International Journal of Infectious Diseases 45 (2016) 103–108

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

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

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ARTICLE INFO

Article history:
Received 9 September 2015
Received in revised form 16 February 2016
Accepted 6 March 2016

Corresponding Editor: Eskild Petersen, Aarhus, Denmark.

Keywords:
Measles
Mass vaccination
China

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

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http://dx.doi.org/10.1016/j.ijid.2016.03.005

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 controlled for a lag 1 autoregressive term (AR1) (to account for correlation in case-counts on successive days) and seasonality of measles. Measles seasonality was the value of weekly measles case-counts that came from the seasonal component of a daily time-series, which was decomposed into seasonal, trend, and remainder components using LOESS;[29] measles seasonality represents the variation in measles incidence over time (with a peak in cases in April and May compared to other months).

The data were analyzed in R,[30] with the packages 'forecast' (for the exploratory time-series analysis) and 'geepack' (for the inferential statistics analysis).[28,31]

2.4. Ethics statement

This study was limited to analyses of de-identified cases. Because it fell under standard public health surveillance activities, the University of Michigan Institutional Review Board determined that the study was exempt from regulation.

3. Results

From January 1, 2005 through December 31, 2014 there were a total of 12 465 cases of measles reported in Tianjin, China. Slightly more cases were male (57.6%) than female. A majority were locals (74.0%), and there was an even distribution of cases from urban (43.0%), suburban (25.1%), and rural (31.9%) districts. Just more than half of the cases (58.1%) occurred before the 2008 SIA; 17.2% of all cases occurred in the 21 months between the two SIAs and 24.8% were reported after the second municipality-wide SIA in 2010.

Table 1 shows the distribution of demographic and vaccination characteristics overall and by residency. There was a bimodal distribution of cases by age, with most cases occurring either in children under 5 years of age or adults over 15 years of age, the majority of whom were under 40 years of age. Compared to locals, non-local cases were more likely to be younger than 30 years of age ($p < 0.0001$). Additionally, most cases aged 8 months to <15 years were unvaccinated (60.2%), and more non-locals (57.8%) than locals (49.8%) in this age category had not received a measles vaccine ($p < 0.0001$).

The count and frequency of demographic characteristics relative to the SIAs is shown in Table 2. The proportion of childhood cases who were vaccinated was lower between the SIAs (19.4%) and after the 2010 SIA (32.3%) relative to prior to the 2008 SIA (36.4%), although there was a sizeable proportion of children with an unknown vaccination status in the early years of this study ($p < 0.0001$). Over time, progressively more measles cases were laboratory-confirmed and not solely diagnosed from clinical criteria; before the 2008 SIA, 54.4% were laboratory-confirmed, whereas 93.6% were after the 2010 SIA ($p < 0.0001$).

Figure 1 shows the decline in the rate of measles over time and that the disparity in rates between non-locals and locals had disappeared by 2010. Figure 2 shows the similar seasonal pattern for both locals and non-locals. A difference in the configuration of measles counts over time was seen across the different age groups. For infants <8 months of age and persons ≥15 years of age, who were not vaccinated in either SIA, there was a sharp increase in the number of cases in 2010 compared to 2009, whereas for children from 8 months through 14 years of age, this increase was in line with predicted values from the time-series forecast. For all time-series graphs, the observed monthly case-count from 2011 through 2013 was less than the predicted values of the counterfactual forecast.

Results of the interaction term between residency and time period in the multivariable regression are presented in Table 3. A substantial disparity in the rate of measles between non-locals and locals was observed before the SIAs (rate ratio (RR) 3.60, 95% confidence interval (CI) 3.27–3.96), but this attenuated, with

Table 1
Demographic characteristics of measles cases in Tianjin, China, 2005–2014

	Overall Count (%)	Local Count (%)[a]	Non-local Count (%)[a]	p-Value[b]
Overall	12465	8833	3097	
Sex				0.3164
Male	7177 (57.6%)	5003 (56.6%)	1828 (59.0%)	
Female	5288 (42.4%)	3830 (43.4%)	1269 (41.0%)	
Urbanicity				<0.0001
Urban	5350 (43.0%)	4006 (45.4%)	1150 (37.2%)	
Suburban	3122 (25.1%)	1415 (16.0%)	1501 (48.5%)	
Rural	3975 (31.9%)	3410 (38.6%)	442 (14.3%)	
Age				<0.0001
<8 months	1684 (13.5%)	1278 (14.5%)	339 (10.9%)	
8 months to <5 years	2301 (18.5%)	1347 (15.2%)	831 (26.8%)	
5 to <15 years	860 (6.9%)	502 (5.7%)	292 (9.4%)	
15 to <30 years	3692 (29.6%)	2385 (27.0%)	1124 (36.3%)	
30 years and above	3928 (31.5%)	3321 (37.6%)	511 (16.5%)	
Time period				<0.0001
Before 2008 SIA	7237 (58.1%)	4727 (53.5%)	2007 (64.8%)	
Between SIAs	2140 (17.2%)	1651 (18.7%)	458 (14.8%)	
After 2010 SIA	3088 (24.8%)	2455 (27.8%)	632 (20.4%)	
Vaccination status[c]				<0.0001
0 doses	1602 (60.2%)	921 (49.8%)	649 (57.8%)	
≥1 dose	1061 (39.8%)	795 (43.0%)	265 (23.6%)	
Unknown	498 (18.7%)	133 (7.2%)	209 (18.6%)	
Case definition				<0.0001
Laboratory	8479 (68.0%)	6342 (71.8%)	2089 (67.5%)	
Clinical	3985 (32.0%)	2490 (28.2%)	1008 (32.5%)	

SIA, supplementary immunization activity.
[a] 535 people with unknown residency status are excluded in these calculations.
[b] From a Pearson's Chi-square test of independence.
[c] For children aged 8 months to <15 years.

Table 2
Distribution of measles cases by timing relative to supplementary immunization activities (SIAs), Tianjin, China, 2005–2014

	Before 2008 SIA Count (%)	Between SIAs Count (%)	After 2010 SIA Count (%)	p-Value[a]
Overall	7237	2140	3088	
Sex				<0.0001
Male	4204 (58.1%)	1306 (61.0%)	1667 (54.0%)	
Female	3033 (41.9%)	834 (39.0%)	1421 (46.0%)	
Residency				<0.0001
Local	4727 (70.2%)	1651 (78.3%)	2455 (79.5%)	
Non-local	2007 (29.8%)	458 (21.7%)	632 (20.5%)	
Urbanicity				<0.0001
Urban	2908 (40.2%)	981 (46.2%)	1461 (47.3%)	
Suburban	1911 (26.4%)	501 (23.6%)	710 (23.0%)	
Rural	2417 (33.4%)	641 (30.2%)	917 (29.7%)	
Age				<0.0001
<8 months	843 (11.6%)	422 (19.7%)	419 (13.6%)	
8 months to <5 years	1585 (21.9%)	399 (18.6%)	317 (10.3%)	
5 to <15 years	796 (11.0%)	28 (1.3%)	36 (1.2%)	
15 to <30 years	2444 (33.8%)	569 (26.6%)	679 (22.0%)	
30 years and above	1569 (21.7%)	722 (33.7%)	1637 (53.0%)	
Vaccination status[b]				<0.0001
0 doses	1071 (45.0%)	298 (69.8%)	233 (66.0%)	
≥1 dose	864 (36.3%)	83 (19.4%)	114 (32.3%)	
Unknown	446 (18.7%)	46 (10.8%)	6 (1.7%)	
Case definition				<0.0001
Laboratory	3935 (54.4%)	1653 (77.2%)	2891 (93.6%)	
Clinical	3301 (45.6%)	487 (22.8%)	197 (6.4%)	

[a] From a Pearson's Chi-square test of independence.
[b] For children aged 8 months to <15 years.

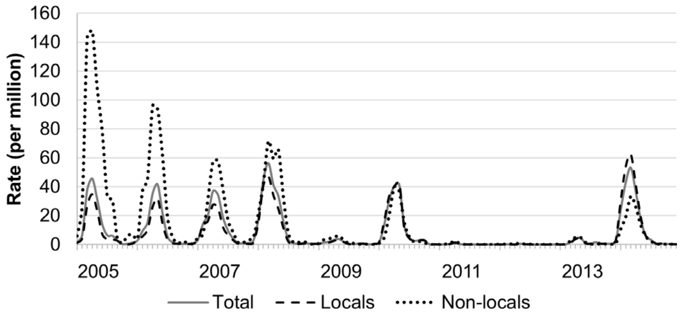

Figure 1. Monthly rate of measles in Tianjin, China, in the total population and by residency.

non-locals exhibiting a rate of measles 1.22 times higher between the SIAs compared to locals (95% CI 1.02–1.45). After the 2010 SIA, non-locals had a lower rate of measles (RR 0.78, 95% CI 0.69–0.87), consistent with the exploratory analysis.

4. Discussion

SIAs have served globally as a strategy to realize progress towards the elimination of vaccine-preventable diseases.[1,32,33] In this study, a substantial reduction in the number of measles cases was found over a 10-year period in Tianjin, China, following the implementation of two municipality-wide SIAs. There was a dramatic reduction in the incidence of disease in non-locals, whereas the incidence stayed more stable in locals. SIAs have been shown to be key in eliminating measles in the Americas,[1] and in reducing the incidence of disease in Eastern Europe.[32] A study of 15 province-wide SIAs in China during 2004–2008 found that there was on average an 88.1% decrease in measles incidence the year after an SIA compared to the average rate in the preceding 5 years.[14] Especially for countries and regions with less capacity to reliably deliver vaccines through routine immunization services,

Table 3
Rate ratio estimates for measles by residency and timing relative to supplementary immunization activities (SIAs), Tianjin, China, 2005–2014

	RR[a]	95% CI
Non-local vs. local		
Before 2008 SIA	3.60	3.27–3.96
Between SIAs	1.22	1.02–1.45
After 2010 SIA	0.78	0.69–0.87

RR, rate ratio; CI, confidence interval.
[a] Poisson regression model using generalized estimating equations controlled for seasonality, count of measles in the previous day, residency, and SIA time points.

SIAs appear to be a cost-effective method to distribute the second dose of measles vaccine.[33]

Nevertheless, there are well-recognized disadvantages to SIAs, including the future accumulation of susceptible children who were too young to have been vaccinated after the SIA. In this study, a large increase in measles cases was observed among young infants and young adults in 2010, 2 years after the first municipality-wide SIA. Similarly, 3 years after a major SIA in Xinjiang, China, a large-scale measles outbreak occurred, predominantly in children born after the SIA.[14] The characterization of measles incidence for several years after an SIA is, therefore, essential in order to avoid the common practice of over-ascribing success in disease control to an SIA. Although SIAs can clearly reduce the number of cases, they may also shift the burden of disease to later birth cohorts or foster the development of a multiannual cycle of heightened measles transmission instead of producing sustained reductions in measles incidence.[14]

The geographic impact of SIAs is limited because SIAs vaccinate people residing within a defined region. Before 2009, provinces in China implemented SIAs at separate times, whereas in 2010 there was a synchronized, nationwide event. This latter SIA would be better able to reach the non-local population that moves in between provinces. This may be one explanation for why a local/non-local disparity in measles incidence persisted in the 2 years

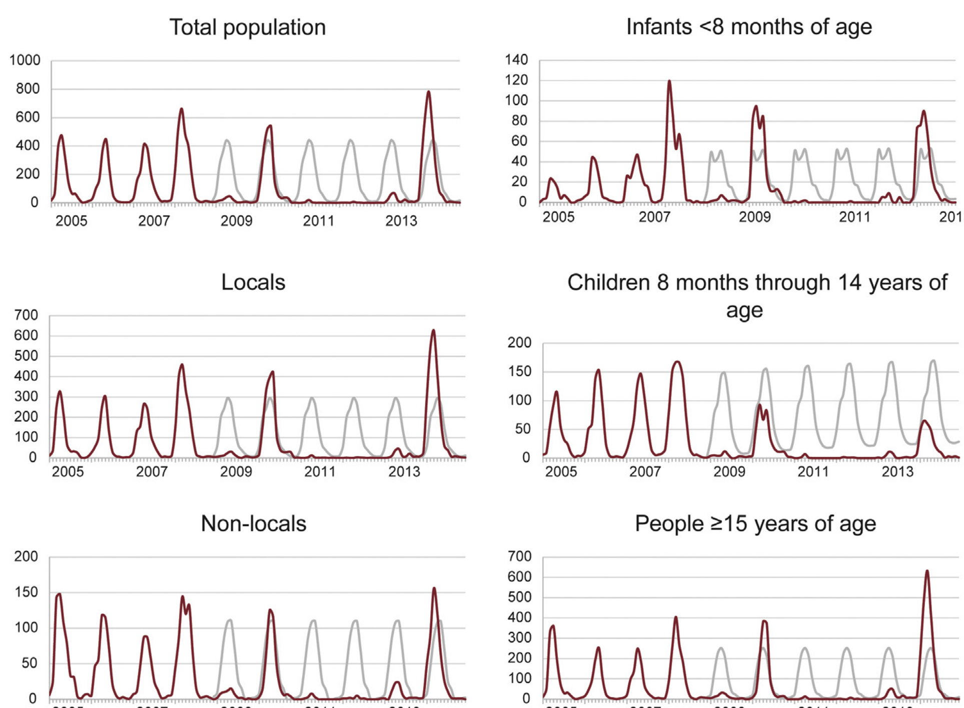

Figure 2. Modeled (grey line) and observed (red line) cases of measles in Tianjin, China. Black arrows indicate the timing of supplementary immunization activities.

after the 2008 SIA, but not after the 2010 SIA. Numerous studies in China have suggested that migrants are a cause of high measles incidence,[6,14,34] although a notable shortcoming has been that these previous studies did not quantify the disparity in rates between locals and non-locals. In fact, it was found in the present study that the decrease in measles incidence over time was largely driven by decreases in the incidence among non-locals. It is important to continue efforts to ensure high vaccination coverage in non-locals, because as unvaccinated migrants enter a population, this theoretically leads to a larger peak number of measles cases every second year.[35,36] As increased numbers of migrants continue to move into Tianjin and other cities, China should consider using its surveillance system (NIDMIS) not only to monitor the seasonality and incidence of measles cases, but also to identify high-risk groups and forecast future epidemiological scenarios. In particular, establishing linkages between NIDMIS and other databases, such as immunization registries, population statistical databases, and hospital records, could increase the usefulness of NIDMIS to identify susceptible populations and could provide data to research correlates of disease. In fact, it was found that the incidence of measles among locals was relatively steady across the entire study period, except for the years immediately following the SIAs.

A limitation of this study is the validity of the population figures, particularly for non-locals. The data on population size came from the China Statistical Yearbook, but China has changed how it estimates the size of the non-local population over time.[37] However, it is widely reported that population growth in Chinese cities over the past decade has primarily been driven by migration and not through natural growth,[38] which is what is observed in the population figures used in this study. In addition, 2014 data on non-local and local population sizes were not available, and the use of 2013 figures for 2014 likely overestimated measles incidence for non-locals in that year given their population growth. Future research that explores vaccination programming in China could better determine why locals and non-locals differ in their changes in incidence over time. Another limitation is that this study estimated the impact of SIAs by comparing measles incidence before and after the intervention, but a number of other conditions could affect incidence, including changing dynamics in who has been vaccinated or has contracted a measles infection, as well as improved routine immunization services for recent migrants. For example, Tianjin has introduced a program in recent years that pays immunization clinic doctors to find migrant children and enroll them at clinics. Lastly, both clinically confirmed and laboratory-confirmed cases of measles were included in this study. The large proportion of cases vaccinated prior to 2008 (and at a time when many cases were not laboratory-confirmed) could be due in part to clinical misdiagnoses.

An important strength of this study is that there was access to disease information from a comprehensive, population-based surveillance system and population information from the China Statistics Yearbook, which enabled a comparison of the burden of disease between locals and non-locals, controlling for different population sizes. Evaluations of interventions in other countries could similarly use existing surveillance databases and follow this approach of first conducting an exploratory analysis and then a formal regression-based model of incidence before and after an intervention.

In conclusion, a time-series analysis of reported measles cases in Tianjin, China, from 2005 through 2014, revealed a steep reduction in measles cases overall and a disparity in rates between locals and non-locals, which eventually disappeared after the second of two municipality-wide SIAs. Because of the ongoing and significant internal migration of people in China, sustained efforts will be needed to keep measles incidence low among non-locals in urban settings: SIAs on a supra-provincial scale could reach future migrants to cities, mop-up SIAs could specifically target new arrivals to an area, and routine immunization services could be improved to more efficiently give new arrivals access to EPI vaccines. During the elimination period, the dissemination of information from disease registries will be an important part of characterizing disease in subpopulations and evaluating ongoing control efforts.

Acknowledgements

We thank the staff at the Tianjin CDC for providing us with the data, and the health care workers at the municipal and district-level CDCs for their diligence in investigating the measles cases. This work was supported by the National Institutes of Health, Institute for Allergy and Infectious Diseases (grant number U01-AI-088671). The study sponsor had no role in the study design, data collection, data analysis and interpretation, manuscript preparation, or decision to submit the manuscript for publication.

Conflict of interest: No competing interest declared.

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