The effectiveness of influenza vaccination among nursery school children in China during the 2016/17 influenza season

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ABSTRACT

Background: The effectiveness of influenza vaccine among nursery school children has not been systematically studied. We conducted a cohort study of children from 13 nursery schools in Suzhou, China, to estimate the effectiveness of influenza vaccine against laboratory-confirmed influenza during 2016–17.

Methods: Children aged 36–72 months were chosen from 13 nursery schools from 3 District in Suzhou. The surveillance started 2 weeks after vaccination during October 2016–February 2017. Class teachers reported the names of students with ILI (influenza-like illness) to study clinicians on each school day. Further, local physicians collected the student's nasopharyngeal swab or throat swab, either at a study clinic or at the child's home. The swabs were sent to the National Influenza Network Laboratory in Suzhou Center for Disease Control and Prevention for influenza testing by RT-PCR.

Result: A total of 4614 children were enrolled, of which 15 children (vaccinated: 2; unvaccinated: 13) were lost to follow-up. Of the remaining 4599 children, 558 swabs were collected. Among these swabs, 70 samples tested positive for influenza virus; 17 in the vaccinated group (B Victoria: 2; H3N2: 15) and 53 in the unvaccinated group (B Victoria: 14; A(H1N1)pdm09: 1; H3N2: 38). The overall influenza vaccine effectiveness (VE) during the influenza season of 2016–2017 was 20.6%. The incidence of developing ILI symptoms and healthcare seeking behavior through clinical visits was significantly lower in vaccinated children than in the unvaccinated group.

Conclusion: Influenza vaccine protection in vaccinated and unvaccinated children showed no statistical difference and the VE percentage varied for different virus subtypes. However, the incidence rate of developing ILI and healthcare seeking behavior was significant lower in the vaccinated group than in the unvaccinated children. Larger studies are required to estimate the VE according to the influenza type, subtype, and lineage during influenza seasons in China in the future.

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1. Introduction

Influenza vaccine is considered the most effective way to protect against infection with the influenza virus [1]. Children aged between 6 and 59 months are at high risk of developing influenza infection and are recommended to have an annual seasonal influenza vaccination [2]. In schools, these young children have more opportunities to contact each other closely, which aids in the spread of influenza virus infection [3]. School children play an important role in the transmission of influenza within schools, families, and communities [4,5].

In China, influenza vaccine is not included in the national immunization program, and recipients themselves have to pay for the cost of influenza vaccination. Influenza vaccine coverage in young children is low [6]. Moreover, influenza vaccine effectiveness (VE) in nursery school children has not been well investigated in the country [7,8].

Here, we conducted a community-based prospective cohort study in nursery school children in Suzhou, China, during the 2016–2017 influenza season. Information on seasonal influenza VE for nursery school children in the local setting may help to increase vaccination coverage in young children.

2. Methods

To evaluate the effectiveness of influenza vaccine in children under 5 years of age, we conducted a cohort study in three districts

of Suzhou beginning November 2016. According to the previous influenza vaccine coverage (more than 30%) and interest of the schools in collaborating, the study was carried out in 13 nursery schools: 4 in the Wuzhong District, 5 in the Taicang District, and 4 in the Xiangcheng District. We selected both public and private nursery schools, which typically enroll children aged 3–6 years residing in the surrounding neighborhoods. The trivalent inactivated influenza vaccine (TIV) used in our study during the 2016–2017 influenza season contained the following subtypes: an A/California/7/2009 (H1N1)pdm09-like virus, an A/Hong Kong/4801/2014 (H3N2)-like virus, and a B/Brisbane/60/2008-like virus, as recommend by the World Health Organization (WHO).

2.1. Sample size

Based on previous health utilization surveys (unpublished), the incidence of influenza-like illness (ILI) is approximately 6.5%, and the ILI attack rate is 39.0% in both vaccinated and unvaccinated children. The influenza positive rate among ILI cases is 10%. We assume that the effectiveness of influenza vaccine is 50%, and that 10% of the study subjects will withdraw or be lost to follow up. According to the formula:

$$n = \frac{\left[Z_\alpha\sqrt{2\bar{p}(1-\bar{p})} + Z_\beta\sqrt{p_1(1-p_1)+p_2(1-p_2)}\right]^2}{(p_1-p_2)^2},$$

(α = 0.05, β = 0.10), we calculated a required sample size of 4252 children.

2.2. Enrollment

From November to December 2016, after the end of local seasonal influenza vaccination services, we enrolled both vaccinated and unvaccinated children with their guardian's informed consent. Information about the influenza vaccination was verified through a vaccination record review using data from a local vaccine clinic, which hosted an electronic record system maintained by the Suzhou Center for Disease Control (CDC) and covered vaccination records for >99% of children living in the district. Teachers from the selected nursery schools offered the guardians of enrolled children a self-administered questionnaire about their demographic information, medical history, family healthcare-seeking behavior, and family health behavior, within the last 1 week.

2.3. Follow-up

Enrolled children were followed up for 24 weeks starting from 2 weeks after the scheduled vaccination day for each nursery school. The teachers in charge of each class were trained to screen all enrolled children for illness on each school day. The teachers were also asked to pay attention to students' attendance and to inquire about the reasons for sick leave by telephone within 1 week. The teachers identified children with ILI according to the following criteria: measured axillary temperature 38 °C or higher, accompanied by cough or sore throat/inflamed pharynx. A repeat illness report within 2 weeks was counted as one episode. In follow-up questionnaires, the teachers recorded weekly the information regarding absenteeism, sick leave, and related healthcare-seeking behaviors, which were collected weekly by the investigators. The guardians were encouraged to take children who met the criteria for ILI to designated community health care centers within 3 days of symptom onset, and designated physicians in the healthcare centers collected nasopharyngeal swab (NP) or throat swab (OP) specimens from the children. If guardians stated that it was not convenient to go to any of the designated healthcare centers, the physicians would visit their home and collect samples within 24 h of the illness report.

2.4. Laboratory test

Specimens were stored at −20 °C in the community healthcare centers. Every Tuesday and Thursday, the specimens were transported to the National Influenza Network Laboratory in the Suzhou CDC laboratory, one of the national ILI network laboratories. From the samples, viral RNA was extracted using High Pure Viral RNA kits (Roche, Shanghai, China) according to the manufacturer's instructions. Real-time reverse transcription polymerase chain reaction (rRT-PCR) was employed to test for influenza A or B virus by using influenza virus A/B dual fluorescent quantitative RT-PCR kits (Bio Perfectus Technology Co., Jiangsu, China). The influenza virus A subtype identification was performed using influenza A (H1N1)/A(H3N2)/A(H1N1)pdm09 real time RT-PCR kits (ZJ Bio-Tec Co., Shanghai, China). The influenza virus B lineage identification was performed using influenza B Yamagata/B Victoria real time RT-PCR kits (ZJ Bio-Tech Co., Shanghai, China).

2.5. Statistical analysis

Unadjusted VE was estimated as: $(1 - RR) \times 100\%$. The risk ratio (RR) was defined as the incidence rate of laboratory-confirmed influenza in the vaccinated group divided by the incidence rate of laboratory-confirmed influenza in the unvaccinated group. In the 2×2 table, we added 0.5 to any cell that was zero. The mid-P exact test was used to compare the two incidence rates by OpenEpi. Other statistical analyses were performed using R, version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were two-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 of the School of Public Health, Fudan University, and received a non-engaged determination from the U.S. Centers for Disease Control and Prevention. Written informed consent was obtained prior to enrollment from parents or guardians on the behalf of children participants enrolled in the study.

3. Result

During the study period, a total of 4614 children (vaccinated: 1358 children, unvaccinated: 3256 children) were enrolled from the 13 selected nursery schools. Among these, 15 children (0.33% of enrolled children: 2 vaccinated children, 13 unvaccinated children) could not be followed-up due to their transfer elsewhere during the study period.

Of the remaining 4599 children (vaccinated: 1356, unvaccinated: 3243) included in the final analysis, the mean age was 57 months (SD: 10.1 months) for vaccinated children and 56 months (SD: 10.3 months) for unvaccinated children (p = 0.521). The overall vaccination rate of influenza vaccine in enrolled children was 29.5% (1356/4599). Of this, influenza coverage of 4 nursery schools was above 30% (coverage >30%: 4 nursery schools, total 1916 children; coverage <30%: 9 nursery schools, total 2683 children). Compared with unvaccinated children, the proportions of vaccinated children with medical insurance and Suzhou household registration were lower (medical insurance: 69.8% vs. 73.9%; residence registration: 27.3% vs. 40.1%). The proportion of children without Suzhou household registration among vaccinated children was much higher than that of unvaccinated children (vaccinated: