Published in final edited form as:

Public Health. 2017 October ; 151: 114–117. doi:10.1016/j.puhe.2017.07.001.

Risk factors for measles among infants in Tianjin, China

Ying Zhang¹, Abram L. Wagner^{2,*}, Xiexiu Wang¹, Bradley F. Carlson², Yaxing Ding¹, JoLynn P. Montgomery², Brenda W. Gillespie³, and Matthew L. Boulton^{2,4}

¹Tianjin Centers for Disease Control and Prevention, Tianjin, China

²Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, MI, USA

³Department of Biostatistics, School of Public Health, University of Michigan, Ann Arbor, MI, USA

⁴Division of Infectious Diseases, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI, USA

MEASLES ELIMINATION IN CHINA

Despite a global goal for measles eradication, measles still resulted in 134,000 deaths in 2015.¹ Vaccination is the key preventive intervention for measles, and global coverage of measles-containing vaccine (MCV) has increased from 72% in 2000 to 85% in 2015.¹ In China, children are administered measles-containing vaccines at 8 months and 18–24 months. Some urban locales, like Beijing, Tianjin, and Shanghai offer a third dose at 4–6 years. Infants <8 months of age are ineligible for vaccination and are at high-risk for disease given the rapid decay of maternal antibodies that we have seen in China.² In recent years, infants have constituted >30% of all measles cases within China.³

Previous case-control studies have identified risk factors for measles in China—notably exposure to hospital settings.^{4,5} However, the generalizability of these results is unclear because of small sample sizes, short study duration, and nonspecific definitions of exposure (e.g. “hospital” vs specific types of hospitals). In this case-control study in Tianjin, China, we enrolled cases and controls between 2011 and 2015, and examined risk factors for measles by comparing infant cases to a community sample of measles IgG-negative controls.

*Corresponding author +001-734-763-2330 awag@umich.edu.

Ethical approval

This study was approved by the University of Michigan Institutional Review Board and the Tianjin Centers for Disease Control and Prevention Ethics Committee.

Competing interests

None declared.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

STUDY DESIGN

Tianjin is one of four province-level municipalities in China. Its 15.2 million residents live in urban, suburban, and rural districts. A finer administrative-level division in Tianjin is the urban community or rural village, with the entire Tianjin population registered as residents in one of over 5,000 communities/villages within the municipality.

This case-control study samples laboratory-confirmed cases from the infectious disease surveillance system in Tianjin. Each week, staff at the Tianjin Centers for Disease Control and Prevention (CDC) downloaded the list of measles cases reported within the proceeding week from the China Information System for Disease Control and Prevention web-based surveillance system and randomly selected cases to enroll into this study. The number selected into the study was based on overall measles case-load and staff availability to perform interviews.

Our community sample of controls was drawn from a population-based, two-stage cluster sample. At the first stage, 120 communities/villages were selected through a probability proportionate to size procedure with each district represented by at least one community/village. At the second stage, we took a sample from immunization clinics whereby infants <1 year of age and their mothers were found and selected in an age-stratified random selection within each community/village. This sample includes locals, those with a residency card, or *hukou*, assigned to Tianjin, and non-locals, who are Tianjin residents whose *hukou* is from another province.

This manuscript's analysis only includes infants. Our original sample size calculations were based on the larger original study which encompassed a greater age range (0–49 years). In the original study, we wanted to select 500 cases and 500 controls, with similar age, neighborhood, and residency status. This sample size could detect associations between a risk factor and measles case status with 90% power if the risk factor had an odds ratio of at least 2.0.

Mothers of the infants consented to their participation before data collection. The mother was interviewed in-person. The interview included questions about socio-demographic characteristics, vaccination history, measles infection history, and exposure to various congregate settings in the prior 21 days (for non-cases) or 21 days prior to disease (for cases).

Mothers were asked if their child had gone to any hospital in the 21-day exposure period, which included township, district, and municipal hospitals. Specialty hospitals, such as infectious disease and pediatric hospitals, were aggregated in the analysis because of low counts.

Mothers who answered “I don’t know” to questions were re-categorized as having missing information.

A bloodspot from the participant's heel was collected using a single-use lancet and tested at the Tianjin CDC laboratory⁶. Measles IgG testing was done with a SERION ELISA classic

measles virus IgG quantitative kit (Institut Virion/Serion GmbH, Würzburg, Germany). The IgG titers were categorized as positive if >200 IU/ml for positive, borderline if 150 to 200 IU/ml, and negative if <150 IU/ml.

Individuals who are measles IgG positive are presumably protected against future infection with measles, so our population of controls only includes those who are IgG negative (which excludes most children who had been vaccinated).

We present a logistic regression model adjusted for child's age, child's sex, urbanicity, and the mother's education. Given that age groups, urbanicity, and sex were related to the sampling design, the strength of association is not interpretable. We present the distribution of the number of children in the household and childcare use between cases and controls, but because of low cell counts, they were not included in the multivariable logistic regression. The precision of the odds ratios (ORs) in all models was examined with 95% confidence intervals (CIs).

OpenClinica version 3.3 (OpenClinica LLC, Waltham, MA, USA) database was used and data analyses were conducted using SAS software, version 9.3 (SAS Institute Inc., Cary, NC, USA).

RISK FACTORS FOR MEASLES IN INFANTS

Initially, 500 controls and 2,818 controls 0–49 years of age were enrolled; 20 measles cases (3.8%) and 173 community members (5.8%) had refused to participate. There were 82 measles cases and 485 controls <1 year of age. Details of covariate distribution by case status among these infants are shown in Table 1.

In the adjusted model, household size was significantly related to measles case status, with infants in larger households (≥ 4 people) having 0.43 times the odds of measles compared to infants in smaller families (95% CI: 0.23, 0.81). Although we did not collect information on household composition, it is possible that larger households represent multigenerational homes, whereas having 3 household family members represents a nuclear family. More people in the household may result in more socializing at home and reduced risk of community measles exposure. Future research could focus on the implications of different familial composition for differential exposure risk in the community.

Exposure to hospital settings within the past 21 days was highly related to measles case status. Infants who had visited township or district hospitals did not have significantly higher odds of measles compared to those who did not visit, but infants who had been at a municipal hospital (OR: 5.21; 95% CI: 1.19, 22.82) or an infectious disease, pediatric, or other hospital (OR: 13.22; 95% CI: 6.13, 28.51) had greater odds of measles. This association with municipal, but not township, hospitals is possibly reflective of the extended period an individual might spend in hospital settings prior to admission to higher-tier municipal hospitals. A 2006 study from Jilin province found the odds of measles to be 9.7 times higher for children with visits to 2 separate hospitals (95% CI: 2.6, 38) but only 5.4 times higher with a visit to one hospital (95% CI: 1.9, 16).⁷ And Ma et al.'s study found that compared to infants with no hospital exposure, those with an outpatient visit had 9.7 times

higher odds of measles (95% CI: 6.9, 13.4), and those with inpatient hospitalization had 97.7 times higher odds of measles (95% CI: 45.4, 210).⁸ Measles could be easily transmitted at health facilities in China particularly if a large group of patients were waiting for treatment in the same room. Patient isolation for a highly infectious disease like measles is particularly important, and it is disconcerting that infectious disease hospitals appeared to be a significant risk factor for measles given their familiarity with and focus on communicable disease transmission. However, because we did not collect information on which hospitals measles cases are more likely to attend, and therefore cannot comprehensively explain any differences in risk of exposure between different types of hospitals as being dependent on disparate levels of infection control programs.

Very few infants were in childcare outside the home or had a non-family childcare provider in the home, and these factors were not significantly associated with measles case status. Only 17.1% of infant cases (and 0.6% of controls) had a known contact with another measles case.

Our controls were drawn from immunization clinics and we may have undersampled non-locals if they are less likely to use these clinics. Additionally, we are unable to assess whether measles cases had underlying conditions which predisposed them to be hospitalized, compared to controls. Our study's strengths included data collection over several years, which broadens its generalizability beyond a single outbreak, and the assessment of measles immunity in controls, enabling accurate identification of the source population. Studies which enroll infant controls regardless of their antibody status into a case-control study would have results that cannot separate the probability of measles acquisition with differential decay of maternal antibodies between different groups.

Measles control programs in China are directed primarily towards young children and adolescents, but most cases occur in infants ineligible for vaccination or adults with unknown vaccination status.^{4,9} Hospitals, particularly tertiary and specialty hospitals, emerged as an important focal point of measles transmission for infants and should be encouraged to enforce more effective infection control programs to reduce communicable disease transmission among infants in the institutional setting.

Acknowledgments

We are grateful for the many doctors and CDC staff in Tianjin who treat cases and report them into the surveillance system.

Funding

This work was supported by the National Institutes of Health, National Institute for Allergy and Infectious Diseases [grant number U01-AI-088671].

References

1. Perry RT, Murray JS, Gacic-Dobo M, Dabbagh A, Mulders MN, Strebel PM, et al. Progress towards regional measles elimination, worldwide, 2000–2014. *Wkly Epidemiol Rec.* 2015; 46(13):623–31.
2. Boulton ML, Wang X, Zhang Y, Montgomery JP, Wagner AL, Carlson BF, et al. A population profile of measles susceptibility in Tianjin, China. *Vaccine* [Internet]. 2016 Jun; 34(27):3037–43. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0264410X16302699>.

3. Ma C, Hao L, Zhang Y, Su Q, Rodewald L, An Z, et al. Monitoring progress towards the elimination of measles in China: an analysis of measles surveillance data. *Bull World Health Organ* [Internet]. 2014 May 1; 92(5):340–7. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4007128&tool=pmcentrez&rendertype=abstract>.
4. Qu J, Gao Z, Wan L, Zhu X, Ding Y, Li Y, et al. Analysis on Risk Factors of Infants Measles Incidence and Strategies of Measles Control. *Chinese J Vaccines Immun*. 2011; 17(2):152–154. [in Chinese].
5. Zhu X, Xie Q, Ren Y, Sun L. Analysis on A Measles Outbreak Caused by Hospital Explore. *Chinese J Vaccines Immun*. 2008; 14(5):398–402. [in Chinese].
6. Downes, F., Clark, P., Nowak, R., Berlin, B. Evaluation of dried blood spot specimens for measles antibody determination in outbreak control. Abstracts of the 92nd General Meeting of the American Society of Microbiology; Washington, DC. 1992;
7. Xiong C, Chen C, Shui T, Tao Y, Li G, Zhou J, et al. Analysis on Risk Factors for Measles Among 0–3 Years Old in Dehui City. *Chinese J Vaccines Immun*. 2006; 10(12):350–352. [in Chinese].
8. 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]
9. Wang X, Boulton ML, Montgomery JP, Carlson B, Zhang Y, Gillespie B, et al. The epidemiology of measles in Tianjin, China, 2005 – 2014. *Vaccine* [Internet]. 2015; 33(46):6186–91. Available from: <http://dx.doi.org/10.1016/j.vaccine.2015.10.008>.

Highlights

- This case-control study evaluated risk factors for acquiring measles.
- Visiting a municipal hospital or a specialty hospital was associated with measles.
- Visiting township or district hospitals was not associated with acquiring measles.

Table 1

Logistic regression comparing risk factors in infant measles cases versus IgG negative controls, Tianjin, China, 2011–2015.

	Control count (%)	Case count (%)	Adjusted OR (95% CI)	P-value ^a
Age				<0.0001
0–5 mo	295 (60.8%)	16 (19.5%)	0.03 (0.01, 0.10)	
6–8 mo	180 (37.1%)	52 (63.4%)	0.21 (0.07, 0.63)	
9–11 mo	10 (2.1%)	14 (17.1%)	ref	
Sex				0.0086
Male	270 (55.7%)	59 (72.0%)	ref	
Female	215 (44.3%)	23 (28.0%)	0.41 (0.21, 0.80)	
Urbanicity				0.0004
Urban	254 (52.4%)	24 (29.3%)	ref	
Suburban	86 (17.7%)	38 (46.3%)	4.80 (2.19, 10.54)	
Rural	145 (29.9%)	20 (24.4%)	2.28 (0.92, 5.63)	
Mother's education				0.2447
<College	229 (47.2%)	55 (67.1%)	1.54 (0.74, 3.19)	
College	256 (52.8%)	27 (32.9%)	ref	
Residency				0.0012
Local	443 (91.3%)	61 (74.4%)	ref	
Non-local	42 (8.7%)	21 (25.6%)	4.63 (1.84, 11.66)	
Travel within China				0.2407
No	474 (97.7%)	77 (93.9%)	ref	
Yes	11 (2.3%)	5 (6.1%)	2.65 (0.52, 13.55)	
Number of people in household				0.0090
3 people	175 (36.1%)	37 (45.1%)	ref	
4 people	310 (63.9%)	45 (54.9%)	0.43 (0.23, 0.81)	
Spent time on bus/train within past 21 days				0.3462
No	447(92.2%)	70(85.4%)	ref	
Yes	38 (7.8%)	12 (14.6%)	1.64 (0.59, 4.58)	
Spent time in hospital within past 21 days				<0.0001
No	327 (67.4%)	31 (37.8%)	ref	
Township hospital	72 (14.8%)	6 (7.3%)	0.81 (0.27, 2.39)	
District hospital	34 (7.0%)	6 (7.3%)	1.57 (0.52, 4.78)	
Municipal hospital	18 (3.7%)	4 (4.9%)	5.21 (1.19, 22.82)	
Infectious disease, pediatric, or other hospital	34 (7.0%)	35 (42.7%)	13.22 (6.13, 28.51)	
Known contact with measles case				
No	482 (99.4%)	68 (82.9%)		

	Control count (%)	Case count (%)	Adjusted OR (95% CI)	P-value ^a
Yes	3 (0.6%)	14 (17.1%)		
Number of children in household				
1	479 (98.8%)	81 (98.8%)		
2	6 (1.2%)	1 (1.2%)		
Childcare outside home				
No	478 (98.6%)	80 (97.6%)		
Yes	5 (1.0%)	0		
Childcare provider inside home				
No	474 (97.7%)	80 (97.6%)		
Yes	9 (1.9%)	0		

Notes:

OR, odds ratio; CI, confidence interval.

^aFrom Wald's Type 3 Chi-square test.