, Andrus JK. The Americas: paving the road toward global measles eradication. J Infect Dis. 2011;204(Suppl 1):S270–8. [PubMed: 21666172]

[4]. Chao M, Lixin H, Jing M, Yan Z, Lei C, Xiaofeng L, et al. Measles epidemiological characteristics and progress of measles elimination in China, 2010. Chin J Vaccin Immun. 2011;17:242–5.

[5]. Progress WHO. towards measles elimination in the Western Pacific Region, 2009–2012. Wkly Epidemiol Rec. 2013;88:233–40. [PubMed: 23757799]

[6]. Ma C, Hao L, Zhang Y, Su Q, Rodewald L, An Z, et al. Monitoring progress towards the elimination of measles in China: epidemiological observations, implications and next steps. Bull World Health Organ 2014;92:340–7. [PubMed: 24839323]

[7]. Zhang Y, Xu S, Wang H, Zhu Z, Ji Y, Liu C, et al. Single endemic genotype of measles virus continuously circulating in China for at least 16 years. PLoS ONE 2012;7:e34401. [PubMed: 22532829]

[8]. Hagan JE, Kriss JL, Takashima Y, Mariano KML, Pastore R, Grabovac V, et al. Progress Toward Measles Elimination - Western Pacific Region, 2013–2017. MMWR Morb Mortal Wkly Rep 2018;67:491–5. [PubMed: 29723171]

[9]. Chao M, Lixin H, Qiru S, Ning W, Chunxiang F, Hong Y, et al. Measles epidemiology in China, 2014. Disease Surveillance. 2015;30:818–23.

[10]. Qiru S, Lixin H, Chao M, Ning W, Chunxiang F, Hong Y, et al. Epidemiology of measles in China, 2015–2016. Chin J Vaccin Immun. 2018;24:146–51.

[11]. Ma C, Yan S, Su Q, Hao L, Tang S, An Z, et al. Measles transmission among adults with spread to children during an outbreak: Implications for measles elimination in China, 2014. Vaccine. 2016;34:6539–44. [PubMed: 27329182]

[12]. Ma C, Gregory CJ, Hao L, Wannemuehler KA, Su Q, An Z, et al. Risk factors for measles infection in 0–7 month old children in China after the 2010 nationwide measles campaign: A multi-site case-control study, 2012–2013. Vaccine. 2016;34:6553–60. [PubMed: 27013438]

[13]. Hao L, Ma C, Wannemuehler KA, Su Q, An Z, Cairns L, et al. Risk factors for measles in children aged 8 months-14 years in China after nationwide measles campaign: A multi-site case-control study, 2012–2013. Vaccine. 2016;34:6545–52. [PubMed: 26876440]

[14]. State The. Council of the people's Republic of China. The Seventh Five Year Plan. 1986.

[15]. Ma C, An Z, Hao L, Cairns KL, Zhang Y, Ma J, et al. Progress toward measles elimination in the People's Republic of China, 2000–2009. J Infect Dis 2011;204(Suppl 1):S447–54. [PubMed: 21666198]

[16]. China Statistical Yearbook 2017. Beijing: China Statistics Press 2018.

[17]. Chao M, Lixin H, Zhijie A, Jing M, Yan Z, Wenbo X, et al. Establishment and performance of measles surveillance system in the People's Republic of China. Chin J Vaccin Immun. 2010;16:297–306.

[18]. Monitoring WHO. progress towards measles elimination. Wkly Epidemiol Rec. 2010;85:490–4. [PubMed: 21140596]

[19]. Llorca J, Delgado-Rodriguez M. A comparison of several procedures to estimate the confidence interval for attributable risk in case-control studies. Stat Med. 2000;19:1089–99. [PubMed: 10790682]

[20]. Joint Symposium on Closing Immunity Gaps in Older Children and Adults - Final Report. https://www.sabin.org/updates/resources/joint-symposium-closing-immunity-gaps-older-children-and-adults-final-report. 2016. (Last accessed 19 May 2019).

[21]. Lebo EJ, Kruszon-Moran DM, Marin M, Bellini WJ, Schmid S, Bialek SR, et al. Seroprevalence of measles, mumps, rubella and varicella antibodies in the United States population, 2009–2010. Open forum infectious diseases 2015;2:ofv006. [PubMed: 26034757]

[22]. Botelho-Nevers E, Gautret P, Biellik R, Brouqui P. Nosocomial transmission of measles: an updated review. Vaccine 2012;30:3996–4001. [PubMed: 22521843]

[23]. Fiebelkorn AP, Seward JF, Orenstein WA. A global perspective of vaccination of healthcare personnel against measles: systematic review. Vaccine 2014;32:4823–39. [PubMed: 24280280]

[24]. Jia H, Ma C, Lu M, Fu J, Rodewald LE, Su Q, et al. Transmission of measles among healthcare Workers in Hospital W, Xinjiang Autonomous Region, China, 2016. BMC Infect Dis 2018;18:36. [PubMed: 29329528]

[25]. Zhang DL, Pan JR, Xie SY, Zhou Y, Shen LZ, Xu GZ, et al. A hospital-associated measles outbreak among individuals not targeted for vaccination in eastern China, 2014. Vaccine 2015;33:4100–4. [PubMed: 26117147]

[26]. “Chunyun” - 3 Billion Passenger Trips in 40 Days, The Largest Human Migration. https://defence.pk/pdf/threads/chunyun-3-billion-passenger-trips-in-40-days-the-largest-human-migration.472278/. 2017. (Last accessed 19 May 2019).

[27]. Wagner AL, Boulton ML, Gillespie BW, Zhang Y, Ding Y, Carlson BF, et al. Risk factors for measles among adults in Tianjin, China: Who should be controls in a case-control study?. PLoS ONE 2017;12:e0185465. [PubMed: 28950011]

[28]. Fiebelkorn AP, Redd SB, Kuhar DT. Measles in Healthcare Facilities in the United States During the Postelimination Era, 2001–2014. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2015;61:615–8. [PubMed: 25979309]

[29]. Hao L, Glasser JW, Su Q, Ma C, Feng Z, Yin Z, et al. Evaluating vaccination policies to accelerate measles elimination in China: a meta-population modelling study. Int J Epidemiol 2019.

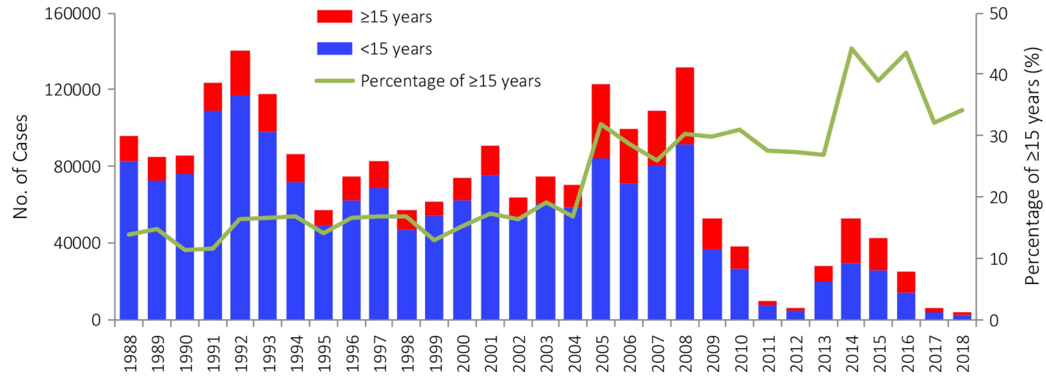


**Fig. 1.**

Adult measles cases in China, 1988–2018, by absolute number and proportion of all reported measles cases.

**Table 1**

Demographic characteristics of measles case-patients and age-matched controls aged > 15 years stratified by geographic area—China, 2012–2013.

| Variable description | Eastern Region, N (%) | | | Central/Western Region, N (%) | | | Total, N (%) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Case (N = 591) | Positive control (N = 1589) | Negative control (N = 108) | Case (N = 308) | Positive control (N = 744) | Negative control (N = 57) | Case (N = 899) | Positive control (N = 2333) | Negative control (N = 165) |
| Sex (Male) | 247 (42) | 668 (42) | 47 (44) | 135 (44) | 360 (48) | 30 (53) | 382 (42) | 1028 (44) | 77 (47) |
| Age (Years) | | | | | | | | | |
| 15–24yrs | 121 (20) | 329 (21) | 22 (20) | 92 (30) | 228 (31) | 20 (35) | 213 (24) | 557 (24) | 42 (25) |
| 25–34yrs | 256 (43) | 687 (43) | 51 (47) | 141 (46) | 342 (46) | 26 (46) | 397 (44) | 1029 (44) | 77 (47) |
| ≥35yrs | 214(36) | 573 (36) | 35 (32) | 75 (24) | 174 (23) | 11 (19) | 289 (32) | 747 (32) | 46 (28) |
| Type of house | | | | | | | | | |
| Multistory building | 308 (52) | 838 (53) | 59 (55) | 123 (40) | 283 (38) | 23 (40) | 431 (48) | 1121 (48) | 82 (50) |
| Single-story house | 231 (39) | 630 (40) | 40 (37) | 150 (49) | 385 (52) | 30 (53) | 381 (43) | 1015 (44) | 70 (42) |
| Dormitory | 36 (6) | 89 (6) | 5 (5) | 20 (7) | 59 (8) | 1 (2) | 56 (6) | 148 (6) | 6 (4) |
| Other | 15 (3) | 29 (2) | 4 (4) | 12 (4) | 13 (2) | 3 (5) | 27 (3) | 42 (2) | 7 (4) |
| Education level | | | | | | | | | |
| ≤Primary school | 98 (17) | 240 (15) | 17 (16) | 107 (35) | 225 (31) | 14 (25) | 205 (23) | 465 (20) | 31 (19) |
| Middle school | 432 (74) | 1153 (73) | 75 (69) | 174 (57) | 438 (60) | 36 (63) | 606 (68) | 1591 (69) | 111 (67) |
| ≥College | 55 (9) | 193 (12) | 16 (15) | 23 (8) | 72 (10) | 7 (12) | 78 (9) | 265 (11) | 23 (14) |
| Occupation College setting | 15 (3) | 98 (6) | 5 (5) | 16 (5) | 58 (8) | . (0) | 31 (3) | 156 (7) | 5 (3) |
| Hospital/HCWs | 13 (2) | 97 (6) | 2 (2) | 10 (3) | 56 (8) | 3 (5) | 23 (3) | 153 (7) | 5 (3) |
| Factory worker | 159 (27) | 362 (23) | 19 (18) | 45 (15) | 84 (11) | 5 (9) | 204 (23) | 446 (19) | 24 (15) |
| Government employee | 16 (3) | 49 (3) | 4 (4) | 7 (2) | 18 (2) | 3 (5) | 23 (3) | 67 (3) | 7 (4) |
| House setting | 87 (15) | 208 (13) | 18 (17) | 22 (7) | 51 (7) | 5 (9) | 109 (12) | 259 (11) | 23 (14) |
| Farmers | 140 (24) | 324 (20) | 22 (21) | 142 (46) | 335 (45) | 32 (56) | 282 (32) | 659 (28) | 54 (33) |
| Others | 156 (27) | 448 (28) | 37 (35) | 65 (21) | 141 (19) | 9 (16) | 221 (25) | 589 (25) | 46 (28) |
| Commute Public Transport | 42 (7) | 108 (7) | 11 (10) | 32 (11) | 59 (9) | 3 (6) | 74 (9) | 167 (8) | 14 (9) |
| Walk | 128 (22) | 410 (27) | 21 (20) | 166 (58) | 412 (60) | 30 (58) | 294 (34) | 822 (37) | 51 (32) |
| Bicycle | 284 (50) | 784 (51) | 52 (49) | 65 (23) | 135 (20) | 13 (25) | 349 (41) | 919 (41) | 65 (41) |
| Private car | 91 (16) | 184 (12) | 18 (17) | 13 (5) | 43 (6) | 2 (4) | 104 (12) | 227 (10) | 20 (13) |

| Variable description | Eastern Region, N (%) | | | Central/Western Region, N (%) | | | Total, N (%) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Case (N = 591) | Positive control (N = 1589) | Negative control (N = 108) | Case (N = 308) | Positive control (N = 744) | Negative control (N = 57) | Case (N = 899) | Positive control (N = 2333) | Negative control (N = 165) |
| Other | 27 (5) | 42 (3) | 4 (4) | 11 (4) | 38 (6) | 4 (8) | 38 (4) | 80 (4) | 8 (5) |
| Number of people living together | | | | | | | | | |
| 0–1 | 114 (19) | 283 (18) | 16 (15) | 33 (11) | 79 (11) | 7 (12) | 147 (16) | 362 (16) | 23 (14) |
| 2–3 | 313 (53) | 889 (56) | 61 (56) | 150 (49) | 322 (43) | 21 (37) | 463 (52) | 1211 (52) | 82 (50) |
| 4+ | 162 (28) | 416 (26) | 31 (29) | 123 (40) | 340 (46) | 29 (51) | 285 (32) | 756 (32) | 60 (36) |
| Child living in the household | | | | | | | | | |
| Yes | 337 (58) | 886 (57) | 59 (55) | 185 (62) | 472 (67) | 33 (58) | 522 (59) | 1358 (60) | 92 (56) |
| No | 247 (42) | 681 (43) | 48 (45) | 112 (38) | 234 (33) | 24 (42) | 359 (41) | 915 (40) | 72 (44) |
| All children received MCV | | | | | | | | | |
| Yes | 384 (95) | 1041 (96) | 70 (99) | 175 (93) | 506 (96) | 28 (82) | 559 (94) | 1547 (96) | 98 (93) |
| No | 22 (5) | 43 (4) | 1 (1) | 14 (7) | 21 (4) | 6 (18) | 36 (6) | 64 (4) | 7 (7) |
| MCV vaccination history | | | | | | | | | |
| Yes | 43 (17) | 560 (56) | 28 (41) | 28 (19) | 251 (56) | 17 (53) | 71 (18) | 811 (56) | 45 (45) |
| No | 208 (83) | 436 (44) | 41 (59) | 118 (81) | 197 (44) | 15 (47) | 326 (82) | 633 (44) | 56 (55) |
| Willingness to get MCV during SIA | | | | | | | | | |
| Yes | 552 (94) | 1506 (95) | 101 (94) | 279 (92) | 702 (95) | 56 (98) | 831 (93) | 2208 (95) | 157 (95) |
| No | 31 (5) | 51 (3) | 4 (4) | 20 (7) | 29 (4) | 1 (2) | 51 (6) | 80 (3) | 5 (3) |
| DK | 7 (1) | 31 (2) | 3 (3) | 5 (2) | 11 (1) | . (0) | 12 (1) | 42 (2) | 3 (2) |
| Migrant provinces | | | | | | | | | |
| Yes | 112 (19) | 299 (19) | 12 (11) | 27 (9) | 38 (5) | 1 (2) | 139 (16) | 337 (15) | 13 (8) |
| No | 478 (81) | 1286 (81) | 96 (89) | 278 (91) | 701 (95) | 56 (98) | 756 (84) | 1987 (85) | 152 (92) |
| Migrant county | | | | | | | | | |
| Yes | 139 (24) | 364 (23) | 19 (18) | 52 (17) | 101 (14) | 4 (7) | 191 (21) | 465 (20) | 23 (14) |
| No | 451 (76) | 1221 (77) | 89 (82) | 253 (83) | 638 (86) | 53 (93) | 704 (79) | 1859 (80) | 142 (86) |
| Travel outside prefecture 1–3 weeks | | | | | | | | | |
| Yes | 72 (12) | 87 (5) | 6 (6) | 54 (18) | 45 (6) | 3 (5) | 126 (14) | 132 (6) | 9 (5) |

| Variable description | Eastern Region, N (%) | | | Central/Western Region, N (%) | | | Total, N (%) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Case (N = 591) | Positive control (N = 1589) | Negative control (N = 108) | Case (N = 308) | Positive control (N = 744) | Negative control (N = 57) | Case (N = 899) | Positive control (N = 2333) | Negative control (N = 165) |
| No | 516 (88) | 1496 (95) | 102 (94) | 251 (82) | 691 (94) | 54 (95) | 767 (86) | 2187 (94) | 156 (95) |
| Hospital visit prior 1–3 weeks | | | | | | | | | |
| Yes | 143 (33) | 63 (4) | 5 (5) | 69 (30) | 34 (5) | 2 (4) | 212 (32) | 97 (4) | 7 (5) |
| No | 294 (67) | 1424 (96) | 94 (95) | 160 (70) | 647 (95) | 50 (96) | 454 (68) | 2071 (96) | 144 (95) |
| Hospital visit type Inpatient Visit | 40 (9) | 6 (0) | . (0) | 29 (13) | 4 (1) | 1 (2) | 69 (10) | 10 (0) | 1 (1) |
| Non-inpatient Visit | 103 (24) | 57 (4) | 5 (5) | 40 (17) | 30 (4) | 1 (2) | 143 (21) | 87 (4) | 6 (4) |
| No Visit | 294 (67) | 1424 (96) | 94 (95) | 160 (70) | 647 (95) | 50 (96) | 454 (68) | 2071 (96) | 144 (95) |
| Hospital visit (fever/cough) | | | | | | | | | |
| Yes | 52 (12) | 17 (1) | . (0) | 38 (17) | 7 (1) | . (0) | 90 (14) | 24 (1) | . (0) |
| No | 385 (88) | 1470 (99) | 99 (100) | 191 (83) | 674 (99) | 52 (100) | 576 (86) | 2144 (99) | 151 (100) |
| Hospital visit (not fever/cough) | | | | | | | | | |
| Yes | 22 (5) | 13 (1) | . (0) | 10 (4) | 8 (1) | 1 (2) | 32 (5) | 21 (1) | 1 (1) |
| No | 415 (95) | 1474 (99) | 99 (100) | 219 (96) | 673 (99) | 51 (98) | 634 (95) | 2147 (99) | 150 (99) |
| Hospital visit (other) | | | | | | | | | |
| Yes | 74 (17) | 33 (2) | 5 (5) | 22 (10) | 19 (3) | 1 (2) | 96 (14) | 52 (2) | 6 (4) |
| No | 363 (83) | 1454 (98) | 94 (95) | 207 (90) | 662 (97) | 51 (98) | 570 (86) | 2116 (98) | 145 (96) |
| Hospital visit (vaccine) | | | | | | | | | |
| Yes | . (0) | 23 (2) | . (0) | . (0) | 1 (0) | 1 (2) | . (0) | 24 (1) | 1 (1) |
| No | 437 (100) | 1464 (98) | 99 (100) | 229 (100) | 680 (100) | 51 (98) | 666 (100) | 2144 (99) | 150 (99) |

**Table 2**

Characteristics associated with measles immunity in adults ≥ 15 years based on comparison of susceptible adults (cases & seronegative controls) to immune adults (seropositive controls), a matched case-control study, China, 2012–2013.

| Demographic Variables | Univariate Analysis | | Multivariable Analysis | |
|---|---|---|---|---|
| | # of matched sets | mOR (95% CI) | # of matched sets | amor (95% CI) |
| Sex (Male: Female) | 893 | 1.04 (0.87,1.23) | – | – |
| Age group | 893 | | – | – |
| 15–24 yrs: ≥35 yrs | | 0.96 (0.60,1.54) | – | – |
| 25–34 yrs: ≥35yrs | | 1.03 (0.72,1.47) | – | – |
| Type of House | 889 | | – | – |
| Multistory: dormitory | | 1.10 (0.67,1.81) | – | – |
| Single story: dormitory | | 1.11 (0.66,1.88) | – | – |
| other: dormitory | | 0.43 (0.18,1.03) | – | – |
| Education Level | 883 | | – | – |
| <= Primary: College + | | 0.58 (0.39,0.84) | – | – |
| Middle: College+ | | 0.71 (0.51,0.97) | – | – |
| Occupation (Factory worker) | 888 | | 882 | |
| College setting | | 4.75 (2.65,8.53) | | 5.11 (2.81, 9.30) |
| Healthcare worker | | 6.75 (3.63,12.5) | | 7.30 (3.85, 13.83) |
| Government/company | | 1.68 (0.93,3.02) | | 1.63 (0.90, 2.93) |
| House setting | | 1.21 (0.86,1.69) | | 1.22 (0.87, 1.71) |
| Farmers | | 1.02 (0.74,1.40) | | 1.01 (0.74,1.40) |
| Others | | 1.36 (1.02,1.81) | | 1.36 (1.03, 1.81) |
| Commute (Public transport) | 851 | | – | – |
| Walk | | 1.32 (0.93,1.88) | – | – |
| Bicycle | | 1.13 (0.80,1.59) | – | – |
| Private car | | 0.96 (0.65,1.42) | – | – |
| Other | | 0.97 (0.54,1.74) | – | – |
| MCV history (yes: no) | 371 | 8.44 (5.67,12.6) | – | – |
| Willingness for MCV in future SIA (yes:no) | 887 | 1.88 (1.28,2.75) | 882 | 1.79 (1.21, 2.65) |
| Migrant history (Yes:No) | | | – | – |

| Demographic Variables | Univariate Analysis | | Multivariable Analysis | |
|---|---|---|---|---|
| | # of matched sets | mOR (95% CI) | # of matched sets | amor (95% CI) |
| Across provinces | 889 | 0.75 (0.54,1.05) | – | – |
| Across prefectures | 889 | 0.77 (0.58,1.03) | – | – |

## Table 3

Characteristics associated with measles infection in adults ≥ 15 years based on comparison of case-patients with seronegative controls, a matched case-control study, China, 2012–2013.

| | Univariate Analysis | | Multivariable Analysis | |
|---|---|---|---|---|
| **Demographic Variables** | **# of matched sets** | **mOR (95% CI)** | **# of matched sets** | **amOR (95% CI)** |
| Gender (Male: Female) | 148 | 0.74 (0.46,1.21) | – | – |
| Occupation | 147 | | | |
| College setting : factory worker | | 0.65 (0.14,2.91) | | |
| Hospital/HCWs : factory worker | | 0.23 (0.02,2.53) | – | – |
| Government/company : factory worker | | 0.51 (0.10,2.59) | – | – |
| House setting : factory worker | | 1.09 (0.38,3.16) | – | – |
| Farmers : factory worker | | 1.05 (0.43,2.57) | – | – |
| Others : factory worker | | 0.74 (0.33,1.69) | – | – |
| Commute | 137 | | | |
| Walk : public transport | | 0.98 (0.35,2.69) | – | – |
| Bicycle : public transport | | 0.92 (0.33,2.57) | – | – |
| Private car : public transport | | 0.98 (0.30,3.19) | – | – |
| Other : public transport | | 1.43 (0.27,7.46) | – | – |
| Children living in the household (yes: no) | 147 | 1.53 (0.84, 2.80) | – | – |
| All children received MCV (yes: no) | 72 | 0.74 (0.20, 2.78) | – | – |
| Hospital visit prior 1–3 weeks (yes: no) | 107 | 15.9 (3.81,66.7) | 107 | 13.86 (3.26,58.96) |
| Travel outside Prefecture prior 1–3 weeks (yes: no) | 148 | 5.35 (2.03,14.1) | | 4.27 (1.07,16.98) |
| Number of people living together | 148 | | | |
| 0–1 : 4+ | | 0.89 (0.41,1.93) | – | – |
| 2–3 : 4+ | | 0.87 (0.50,1.52) | – | – |