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Factors that may explain observed associations between trivalent influenza vaccination and gastrointestinal illness in young children☆,☆☆

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ABSTRACT

Background: Previously published studies reported an increased risk of gastrointestinal illness in the 14 days following trivalent influenza vaccination (TIV) in young children. While gastrointestinal illness may be a true adverse effect of TIV, other factors may influence this observed association, such as seasonal illness patterns and children being exposed to gastrointestinal pathogens at medical visits. The objective of this study was to examine factors influencing the association between TIV and gastrointestinal illness. Specifically, using data from a previous influenza vaccine safety study, we examined the association between medical encounters without TIV and gastrointestinal illness.

Methods: Using electronic health record (EHR) data from 6 managed care organizations (MCOs), we identified medically attended gastrointestinal illness cases among children 24–59 months in the 2002–2006 influenza seasons. We matched each case to four controls on sex, birthdate (month/year), MCO, influenza season, and presence of a chronic condition. We then looked 1–14 days prior to the index date (gastrointestinal illness diagnosis date) to determine whether the child had a medical encounter. We excluded previous medical encounters with gastrointestinal-related diagnoses or TIV. Conditional logistic regression was used to calculate odds ratios and 95% confidence intervals.

Results: We identified 2062 gastrointestinal illness cases and matched them to 8248 controls. We observed increased odds of gastrointestinal illness within 14 days after a medical encounter (odds ratio = 1.9; 95% confidence interval [CI]: 1.7–2.2) among children without chronic conditions. Among children with chronic conditions, the odds ratio was 3.9 (95% CI: 2.5–6.2).

Conclusions: We demonstrated that another exposure related to vaccination, medical visits, is also associated with increased odds for gastrointestinal illness. This study highlights challenges of interpreting results from observational vaccine safety studies when there are co-occurring exposures, and the importance of investigating confounding in EHR data, which are an essential resource for vaccine safety research.

Abbreviations: TIV, trivalent influenza vaccination; GI, gastrointestinal; ED, emergency department; VSD, Vaccine Safety Datalink; MCO, managed care organization; ICD-9, International Classification of Diseases – 9th revision; SD, standard deviation; CI, confidence interval; mOR, matched odds ratio.

☆ The findings and conclusions in this study are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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1. Introduction

Results from two previously published vaccine safety studies suggest an association between the inactivated trivalent influenza vaccination (TIV) and subsequent gastrointestinal illness in children younger than 59 months of age. These studies observed an increased risk of vomiting and diarrhea, other gastrointestinal disorders (primarily consisting of non-specific abdominal pain) and gastritis within 1–14 days after TIV [1,2].

There are several possible explanations for the observed signal between TIV and gastrointestinal illness. First, gastrointestinal illness may represent a true adverse reaction to TIV [2]. There is evidence that the live attenuated influenza vaccine causes mild gastrointestinal illness in children [3], which is not surprising given that influenza infection is known to cause gastrointestinal illness in young children. However, there is no clear biological plausibility for a causal relationship between the inactivated TIV and gastrointestinal illness.

Second, the association between TIV and gastrointestinal illness may be confounded by other factors related to the medical visit where TIV was administered. As the authors of the previous influenza vaccine safety studies [1,2] hypothesized, the association between TIV and gastrointestinal illness may be due to the child being exposed to infectious gastrointestinal pathogens while at a medical visit. While medical waiting rooms offer opportunities for transmission of infectious diseases [4,5], and there have been case reports of children acquiring infectious diseases in such settings [6,7], there is limited empirical evidence on the risk of acquiring infectious gastrointestinal illnesses in waiting areas [8,9]. Gastrointestinal illness may also be a side effect of a treatment received during a medical visit where TIV was administered. For example, gastrointestinal illness is a known side effect of antibiotic therapy in children. Therefore, results from previous TIV safety studies may be confounded by unmeasured exposures related to the medical encounter that are co-occurring with TIV administration.

A third potential explanation for the observed association between TIV and gastrointestinal illness is the overlapping seasonal patterns of TIV administration and gastrointestinal illness. TIV is primarily administered in the late fall and early winter months (October–December) immediately before the winter-to-spring peak of gastrointestinal illness [10,11]. Due to these overlapping seasonal patterns, expected background incidence rates of GI illness may be higher after TIV administration than in time periods before TIV administration, thus potentially creating a spurious association.

Lastly, both influenza vaccine safety studies [1,2] used electronic health record data in their analyses. While the ability to analyze electronic health record data on large, nationally representative groups of children is a rich resource for studying the risk of rare adverse events following vaccination [12], these data are not collected for research purposes. Exposure and outcome data are collected via procedure and diagnosis codes in patients' electronic health records, and misclassification of these data does exist, especially for some health outcomes [12,13]. Such misclassification may lead to detecting false associations in vaccine safety research [13]. For example, both previously mentioned influenza safety studies [1,2] identified a possible association between TIV and gastrointestinal illness in analyses using electronic health record data. In both studies, medical record reviews were conducted to validate the gastrointestinal illness outcome. In one study of children 6–23 months of age, the association between TIV and gastrointestinal illness was no longer evident after medical record review [2]. However, in the study of children ages 24–59 months, the association between TIV and gastrointestinal illness remained after medical record review [1].

The objective of this study was to further examine factors influencing the previously observed association between TIV and gastrointestinal illness. Specifically, we used a case–control design to examine whether children ages 24–59 months with medically attended gastrointestinal illness in inpatient or emergency department (ED) settings were more likely to have had a medical encounter in the 14 days prior, as compared with children who did not have medically attended gastrointestinal illness. We believe the results from this study will help in appropriately interpreting findings from previous TIV safety studies, and the study will also inform future safety studies that use electronic health record data to examine associations between vaccinations and adverse events.

2. Materials and methods

2.1. Study design and setting

We conducted a matched case–control study within the pediatric population of the Vaccine Safety Datalink (VSD). The VSD is a collaborative project between the Centers for Disease Control and Prevention and 10 managed care organizations (MCOs) across the U.S. [12] The 10 participating MCOs comprise a population of over 9 million members annually (3% of the U.S. population) [12]. Each MCO prepares electronic data sets with information on demographics, vaccinations, and medical encounters in outpatient, emergency department and inpatient settings.

The current study was conducted with data from a previously published VSD study that examined the safety of TIV in children 24–59 months [1]. That study included data from seven MCOs, and six of the MCO sites contributed data to the current analyses. Each participating site's institutional review board approved this study.

2.2. Study population

In the previously published study that provided the source data for the current analyses [1], we identified children between 24 and 59 months of age who were continuously enrolled in their MCO from September to March during at least one of four influenza seasons (2002–2003, 2003–2004, 2004–2005, and 2005–2006). This group of children represents our starting cohort. Within this cohort, we identified a nested cohort of children that had at least one well child visit (International Classification of Diseases – 9th revision [ICD-9] codes of V20.x or V70.x) during the influenza season. We applied this criterion to ensure we were studying a population of children whose parents actively sought preventive care and had some health care utilization during the study period. This nested cohort served as the source population for the cases and controls in this current study.

2.3. Cases and controls

Using the case definition in the prior TIV safety study [1], cases were defined as children with medically attended gastrointestinal illness diagnoses from an emergency department (ED) or inpatient setting. The ICD-9 codes used to identify gastrointestinal illness are in Table 1. If children had multiple ED or inpatient visits for gastrointestinal illness in the same influenza season, only the first was considered for analysis. A child could be a case in multiple influenza seasons and those gastrointestinal illnesses were treated as independent events.

Using incidence density sampling, cases of gastrointestinal illness were matched to four controls on sex, month and year of birth, MCO site, influenza season, and presence of a chronic medical condition (yes/no). Chronic medical conditions were identified using ICD-9 codes, with codes selected based on several prior influenza vaccine studies [1,2,14]. Chronic medical conditions included neurologic, pulmonary, cardiac and other conditions, but chronic gastrointestinal conditions were not on the list. A full list