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Short communication

## Assessing measles vaccine failure in Tianjin, China

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## ABSTRACT

Despite increasing global measles vaccination coverage, progress toward measles elimination has slowed in recent years. In China, children receive a measles-containing vaccine (MCV) at 8 months, 18–24 months, and some urban areas offer a third dose at age 4–6 years. However, substantial measles cases in Tianjin, China, occur among individuals who have received multiple MCV doses. This study describes the vaccination history of measles cases 8 months – 19 years old. Data came from measles cases in Tianjin's reportable disease surveillance system (2009–2013), and from a case control study (2011–2015). Twenty-nine percent of those in the surveillance dataset and 54.4% of those in the case series received at least one dose of MCV. The minimum and median time-to-diagnosis since vaccination revealed an increase in time since vaccination for incremental doses. Considerable measles cases in Tianjin occur in vaccinated children, and further research is needed to understand the reasons for vaccine failure.

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## 1. Introduction

Measles is a highly communicable disease with a high burden among children in low- and middle- income countries (LMICs) [1]. Edmonston-derived vaccine strains are the most commonly used measles-containing vaccines (MCV) in the US and Europe. China uses a vaccine from a locally-isolated strain, the Shanghai- (or Hu-) 191 strain, which has been shown to have comparable safety and immunogenicity to the Edmonston-derived vaccine [2,3]. With these vaccines, measles has been targeted for elimination efforts across the globe [4,5]. Despite significant improvement in measles vaccination coverage, progress toward elimination has slowed in recent years [6]. Achieving elimination is complicated by the high communicability of measles, which requires high vaccination coverage in tandem with high vaccine efficacy.

Vaccine effectiveness (VE) of a single MCV dose, under ideal conditions, has ranged from 85% when administered at 9 months to 90–95% when given at 12 months [7,8]. The immune response to vaccination can be influenced by various host factors, including antibodies acquired through maternal antibody transfer, HIV infection, malnutrition, or other forms of immunosuppression [8]. Given

this variability of immune response, a universal recommendation to implement a two-dose MCV schedule was put forth by WHO in 2009 [9]. Whereas VE of MCV1 was reported to be as low as 73% in the WHO African region and 77% in the South-East Asian Region, after widespread adoption of the two-dose schedule, median VE was reported to be 94.1% (IQR, 88.3–98.3%). [10] Despite very high VE under test conditions and significant utilization of the two-dose schedule globally, VE is lower and much more variable than originally anticipated. Further investigations are necessary as to the cause of this discrepancy to reach immunity thresholds necessary for global elimination.

In China, children receive MCV at 8 months, 18–24 months, and in some large urban areas, including Beijing, Tianjin, and Shanghai, a third dose is provided at 4–6 years of age; vaccination coverage is high among children (>97% for the 1st and 2nd dose in Tianjin), although vaccination records for adults are unavailable [11]. Public health officials in China are concerned about the high number of measles cases which are occurring among individuals with multiple vaccinations<sup>1</sup>. This study sought to characterize the prevalence of vaccine failure by exploring (1) the vaccination history of childhood measles cases and (2) the differences in time-to-measles-diagnosis based on vaccination history in Tianjin.

Abbreviations: LMICs, low and middle income countries; MCV, measles-containing vaccine; VE, vaccine effectiveness.

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## 2. Methods

This study includes data from two datasets. The Tianjin surveillance dataset is described in detail elsewhere [12]. Measles is a nationally notifiable disease in China, and data regarding cases are reported into the China Information System for Disease Control and Prevention (CISDCP), a web-based communicable disease surveillance system. After a diagnosis of laboratory-confirmed measles, health care providers report the case through CISDCP. National, provincial, and district-level Centers for Disease Control and Prevention (CDCs) in China have access to disease data within their jurisdiction. This analysis includes measles data from 2009 to 2013 within Tianjin.

The International Collaborations in Infectious Diseases Research (ICIDR) dataset is described in detail elsewhere [11]. During the study period of 2011–2015, measles cases were enrolled into a case-control study. Every week, staff at the Tianjin CDC downloaded cases reported into CISDCP from the past week and randomly selected between 1 and 37 cases to enroll into this study based on overall case-load. For weeks with few cases, most cases would be enrolled, for weeks with more than 40 cases, only a fraction would be approached. This dataset did not contain individual birthdate records, only the age of the individual at the survey date, and their vaccination history. Birthdates were imputed based on the age at the survey date to approximate age at measles diagnosis. Age at case-diagnosis was determined by subtracting the imputed birth date from the date of diagnosis. The surveillance system collected information on whether the individual had 0, 1, or 2 or more doses, whereas in the case-series, selection options were 0, 1, 2, 3, or 4 doses given. More details about the surveillance system and the ICIDR study are available at <https://doi.org/10.6084/m9.figshare.7597277>.

This study focuses on individuals 8 months–19 years of age. Vaccination status was assessed through dates on vaccination cards, and this age group was selected to encompass those who were old enough to have received the measles vaccine based on Tianjin's vaccination schedule, but were not so old as to lack vaccination data. We reasoned this age group represented the population segment most likely to be vaccinated and not yet experiencing waning immunity from the vaccine; thus their vaccinations would be the best indication of protection against measles. Within this age range, the distribution of cases is reported by more specific age groupings, and the impact of vaccination is assessed by calculating the time interval between age at vaccination and age at disease, stratified by number of MCV doses. Statistical analysis was

conducted in SAS version 9.4 and R version 3.3.3 using the survival & survminer packages.

### 2.1. Ethical consideration

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

## 3. Results

The surveillance dataset contained data for 2945 measles cases from 2009 to 2013 and the case series dataset contained 500 measles cases from 2011 to 2015. Most cases were  $\geq 19$  years of age (61.1% and 78.0% in the surveillance and case series datasets, respectively). 19.0% of the cases in the surveillance dataset and 12.4% of the cases in the case series were in the study's target age range, 8 months–19 years (Table S1). Among the target age group, in the surveillance dataset, 57.4% of cases did not receive the measles vaccine, 29.0% received at least one dose MCV, and the remaining 13.6% did not know their vaccination status. In the case series, 43.5% of cases were unvaccinated and 54.4% of cases had received at least one dose of MCV, with 1 case unaware of vaccination status.

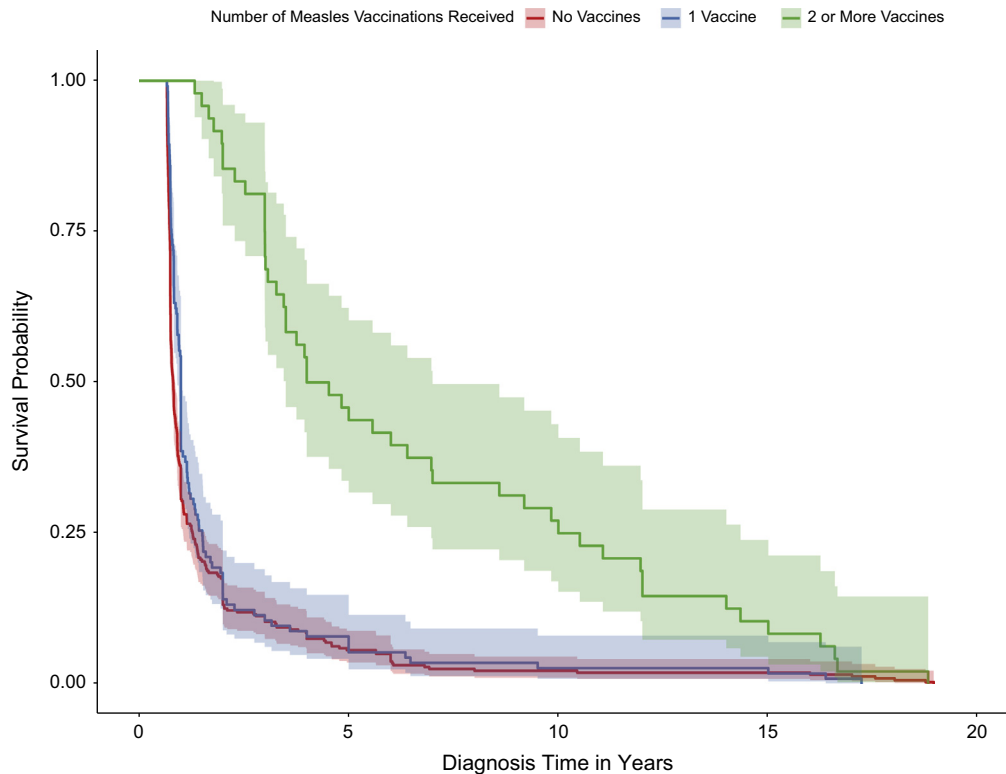
Analysis of the time-to-measles diagnosis stratified by vaccination status revealed increasing time-to-measles diagnosis with each successive dose for the case series and surveillance datasets (Table 1). Within the surveillance dataset, the median time-to-diagnosis was considerably longest for those who received two doses of MCV: 4.26 years for those with two doses, 1.00 year for those with one dose, and 0.82 years (9.8 months) for those unvaccinated. The minimum time-to-diagnosis since the first measles vaccination (administered at  $\sim 8$  months) also increased with the number of doses received. A similar trend was observed in the case-control dataset, with median time-to-diagnosis increasing from 301 days for those who received only one vaccine (approximately 9.8 months), to 7.49 years for those who received two or more vaccinations.

Kaplan-Meier survival curves from the Tianjin surveillance dataset (Fig. 1) corroborate the findings in Table 1, and reveal that those who received zero measles vaccinations were the youngest at diagnosis. The results showed statistically significantly different time-to-disease onset by dose (log-rank p-value < 0.0001). While one dose of measles vaccine somewhat delayed the diagnostic onset for measles, having  $\geq 2$  vaccinations significantly delayed the time-to-diagnosis.

**Table 1**  
Distribution of Measles time-to-diagnosis since in days (and years) stratified by measles vaccination history, children aged 8 months – 19 years, surveillance and case-control datasets.

| Measles Diagnosis Time Since Vaccine       | Minimum    | Median       | Mean         | Maximum      |
|--|------------|--------------|--------------|--------------|
| <i>Case-Control Dataset (2011–2015)</i>    |            |              |              |              |
| Missing/No Dose Information (n = 21)       | 247 (0.68) | 518 (1.42)   | 1136 (3.11)  | 6381 (17.48) |
| 1 Dose Received (n = 13)                   | 248 (0.68) | 301 (0.82)   | 1270 (3.48)  | 5657 (15.50) |
| Diagnosis time since vaccination (n = 12)* | 4 (0.01)   | 41 (0.08)    | 649 (1.78)   | 4222 (11.57) |
| At least 2 doses received (n = 12)         | 560 (1.53) | 2735 (7.49)  | 2434 (6.67)  | 4935 (13.52) |
| Diagnosis time since vaccination (n = 12)* | 372 (1.02) | 2349 (6.44)  | 2134 (5.86)  | 4593 (12.58) |
| <i>Surveillance Dataset (2009–2013)</i>    |            |              |              |              |
| Missing/No Dose Information (n = 76)       | 272 (0.75) | 5655 (15.49) | 4011 (10.99) | 6909 (18.93) |
| Non-Vaccinated (n = 321)                   | 242 (0.66) | 298 (0.82)   | 601 (1.65)   | 6919 (18.96) |
| 1 Dose Received (n = 114)                  | 242 (0.66) | 364 (1.00)   | 664 (1.82)   | 6291 (17.24) |
| Diagnosis time since vaccination (n = 99)* | 0 (0)      | 24 (0.07)    | 186 (0.51)   | 3253 (8.91)  |
| At least 2 doses received (n = 48)         | 485 (1.33) | 1557 (4.26)  | 2439 (6.68)  | 6871 (18.82) |
| Diagnosis time since vaccination (n = 33)* | 301 (0.82) | 1192 (3.27)  | 1778 (4.87)  | 5806 (15.91) |

\* Additionally, for those who received any doses of the measles vaccine, we report the distribution of time-to infection since the first dose of measles vaccine in days (i.e. at approximately 8 months). This was included to clarify the time to infection since initiating the vaccination schedule.



**Fig. 1.** Product-Limit Survival Estimates of diagnosis time, in years, of measles diagnosis, stratified by the number of measles vaccinations received: 0, 1, or 2 or more for the Tianjin surveillance dataset among individuals aged 8 months – 19 years.

#### 4. Discussion

This analysis revealed that over a quarter of cases of measles in Tianjin, China had received  $\geq 1$  dose prior to contracting the disease. Time-to-event analysis also showed that those with two doses or more of MCV had significantly delayed onset of measles, though the onset of measles for those who received only one dose MCV was similar to those who were unvaccinated. This evidence points to the fact that one vaccine is insufficient, and perhaps that the dose administered at 8 months of age, one of the earliest suggested dose times in the world for MCV, may have a reduced immune response, producing the similar time-to-measles diagnosis curves. Accordingly, the second dose at 18–24 months is necessary for full protection.

This study reveals that within a small subset of measles cases in Tianjin who have recorded vaccination history, there is a high burden of measles among those who have been vaccinated. As such, a vaccine effectiveness (VE) study may be warranted to explore potential reasons for these breakthrough cases. Measles VE studies have found variable effectiveness of the measles vaccine, ranging from 23.1% for one dose and 63.4% for two doses in Micronesia [13], to 70% in Uganda [14] to 96.7% for one dose and 99.7% for two doses with waning immunity in Australia [15]. Potential reasons for variable VE and vaccine failure were suspected to be due to improper cold chain management [13,16] and waning immunity [13,15]. Our findings are similar to those of Durrheim et al., in which multiple countries approaching elimination found that a large proportion of cases were vaccinated [16]. Long-term VE could also vary by age at administration. A recent study in China found similar immunogenicity of measles-containing vaccine given at 8 versus 12 months [17], but a long-term study of measles antibodies in children who had been vaccinated early (at 9 months) during an outbreak in The Netherlands found that children vaccinated at

9 months had significantly lower concentrations of measles antibodies compared to a control group at 4 years of age [18].

This study has limitations: first, these two datasets may not be representative beyond Tianjin to all of China, limiting the generalizability of the findings. Given the small number of cases for whom there was available vaccination data in both datasets, there may be bias due to missing data. Additionally, potential measurement error may have resulted in misclassification of the number of doses received or if vaccination status was unknown, small numbers of cases in certain groupings decrease potential for statistical significance testing, and there may be duplicate cases between the two datasets. There may also be bias in the selection of cases into the ICIDR case-series. Finally, the lack of more recent data from Tianjin limits the potential to explore trends in measles vaccination and subsequent disease. Given these limitations, this study can primarily serve for hypotheses generation indicating areas for further study.

#### 5. Conclusions

This analysis of measles cases in Tianjin found that among children with a recorded vaccine history, a substantial number of those who contracted measles had received at least one MCV dose. Although time-to-diagnosis following vaccination increases with receipt of each successive dose of measles vaccine, the fact that 8.5% of cases in the surveillance dataset and 26% in the case series contracted measles despite 2 or more doses of MCV is surprising. This also has implications for the VE of the measles vaccine series in Tianjin. Future research is needed to identify whether this is due to primary or secondary vaccine failure, and whether cold chain management, low vaccine efficacy, scheduled dose timing, or host factors such as co-morbidities and waning immunity might be

responsible. This analysis motivates further research to discern the cause of these breakthrough cases in both outbreak and isolated case settings.

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### Declaration of Competing Interest

The authors have no potential, perceived, or real conflicts of interest relevant to this article to disclose. NBM wrote the first draft of the article.

### Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2019.05.005>.

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