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The impact of supplementary immunization activities on the epidemiology of measles in Tianjin, China

Abram L. Wagner [a,*], Ying Zhang [b], Bhramar Mukherjee [c], Yaxing Ding [b], Eden V. Wells [a], Matthew L. Boulton [a]

[a] University of Michigan, Ann Arbor, Department of Epidemiology, 1415 Washington Heights, Ann Arbor, MI 48109, USA
[b] Division of Expanded Programs on Immunization, Tianjin Centers for Disease Control and Prevention, Hedong District, Tianjin, China
[c] University of Michigan, Ann Arbor, Department of Biostatistics, Ann Arbor, Michigan, USA

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SUMMARY

Objectives: China has repeatedly used supplemental immunization activities (SIAs) to work towards measles elimination, but it is unknown if the SIAs are reaching non-locals – migrants from rural to urban areas. This study characterized temporal trends in measles incidence by local and non-local residency and evaluated the impact of SIAs on measles incidence in Tianjin, China.
Methods: Daily measles case-counts were tabulated separately by residency. These two datasets were combined so that each day had two observations. Poisson regression was conducted using generalized estimating equations with an exchangeable working correlation structure to estimate rate ratios (RRs).
Results: There were 12 465 measles cases in Tianjin over the 10-year period. The rate of measles was higher in non-locals than locals before the 2008 SIA (RR 3.60, 95% confidence interval (CI) 3.27–3.96), but this attenuated to a RR of 1.22 between the 2008 and 2010 SIAs (95% CI 1.02–1.45). Following the 2010 SIA, non-locals had a lower rate of measles (RR 0.78, 95% CI 0.69–0.87).
Conclusions: The disparity in measles incidence between locals and non-locals was reduced following two SIAs. Sustained public health interventions will be needed to maintain low measles incidence among non-locals given the ongoing migration of people throughout China.

1. Introduction

Measles was officially eliminated in the Americas in 2002,[1] and the other five regions of the World Health Organization (WHO) are slated for measles elimination by 2020.[2] This remarkable public health success in control of a highly infectious disease has been made possible through the universal recommendation of measles vaccination. Prior to the advent of the measles vaccine, 90% of people were infected by age 20 years, resulting in 100 million cases and six million deaths worldwide each year.[3] As vaccination coverage has increased, the number of deaths from measles globally has decreased: there were 631 200 deaths in 1990 and 125 400 in 2010.[4] In 2014, there were 114 900 deaths due to measles.[5]

The Chinese government is committed to national measles elimination, even though the country did not meet its original elimination target in 2012. China's initial goal to reduce measles incidence by 90% between 1965 and 1995 resulted in an impressive decline from over 1000 cases per 100 000 in the 1960s, prior to measles vaccine availability, to 5.7 cases per 100 000 in the late 1990s.[6] The Chinese government's subsequent goals to reduce measles incidence by 90% from 2000 to 2010 and to eliminate measles by 2012 were not realized, as disease incidence decreased more gradually from 6 cases per 100 000 in 2000 to only 2.86 in 2010,[7–9] followed by a slight increase in cases between 2011 and 2014. It is unclear why there have been increases in the number of cases in some recent years, and, more broadly, why China has been unable to achieve sustained reductions in measles leading to elimination, especially given that China has invested heavily in both routine immunization services and repeated supplementary immunization activities (SIAs).[7]

China introduced its own measles-containing vaccine (MCV) to market in 1966,[10] which was subsequently integrated into the Expanded Program on Immunization (EPI) in 1978. The EPI is a government-funded initiative to provide select vaccines for free to all children.[11] Nationwide, the EPI in China offers a first dose of

* Corresponding author.
E-mail address: awag@umich.edu (A.L. Wagner).

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MCV at 8 months and the second at 18 to 24 months.[11] Additionally, some administrative divisions offer a third dose of MCV when the child is 5 years of age (since 2007 in Tianjin), because MCV dose 1 has low immunogenicity when administered to infants under 1 year of age.[12]

According to the WHO, MCV dose 2 can be given either as part of routine immunization services or in SIAs, which are mass immunization events within a defined geographical region.[13] Between 2004 and 2009, 25 of 31 province-level administrative divisions in mainland China implemented measles SIAs, collectively vaccinating 164 million children.[14] In 2010, a single SIA delivered 102.3 million doses nationwide.[15] In Tianjin, the 2008 SIA administered 1.3 million doses of measles vaccine to children between the ages of 8 months and 14 years; the 2010 SIA, which targeted all children aged 8 months to 4 years, resulted in the administration of 450 000 MCV doses.[16]

Some researchers have suggested that measles outbreaks in China are potentiated by the over 260 million members of the country's highly mobile population, the so-called floating population,[6,7,17] who move from the countryside into cities.[18,19] In contrast to locals, these 'non-locals' do not reside in the province recorded in their official residency papers, or 'hukou', and lack access to some government entitlement programs.[19,20] Non-local children are offered EPI vaccines for free, just like local children, but some studies have shown that non-locals have lower coverage of EPI vaccines,[21] possibly due to the difficulties in trying to find and identify children who have newly relocated.[7] For example, one study in Zhejiang Province showed that appropriate-for-age MCV dose 1 coverage was 72.0% in locals and 36.3% in non-locals.[22] Previous research on measles cases in China has not adequately addressed the role of non-locals in measles incidence, particularly given that the non-local population has increased rapidly in recent years, they can obtain measles vaccinations for free, and that both their place of origin and destination province likely had two SIAs within the past decade.[6,7,14] Therefore, additional research is needed to fully characterize the changing epidemiology of measles in China in the elimination era. In this study, data from the Tianjin notifiable disease surveillance system were used to characterize temporal trends in measles incidence in non-locals versus locals and to evaluate the impact of SIAs on measles incidence.

2. Methods

2.1. Study population

Tianjin is a wealthy municipality 120 km southeast of Beijing. There has been substantial migration into this city from outside areas: in 2013, an estimated 4.7 million of the 14.7 million persons residing in Tianjin were non-locals.[23] Although Tianjin does contain densely-populated urban districts, the adjacent suburban districts and rural counties also figure in the municipality's administration. The health infrastructure in Tianjin includes both a municipality-wide Center for Disease Control and Prevention (CDC) with jurisdiction over the entire municipality, as well as district-level CDCs.

Measles is a notifiable infectious disease in China,[24] and after undergoing a clinical diagnosis by a physician, suspected cases in hospitals are reported to the National Infectious Disease Monitoring Information System (NIDMIS). These cases are investigated by staff from district-level CDCs. NIDMIS includes demographic information for each case (birth date, sex, district of residence, residency), vaccination status (unknown, $\geq$1 dose, or 0 doses), and dates of measles diagnosis and report. Both laboratory-confirmed and clinically confirmed measles cases were included in this study. Laboratory-confirmed cases are required to have a positive IgM result reported from serum, or to include a report of wild-type measles virus isolated by RT-PCR.[25] A case with a clinical diagnosis is one in which the patient demonstrates symptoms of fever and rash, in combination with the classic prodrome of cough, coryza, and/or conjunctivitis.

2.2. Derived variables

The first of the two municipal-wide SIAs in Tianjin occurred in December 2008 and the second in September 2010. Measles cases were grouped into three time periods, depending on when they were reported to NIDMIS relative to the SIAs. Cases reported on January 1, 2005 through December 4, 2008 were considered 'before the 2008 SIA'; cases that were reported on December 5, 2008 through September 20, 2010 occurred 'between the 2008 and 2010 SIAs'; all cases reported on September 21, 2010 through December 31, 2014 were 'after the 2010 SIA'.

Provinces in China are divided into district-level administrative regions (either districts or counties, with the difference between the two based on historical designations). The districts in Tianjin were grouped by urbanicity, based on typical government categorizations. Urban areas are home to more high-income industries and have better access to public services than suburban and rural areas.[26,27] The seven urban districts in Tianjin are Heping, Hedong, Hexi, Nankai, Hebei, Hongqiao, and Binhai New Area. Four districts are categorized as suburban: Jinnan, Dongli, Xiqing, and Beichen. Two districts (Baodi and Wuqing) and three counties (Ji, Jinghai, and Ninghe) are considered rural.

2.3. Statistical analysis

The distribution of cases was cross-tabulated by sex, urbanicity, residency (non-local vs. local), vaccination status, and time period. The rate of measles was plotted over time, with the rate calculated by dividing case-counts by annual municipal population figures that were available from the China Statistical Yearbook.[23] Separate population figures were available each year for both locals and non-locals, except for 2014, for which data were not available and the 2013 figures were used instead.

An interesting exploratory analysis of the time-series of measles was first performed. Monthly case-counts from January 2005 to December 2014 were tabulated for the total population and separately by residency and age group. Ages were categorized into three groups based on whether the person would have been targeted in the 2008 SIA: $<$8 months, 8 months to $<$15 years, and $\geq$15 years. Subsequently, observed monthly case-counts from January 2005 to November 2008 were used to forecast monthly case-counts from December 2008 to December 2014, according to a standard time-series analysis using exponential smoothing with additive error, long-term secular trend, and seasonal components.[28] The observed case-count series was then compared with the predicted case-count series, with the understanding that predicted case-counts based on data prior to the SIA reflect the counterfactual case-counts that would be expected if the SIA had not taken place.

To make formal inferences about rates in locals and non-locals, daily case-counts were calculated separately for these two groups. These two datasets were then combined into a single dataset, whereby each day had two observations, one for locals and the other for non-locals. Multivariable Poisson regression was conducted using generalized estimating equations with an exchangeable working correlation structure, and robust standard errors were used to account for potential correlation on the counts observed on the same day. The natural log of the population by residency was added to the model as an offset to obtain rates. The main predictors in this model were residency, time period, and an interaction between residency and time period. This model also