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Seasonal influenza vaccine effectiveness against medically attended influenza illness among children aged 6–59 months, October 2011–September 2012: A matched test-negative case–control study in Suzhou, China

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Abstract

Background: Seasonal influenza infections among young children in China lead to substantial numbers of hospitalizations and financial burden. This study assessed the seasonal influenza vaccine effectiveness (VE) against laboratory confirmed medically attended influenza illness among children in Suzhou, China, from October 2011–September 2012.

Methods: We conducted a test-negative case–control study among children aged 6–59 months who sought care at Soochow University Affiliated Children's Hospital (SCH) from October 2011–September 2012. A case was defined as a child with influenza-like illness (ILI) or severe acute respiratory infection (SARI) with an influenza-positive nasopharyngeal swab by rRT-PCR. Controls were selected from children presenting with ILI or SARI without laboratory confirmed influenza. We conducted 1:1 matching by age and admission date. Vaccination status was verified from the citywide immunization system database. VE was calculated with conditional logistic regression: (1 − OR) × 100%.

Result: During the study period, 2634 children aged 6–59 months presented to SCH with ILI (1975) or SARI (659) and were tested for influenza. The vaccination records were available for 69% (1829; ILI: 1354, SARI: 475). Among those, 23% (427) tested positive for influenza, and were included as cases. Among influenza positive cases, the vaccination rates were 3.2% for SARI and 4.5% for ILI. Among controls, the vaccination rates were 13% for SARI, and 11% for ILI. The overall VE against lab-confirmed medically attended influenza virus infection was 67% (95% CI: 41–82). The VE for SARI was 75% (95% CI: 11–93) and for ILI was 64% (95% CI: 31–82).

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Conclusions: The seasonal influenza vaccine was effective against medically attended lab-confirmed influenza infection in children aged 6–59 months in Suzhou, China in the 2011–12 influenza season. Increasing seasonal influenza vaccination among young children in Suzhou may decrease medically attended influenza-associated ILI and SARI cases in this population.

Keywords

Influenza; Children; Test-negative case–control; Vaccine effectiveness; China

1. Introduction

Seasonal influenza epidemics cause substantial morbidity and mortality in children, generating increased healthcare utilization [1–3]. Children younger than 5 years of age have high rates of hospitalization attributable to influenza which may be similar to or greater than rates among the elderly [4–7]. Although the World Health Organization (WHO) and the Chinese Center for Disease Control and Prevention (China CDC) recommend annual vaccination with influenza vaccine for young children aged 6 months to 5 years [8,9], influenza vaccination coverage among children less than 5 years of age in China has been low, varying from a low of 8.6% to a high of 26.4% between the 2009 and the 2012 influenza seasons, with no increasing trend by year [10,11]. Limited data from China regarding seasonal influenza vaccine effectiveness among young children is one of the obstacles to increasing influenza vaccine coverage in this population in China.

Although randomized, placebo-controlled trials provide convincing data about the protection against infection and illness conferred by the influenza vaccine, they are not always feasible [12,13]. In recent years, an observational study design termed “test-negative case–control” has become popular for post-licensure observational studies of the effectiveness of influenza vaccination. Two of the advantages of the test-negative design to estimate VE against medically attended influenza illness are that it is less susceptible to bias from misclassification of influenza infection and to confounding by health care-seeking behavior [14,15].

In this study, we assessed the effectiveness of influenza vaccine in preventing laboratory-confirmed influenza infection among children aged 6–59 months who sought care in Soochow University Affiliated Children’s Hospital (SCH) for influenza-like illness (ILI) or severe acute respiratory infection (SARI) during October 2011–September 2012 influenza.

2. Methods

2.1. Study site

This study was conducted at SCH in Jiangsu Province, China. SCH is the single tertiary children’s hospital serving Suzhou district. Suzhou is the most economically developed city in Jiangsu province with a resident population of 10,460,000 of which 960,000 are children less than 14 years of age, per the 2010 Census. An investigation of medical records showed that in 2011 the total number of outpatient visits among children less than 5 years of age at this hospital was 396,568, which accounted for approximately 28.5% of all outpatient visits among children this age in the municipal district of Suzhou [16]. A health care utilization survey conducted in 2012 showed that among the municipal districts of Suzhou, 65.2% of children less than 5 years old requiring hospitalization were admitted at SCH (data unpublished).

2.2. Study subjects

This test-negative case–control study was conducted among children who sought care in SCH. From October 8th 2011 to September 30th 2012, we conducted enhanced influenza surveillance among children presenting with ILI (measured axillary temperature ≥38 °C, and cough or sore throat/inflamed or red pharynx) in the outpatient clinics, and children presenting with SARI (ILI requiring hospitalization) in the respiratory wards.

We provided training to SCH physicians on implementing our ILI surveillance system. Every month from October 2011–September 2012, we randomly selected 1–3 trained physicians who were serving in the outpatient and emergency departments to enroll ILI patients from Monday to Friday. Physicians were asked to randomly enroll at least 20 patients meeting the case definition per week. For SARI cases, all eligible SARI cases hospitalized in the respiratory wards and ICU who provided consent were enrolled during the study period.

A case was defined as a child with ILI or SARI aged 6–59 months with a respiratory specimen that tested positive for influenza by real time reverse-transcription polymerase chain reaction (rRT-PCR). Controls were selected from children presenting with ILI or SARI who tested negative for influenza through RT-PCR. Controls were matched to cases by age (range ±6 months) and admission date (within two months) with a ratio of 1:1.

2.3. Data collection

Upon enrollment, the investigator collected information related to the patient's demographics, clinical features of the illness, and self-reported influenza vaccination history for the current and previous influenza seasons. Influenza vaccination records were verified through the electronic immunization information system maintained by Suzhou CDC, which records immunization information on all resident children and 90% of the migrant children including date of vaccination, dose and type of vaccine (Suzhou CDC unpublished data). Self-report influenza vaccination history was compared with recorded immunization history. There was discordance between self-reported history and immunization records (Kappa value = 0.016, $p < 0.001$) (Appendix A). Thus, we determined vaccination status using the immunization records alone, and we excluded children from the study if none of their vaccination records could be traced in the immunization information system.

Clinical investigators collected nasopharyngeal and/or oropharyngeal swabs from patients enrolled in the outpatient setting on the day of enrollment, and collected nasopharyngeal aspirate specimens for hospitalized patients within 24 h of admission. Specimens were stored at −20 °C and sent to Suzhou CDC laboratory, one of the national ILI network laboratories, every 2 days to test for influenza by rRT-PCR [16].

2.4. Influenza vaccination status

Influenza vaccination status was categorized as vaccinated (fully vaccinated or partially vaccinated for children aged 6–35 months) or unvaccinated. Consistent with the instructions provided in the vaccine package [17], children aged 6–35 months were defined as being fully vaccinated if they received 2 doses of the seasonal influenza vaccine at least 28 days apart in the current influenza season, with the second dose given at least 14 days before ILI/SARI onset, or at least 1 dose in the past influenza season and 1 dose in the current season, administered at least 14 days prior to ILI/SARI onset. Children aged 6–35 months were defined as being partially vaccinated if they received only 1 dose during the current season at least 14 days before ILI/SARI onset, and no dose in a previous influenza season. As the number of children aged 6–35 months both partially and fully vaccinated was small, we included both groups in the vaccinated group when estimating VE. Children were considered to be unvaccinated if they had not received any seasonal influenza vaccine during the study season, or if they received their first dose within 14 days of ILI/SARI onset. Children aged 36–59 months were considered to be vaccinated if they received at least 1 dose of seasonal influenza vaccine during the current season at least 14 days before ILI/SARI onset. All other enrolled children 36–59 months were considered unvaccinated.

2.5. Statistical analysis

The odds ratio (OR) was defined as the odds of influenza vaccination among cases divided by the odds of influenza vaccination among controls. The unadjusted and adjusted ORs were estimated using conditional logistic regression models, and VE was estimated as: $(1 - OR) \times 100\%$. Adjusted ORs were estimated from models that included medical insurance, comorbidity (defined as having at least one of the following: congenital heart disease, asthma or other chronic lung disease, neuromuscular disease, kidney disease, blood dyscrasia and HIV), family income and place of residence covariates. When the sample size was adequate, stratified VEs were also estimated by disease severity (ILI and SARI) and age groups (6–35 months, 36–59 months). All statistical analyses were performed in SPSS statistical package version 17.0 (SPSS Inc., Chicago, IL, USA). Statistical tests were all 2-sided. The level of significance was defined as $p < 0.05$ for all statistical tests and confidence intervals.

2.6. Ethics statement

This study was approved by the institutional review board (IRB) of the School of Public Health, Fudan University, and received a non-engaged determination from the US Centers for Disease Control and Prevention (CDC). Verbal informed consent was obtained from parents or guardians on behalf of children participants involved in the study prior to questionnaire administration and specimen collection.

3. Results

3.1. Epidemic trend

During the study period, a total of 2634 children aged 6–59 months who sought care in SCH were enrolled into the influenza surveillance system and were eligible for the test negative case–control study; 22.7% (597) were positive for influenza. The number of influenza positive cases was greatest during two periods: from December to March and from July to September. More specifically, the peak of influenza percent positive cases, when at least 10% of the total number of ILI and SARI cases were influenza positive for any two consecutive weeks, was during weeks six and seven in 2012, while the highest influenza percent positive (50.0%) occurred in the third week of 2012 (Fig. 1).

3.2. Demographic characteristics

Among eligible ILI and SARI patients, 805 (31%) children did not have vaccination records within the immunization information system and were excluded from data analysis (Fig. 2). The seasonal distribution, influenza virus positive proportion, and gender distribution were similar between the 1829 cases included in the final analysis and the 805 cases excluded. Excluded children were younger and more often lived outside of Suzhou city (Table 1). Among the 1829 ILI and SARI cases included in the study (ILI: 1354, SARI: 475), 4.1% (95% CI: 3.2–5.0%) were vaccinated (ILI: 59; SARI: 16), and 427 (23%) had laboratory-confirmed influenza. Matching by age and date of presentation, 427 test negative children were included as controls for a case–control ratio of 1:1.

Demographic information, such as gender, area of residence and medical insurance was similar between lab-confirmed influenza cases and test negative controls (Table 2). The vaccination rates, per the immunization records, among both lab-confirmed influenza cases and test negative controls were low. Among influenza positive cases included in the analysis, the vaccination rates were 3.2% for SARI and 4.5% for ILI. Among the influenza negative controls, the vaccination rates were 12.9% for SARI and 11.1% ILI. Among influenza-positive case-patients aged 6–35 months, 2.1% (95% CI: 0.4–3.7%) were either fully or partially vaccinated. Among controls aged 6–35 months, 2.1% (95% CI: 0.4–3.7%) were fully vaccinated and 11% (95% CI: 7.4–15%) were partially vaccinated. Among children aged 36–59 months, 4.4% (95% CI: 1.0–7.9%) of influenza-positive patients were vaccinated, compared with 8.1% (95% CI: 3.5–12.8%) of controls (Table 2). Among 17 vaccinated children aged 36–59 months, 3 (17.6%) were primed with at least one dose before the study season.

3.3. Vaccine effectiveness

The overall VE of vaccination against lab-confirmed medically attended influenza virus infection was 67% (95% CI: 41–82) in the 2011–2012 season. The point estimate for VE for SARI (75% [95% CI: 11–93]) was higher than that for ILI (64% [95% CI: 31–82]), but the difference is not statistically significant ($p > 0.05$). During this season the point estimate for VE among children aged 36–59 months old was 50% (95% CI: −46.3 to 82.9), which was not significant and lower than that for children aged 6–35 months old (72%, 95% CI: 43–86) (Table 3).

4. Discussion

Building upon our systematic surveillance of medically attended influenza infection among children in Suzhou launched in 2011, we used a test-negative case–control design to estimate VE during the influenza season October 2011–September 2012. We estimated that VE among all children 6–59 months was 67%, and the point estimate for VE for SARI prevention was higher than that for ILI prevention (75% vs. 64%). Our study suggests that although only 1 in 25 children were vaccinated during 2011–2012, those who were vaccinated were substantially protected from developing influenza illness that would have required medical attention.

Our post-licensing estimates for VE against medically-attended influenza illness among children aged 6–59 months are similar to those found in other countries but slightly higher than those found previously in Guangzhou (52.9% in 2011–2012) and Hong Kong (51.4% in 2011–2012), China [18,19]. This might be explained by different patterns of virus circulation in each region during each season. However, important differences in study design may also impact VE estimates. For example, in our study, the sensitivity and specificity of self-reported influenza vaccination were 61.3% and 77.9%, respectively, strongly suggesting that self-reported influenza vaccination data in Suzhou, China, are too unreliable to be used to estimate vaccine effectiveness. Thus, to limit recall bias in this study, we based vaccination status on electronic immunization records, and not parents' or guardians' self-report [20] (Appendix A). The Guangzhou study also used database-verified vaccination history, but only included ILI cases, which might explain why their VE was slightly lower.

Influenza vaccination is widely recognized as the most effective way to prevent influenza related diseases [21,22]. However, the effectiveness varies by year, depending upon the epidemic situation, and upon how well the circulating virus matches the vaccine virus types. Despite this annual variation in VE, our estimated VE was consistent with the VE range reported in other countries. For example, in a matched case–control study conducted by Joshi in the United States during the 8 influenza seasons between 1999–2000 and 2006–2007, the vaccine effectiveness among children less than 5 years old was greater than 70%, even for partial vaccination [23]. Similarly, a study in Western Australia among children aged 6–59 months found the vaccine effectiveness in the 2008 influenza season was greater than 58% [24].

Our study found a higher point estimation of VE for SARI prevention than for ILI prevention in the 2011–2012 influenza season. This finding should be interpreted with caution, as the small sample size within our study led to a wide 95% confidence interval for VE for prevention of medically-attended ILI, and the difference between the VE point estimate for SARI prevention and ILI prevention was not statistically significant. Still, the fact that the VE point estimate was higher for SARI than for ILI lends additional support to the finding that vaccination may be more effective in the prevention of influenza infection leading to severe acute respiratory infection and hospitalization [25] compared with milder illness.

In our study, there was no statistically significant evidence that VE differed among younger children aged 6–35 months and children aged 36–59 months. However, our study was not powered to examine VE stratified into these two age groups. A 2008–2012 study from Australia noted a higher VE among children 6–35 months compared with older children

[21]. In contrast, studies from Hong Kong [19] and Guangzhou, China [26] found a lower VE among the younger children. As vaccine coverage in China increases, it will be important to assess VE by age group. This assessment is particularly important in China, where the seasonal influenza vaccine package insert recommends only 1 vaccine dose for children aged 36–59 months, while in many other countries, the recommendation is for children who have not been vaccinated in prior years to receive 2 doses until 9 years of age [27,28]. In our study, due to very low vaccination coverage, we included both "fully" and "partially" vaccinated children aged 6–35 months in our definition of "vaccinated", although only 24% (12/50) of these vaccinated children were "fully" vaccinated. Among vaccinated children aged 36–59 months in our study, only 17.6% would be considered "fully" vaccinated in countries recommending 2 doses of vaccine in previously unvaccinated children less than 9 years of age. In future studies, it will be important to assess VE among "partially" vaccinated children aged 6–35 months compared with fully vaccinated children in this age group.

It is important to highlight that the seasonal influenza vaccine coverage among young children in China is very low. In 2011, a population-based telephone survey estimated the influenza vaccine coverage rate among children 6–59 months to be 11.85% [29]. In our study, the influenza vaccine coverage rate was only 4.1% among this same age group, much lower than both the 2011 China estimate and the vaccination coverage rate in other countries. For instance, in the US, the live attenuated influenza vaccine coverage for children 2–8 years of age was approximately 50% in 2013–14 [29]. In Thailand, the influenza vaccination coverage in young children was around 30% in 2011–2013 [30]. The low coverage in China might be explained by the fact that influenza vaccination is not included in the national expanded program on immunizations (EPI). Policy-makers, healthcare workers and public health professionals lack local data on the effectiveness of influenza vaccination in China, and this may be one reason why seasonal influenza vaccination is not routinely recommended in any setting. In addition, throughout most of the country, those who want to receive the seasonal influenza vaccination must pay for it out-of-pocket, at the price of 60–100 RMB (~10–15USD).

This study has several limitations. First, approximately 30% of the study subjects could not be traced in the computerized immunization system. It is possible that some of the children without electronic immunization data were hospitalized under different names than those recorded in the immunization database. In China, many infants may not receive their official name until one month of age, after they are already registered under a non-official name in the immunization system. Others came from neighboring cities and thus have immunization records outside of Suzhou. While it is possible that the exclusion of these study subjects may reduce the generalizability of our study findings, we found that the excluded children were similar to children enrolled in the study by gender, comorbidities, and influenza positive rate. However, excluded children were younger, which may have biased our findings by age group. A second limitation was the small sample size, in addition to the very low vaccination coverage among children less than 5 years of age in Suzhou, which may have resulted in a statistical power too low to calculate VE precisely. Third, the VE estimates based on the subjects from SCH may not be representative of all of the influenza cases in Suzhou, as not all cases of influenza go to the hospital to seek treatment. Thus, our study only looks at the

VE among influenza cases with illness serious enough to seek medical care. Finally, even among patients with ILI who sought care at SCH, study physicians only enrolled a random sample of patients, introducing the possibility of selection bias. It is not clear, however, whether physicians more likely selected severely ill children for whom they had greater clinical concern, or less severely ill children from whom it may have been easier to collect samples. In the future, it will be important to collect more detailed information on illness severity of all enrolled subjects.

In conclusion, seasonal influenza vaccination was effective in preventing medically attended laboratory-confirmed influenza infection among children aged less than 5 years in Suzhou in both the 2011–2012 influenza season. Although additional studies are needed to compare VE within age groups and VE in preventing medically-attended SARI vs. ILI, this study demonstrates that timely seasonal influenza vaccination will decrease the burden of medically attended influenza illness among young children in Suzhou.

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Appendix A.: Validity of self-reported vaccination status as compared to immunization records from October 2011 to September 2012 in Suzhou, China.

Self-report	Immunization records		Sensitivity (95% CI)	Specificity (95% CI)
	Vaccinated	Unvaccinated		
Vaccinated	46	388	61.3%	77.9%
Unvaccinated	29	1366	50.3–72.4	75.9–79.8

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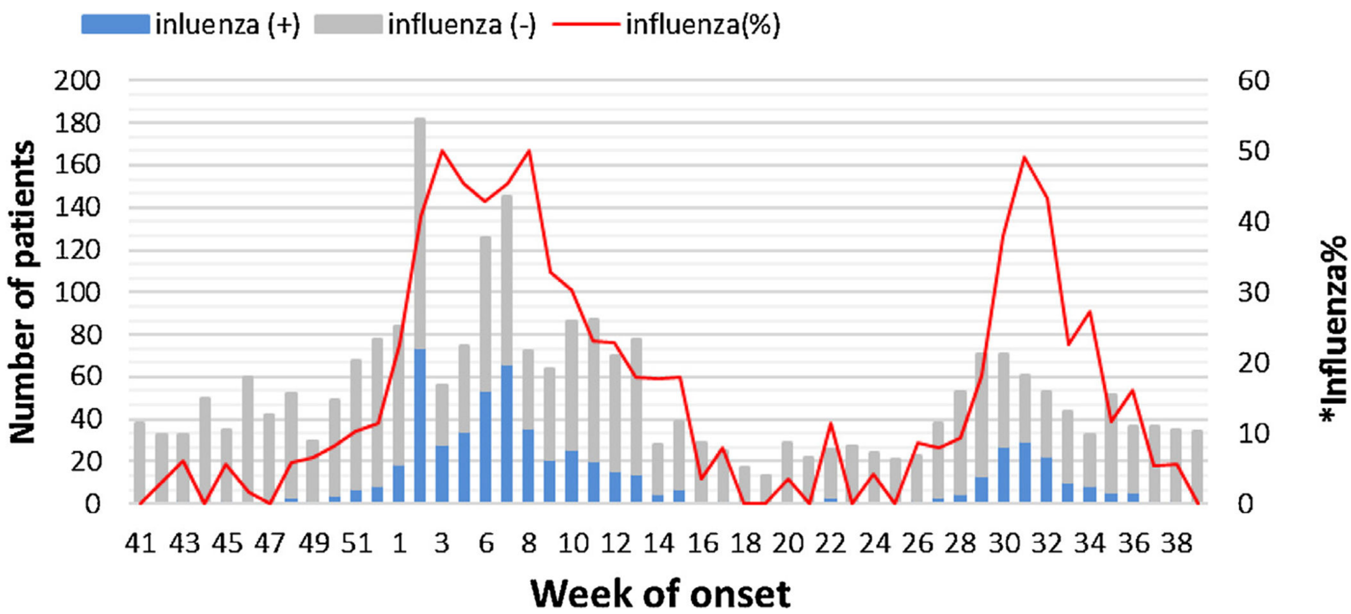

Fig. 1.

Distribution of enrolled ILI and SARI cases and laboratory confirmed influenza cases between October 2011 and September 2012, Suzhou, China.

*Influenza% = proportion of influenza virus positive patients among all ILI and SARI patients enrolled during the study period.

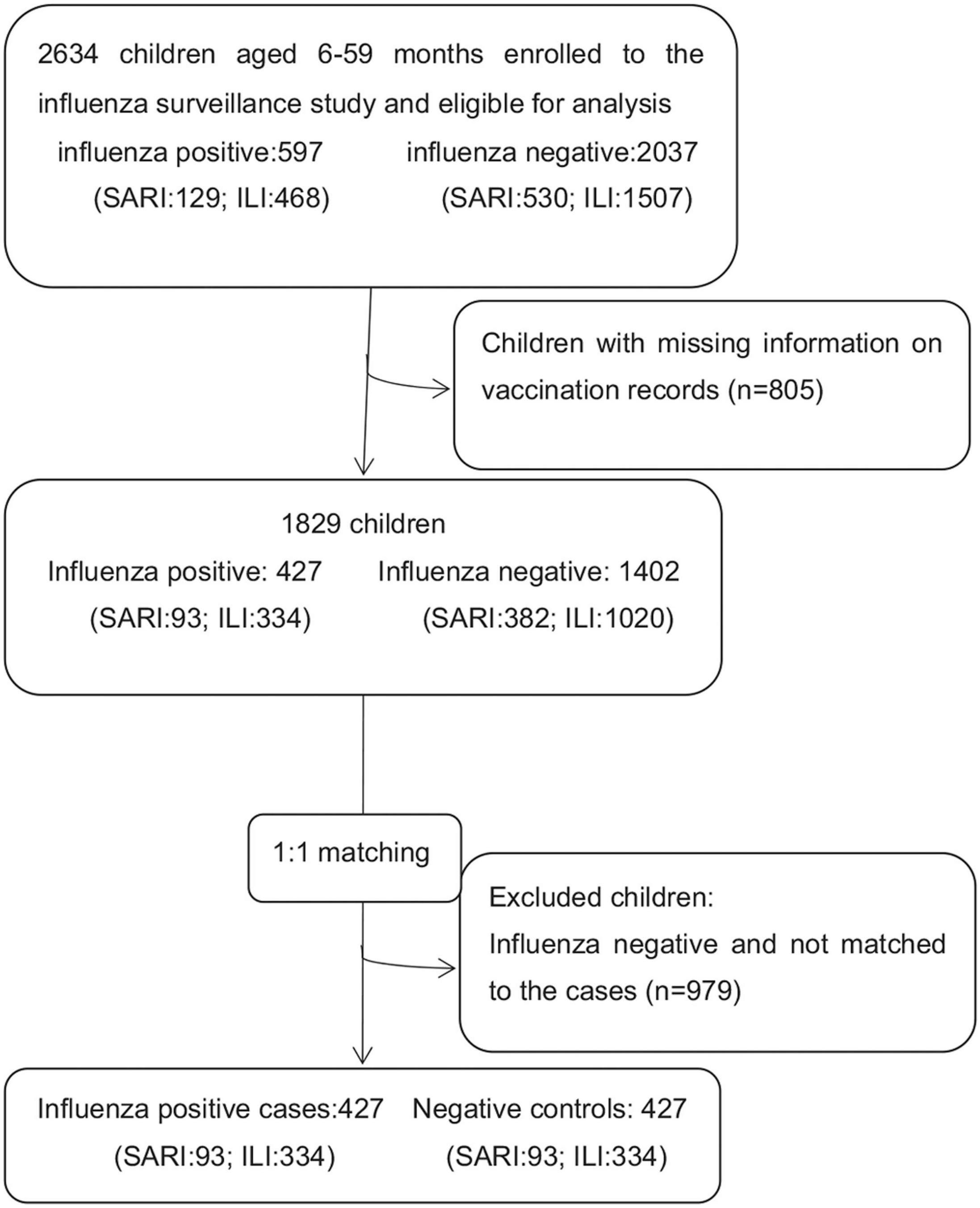

Fig. 2.

Enrollment of subjects for estimating influenza vaccine effectiveness from October 2011 to September 2012 in Suzhou, China.

Table 1

Comparison of the excluded 805 children without electronic vaccination records and the 1829 qualified children with electronic vaccination records in Suzhou, 2011–2012.

	Qualified (*N*=1829)		Excluded (*N*=805)		*p* value
	n	**%**	***n***	**%**	
SARI[a]					
Influenza					
Positive	93	5.1	35	4.3	0.871
Negative	382	20.9	149	18.5	
Age					
6–35 months	361	19.7	129	16.0	0.120
36–59 months	114	6.2	55	6.8	
Gender					
Male	290	15.9	112	13.9	0.966
Female	185	10.1	72	8.9	
Area of residence					
Suzhou	395	21.6	119	14.8	<0.01
Other	80	4.4	65	8.1	
ILI[b]					
Influenza					
Positive	334	18.3	134	16.6	0.134
Negative	1020	55.8	487	60.5	
Age					
6–35 months	938	51.3	515	64.0	<0.01
36–59 months	416	22.7	106	13.2	
Gender					
Male	763	41.7	354	44.0	0.786
Female	591	32.3	267	33.2	
Area of residence					
Suzhou	890	48.7	327	40.6	<0.01
Other	464	25.4	294	36.5	

[a]Severe acute respiratory infection.

[b]Influenza-like illness.

Table 2

Characteristics among medically attended children aged 6–59 months by influenza positive patients (cases) and influenza negative patients (controls) in Suzhou, 2011–2012 (%).

	6m–35m			36m–59m			6m–59m		
	Cases	**Controls**	***P* value**[b]	**Cases**	**Controls**	***P* value**[b]	**Cases**	**Controls**	***p* value**[b]
Gender									
Male	172 (58.9)	182 (62.3)	0.397	65 (48.1)	70 (51.9)	0.543	237 (55.5)	252 (59.0)	0.299
Female	120 (41.1)	110 (37.7)		70 (51.9)	65 (48.1)		190 (44.5)	175 (41.0)	
Area of residence									
Suzhou	202 (69.2)	180 (61.6)	0.056	107 (79.3)	101 (74.8)	0.385	309 (72.4)	281 (65.8)	0.038
Other	90 (30.8)	112 (38.4)		28 (20.7)	34 (25.2)		118 (27.6)	146 (34.2)	
Medical insurance									
Yes	158 (54.1)	183 (62.7)	0.036	40 (29.6)	55 (40.7)	0.056	198 (46.4)	238 (55.7)	0.006
No	134 (45.9)	109 (37.3)		95 (70.4)	80 (59.3)		229 (53.6)	189 (44.3)	
Family income (RMB/year)									
<10,000	143 (49.0)	157 (53.8)	0.408	50 (37.0)	55 (40.7)	0.813	193 (45.2)	212 (49.6)	0.353
10,000–25,000	134 (45.9)	118 (40.4)		74 (54.8)	69 (51.1)		208 (48.7)	187 (43.8)	
>25,000	15 (5.1)	17 (5.8)		11 (8.1)	11 (8.1)		26 (6.1)	28 (6.6)	
Comorbidity[a]									
Yes	9 (3.1)	8 (2.7)	0.806	4 (3.0)	13 (9.6)	0.024	13 (3.0)	21 (4.9)	0.161
No	283 (96.9)	284 (97.3)		131 (97.0)	122 (90.4)		414 (97.0)	406 (95.1)	
Respiratory-related diseases within 3 months									
Common cold	75 (25.7)	75 (25.7)	1.000	53 (39.3)	58 (43.0)	0.536	128 (30.0)	133 (31.1)	0.710
Tracheitis	2 (0.7)	6 (2.1)	0.154	3 (2.2)	2 (1.5)	0.652	5 (1.2)	8 (1.9)	0.402
Asthma	0 (0.0)	1 (0.3)	0.317	0 (0.0)	0 (0.0)	/	0 (0.0)	1 (0.2)	0.317
Pneumonia	22 (7.5)	28 (9.6)	0.375	4 (3.0)	5 (3.7)	0.735	26 (6.1)	33 (7.7)	0.345
Vaccination status									
No vaccination	280 (95.8)	254 (87.0)		129 (95.6)	124 (91.9)		409 (95.8)	378 (88.5)	
Vaccination[c]	12 (4.2)	38 (13.1)	<0.001	6 (4.4)	11 (8.1)	0.210	18 (4.2)	49 (11.5)	<0.001
Partial vaccination	6 (2.1)	32 (11.0)	<0.001						

	6m–35m			36m–59m			6m–59m		
	Cases	**Controls**	***P* value[b]**	**Cases**	**Controls**	***P* value[b]**	**Cases**	**Controls**	***p* value[b]**
Full vaccination	6 (2.1)	6 (2.1)	0.867						

[a]Comorbidity includes congenital heart disease, asthma and other chronic lung disease, neuromuscular disease, kidney disease, blood dyscrasia and HIV.

[b]Chi-square or two-tailed Fisher's exact test were used to compare groups.

[c]Includes both partial and full vaccination for those 6–35 months of age.

Table 3

Seasonal influenza vaccine effectiveness against lab-confirmed medical attended illness during 2011–2012 season in children aged 6–59 months in Suzhou, China.

	Lab-confirmed cases		Test-negative controls		Vaccine effectiveness	
	N	Vaccinated (%)	*N*	Vaccinated (%)	%	95% CI
	427	18 (4.2)	427	49 (11.5)	67.1	41.0–81.6
Severity						
SARI[a]	93	3 (3.2)	93	12 (12.9)	75.0	11.4–92.9
ILI[b]	334	15 (4.5)	334	37 (11.1)	64.3	30.9–81.5
Age						
6–35 months	292	12 (4.1)	292	38 (13.0)	71.9	43.3–86.1
36–59 months	135	6 (4.4)	135	11 (8.1)	50.0	−46.3 to 82.9

[a] Severe acute respiratory infection.

[b] Influenza-like illness.