Evidence of residual confounding in healthcare database studies of oseltamivir and influenza complications

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Background

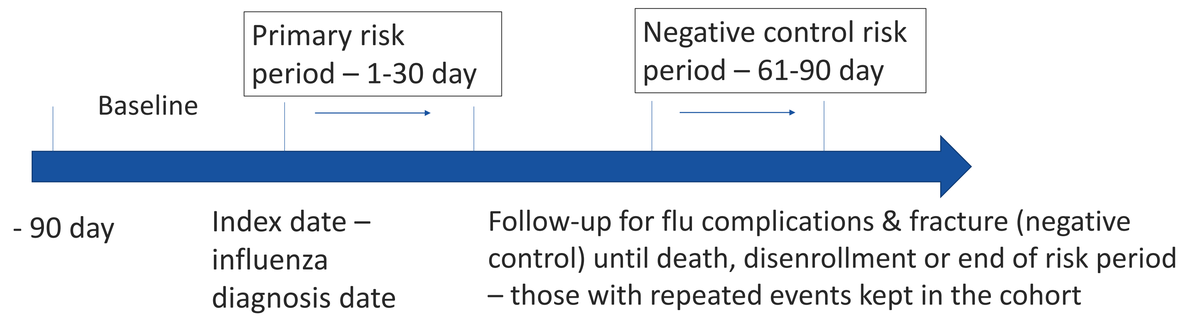
- U.S. government agencies stockpile medical countermeasures (MCM), including antivirals in preparation for disease outbreaks and public health emergencies
- Oseltamivir is an oral antiviral agent, approved for treatment and prevention of acute, uncomplicated influenza
- Oseltamivir reduces influenza symptoms but its effect on complications (pneumonia, all-cause hospitalizations) is less clear, with conflicted findings (1-3)
- Residual confounding is expected in observational studies, and could explain conflicting results, but has not been explicitly demonstrated

Objective

- To demonstrate residual confounding in estimating the effect of oseltamivir on influenza complications (inpatient pneumonia, all-cause hospitalizations) using negative control risk windows and a negative control outcome (fractures)

Methods

- Using MarketScan® Databases (Sentinel Common Data Model format), we identified incident outpatient influenza diagnoses (90-day washout) among those ≥18 yrs and with 365 days of medical and pharmacy enrollment
- We identified oseltamivir new users (same day users) vs. non-users (no oseltamivir on diagnosis date)
- Three influenza seasons were assessed separately and pooled: from 2014-17
- We estimated risk ratios by log binomial models, after propensity score (PS) matching, and pooled estimates by random effect models



Results

Table 1. Select baseline characteristics of newly diagnosed influenza patients (2014-15 season) after PS matching

Characteristic	Oseltamivir (n=57,929)	No oseltamivir (n=57,929)	Standardized mean difference
Age (mean, SD)	44 (15)	44 (16)	0.02
Sex (male) (%)	41	43	-0.03
Cardiovascular disorders (%)	10	10	0.02
Chronic lung disorders (%)	7	6	0.02
Influenza test (%)	55	59	-0.07
Influenza vaccination (%)	17	17	0.01
Corticosteroids (%)	35	34	0.02

Table 2. Incidence of influenza complications and negative control outcome: fractures during primary risk window (1-30 days after diagnosis: 2014-15 season)

Cohort	No. of events	Sample size	Risk ratio (PS matched)
Inpatient Pneumonia			
Oseltamivir	142	57,929	0.70 (0.64, 0.77)
No oseltamivir	203	57,929	-
Hospitalization			
Oseltamivir	527	57,929	0.72 (0.69, 0.76)
No oseltamivir	727	57,929	-
Fracture (negative control outcome)			
Oseltamivir	27	57,520	1.00 (0.79, 1.27)
No oseltamivir	27	57,520	-

Table 3. Incidence of influenza complications during negative control risk window (61-90 days after diagnosis: 2014-15 season)

Cohort	No. of events	Sample size	Risk ratio (PS matched)
Inpatient Pneumonia			
Oseltamivir	16	51,726	0.73 (0.55, 0.97)
No oseltamivir	22	51,726	-
Hospitalization			
Oseltamivir	261	51,726	0.90 (0.84, 0.97)
No oseltamivir	290	51,726	-

Fig 1. Risk ratios (RR) for the effect of oseltamivir on fracture (negative control)

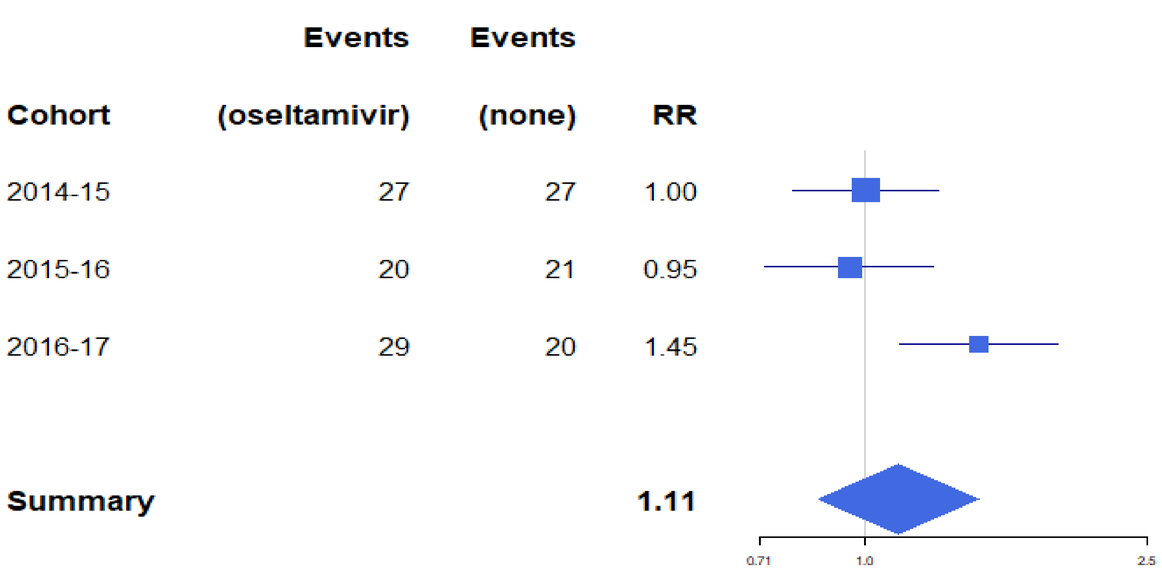


Fig 2. Risk ratios (RR) and pooled estimate for the effect of oseltamivir on inpatient pneumonia in negative control risk window (61st-90th day)

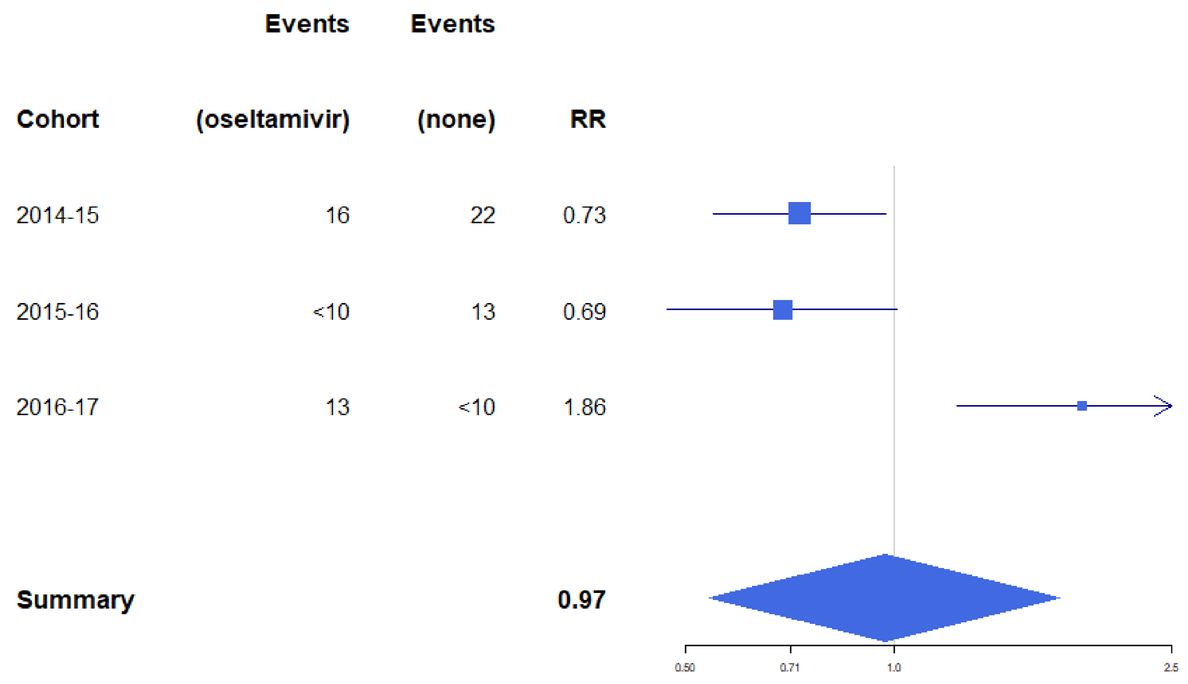
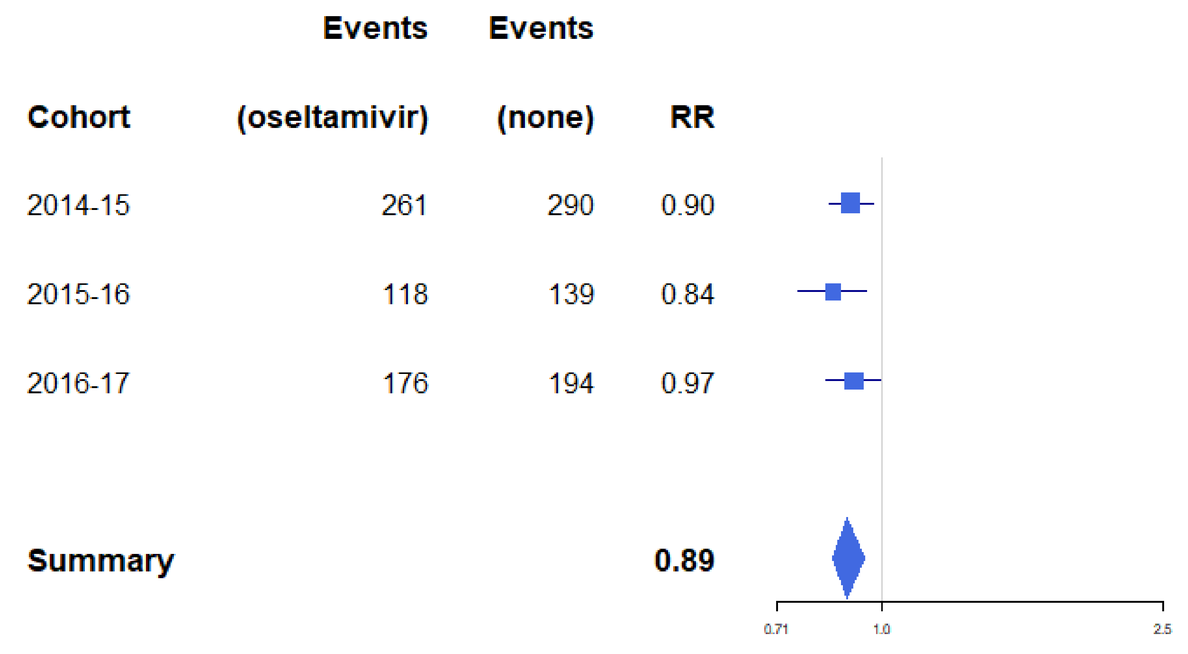


Fig 3. Risk ratios (RR) and pooled estimate for the effect of oseltamivir on all-cause hospitalization in negative control risk window (61st-90th day)



Discussion

- We observed evidence of a protective effect of oseltamivir on two influenza complications in the primary risk window (1-30th day) .
- Estimates are still protective but slightly closer to the null in the negative control risk window (61-90 days), which suggests residual confounding in our analysis of the effect of oseltamivir on influenza complications.
- The effect on fracture (negative control outcome) and negative control risk window estimates are near-null after pooling.
- Limitation: influenza diagnoses are not lab confirmed.
- Next steps include replicating this analysis in a larger database (i.e., the Sentinel Distributed Database).

Conflicts of Interest

- This article reflects the views of the author and should not be construed to represent the U.S. Food and Drug Administration's views or policies.

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