Identification of ordinal endpoints indicating influenza complications: A feasibility analysis relevant to the study of medical countermeasures

Austin Cosgrove1, Nicole Haug1, Catherine Panozzo1, Gregory Measer2, Robert Orr2, Alfred Sorbello2, Henry Francis2, Crystal Garcia3, Sarah Dutcher2, Noelle Cocoros1

1Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA
2U.S. Food and Drug Administration, Silver Spring, MD

Background
• Medical countermeasures (MCMs) are FDA-regulated products (biologics, drugs, devices) that may be used in the event of a potential public health emergency
• “Ordinal endpoints” (categorical outcomes evaluated on an ordered scale of increasing severity) of influenza complications may be useful in evaluating the utilization, safety, and/or effectiveness of influenza-related MCMs
• Influenza is a test case and serves as a proxy for other public health emergency events
• FDA’s Sentinel System is an active surveillance system that uses routine querying and pre-existing electronic healthcare data from multiple Data Partners to monitor the safety of regulated medical products

Objectives
• To determine whether ordinal endpoints can be identified for patients with evidence of influenza and influenza-related conditions in the Sentinel System
• To describe underlying conditions and influenza testing patterns of patients with influenza-related endpoints

Methods
• Members aged ≥ 6 months of age with at least 183 days of continuous enrollment in medical and drug coverage
• Cohort entry diagnosis of incident A) influenza-like illness (ILI), B) pneumonia and influenza (P&I), or C) medically attended acute respiratory illness (MAARI) in the outpatient and emergency department care settings; incidence assessed with respect to a washout of 30 days
• Identified influenza testing in the outpatient and emergency department care settings within 30 days after cohort entry
• Identified ordinal endpoints within 30 days after cohort entry, including: 1) inpatient encounters; administration of 2) biphasic positive airway pressure (BiPAP), 3) supplemental oxygen, and 4) mechanical ventilation; and 5) extracorporeal membrane oxygenation (ECMO)
• Evaluated underlying conditions in the 183 days prior to cohort entry diagnosis
• Data from 14 participating Data Partners contributing to the Sentinel System

Results

Table 1. Number of patients per cohort, by influenza season

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ILI</td>
<td>1,078,978</td>
<td>570,290</td>
<td>988,101</td>
</tr>
<tr>
<td>P&amp;I</td>
<td>3,614,409</td>
<td>3,125,995</td>
<td>3,108,933</td>
</tr>
<tr>
<td>MAARI</td>
<td>12,727,154</td>
<td>11,688,443</td>
<td>12,623,014</td>
</tr>
</tbody>
</table>

Table 2. Proportion of patients with an influenza vaccination prior to cohort entry, by influenza season

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ILI</td>
<td>35%</td>
<td>23%</td>
<td>30%</td>
</tr>
<tr>
<td>P&amp;I</td>
<td>32%</td>
<td>29%</td>
<td>31%</td>
</tr>
<tr>
<td>MAARI</td>
<td>28%</td>
<td>26%</td>
<td>27%</td>
</tr>
</tbody>
</table>

Table 3. Proportion of patients tested for influenza in the 30 days after cohort entry, by influenza season

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ILI</td>
<td>57%</td>
<td>54%</td>
<td>62%</td>
</tr>
<tr>
<td>P&amp;I</td>
<td>20%</td>
<td>13%</td>
<td>20%</td>
</tr>
<tr>
<td>MAARI</td>
<td>11%</td>
<td>8%</td>
<td>11%</td>
</tr>
</tbody>
</table>

Conclusions and Discussion
• Differences in cohort sizes across seasons were expected, as 2014-15 was a moderate influenza season with a poor vaccination match, 2015-16 was mild with a good match, and 2016-17 was moderate with a decent match
• The ILI cohort had the highest rate of influenza testing, with the youngest age groups tested most frequently
• The P&I cohort had the highest proportion of all underlying conditions at baseline and the largest capture of ordinal endpoints
• Ordinal endpoints relevant to MCMs are identifiable in administrative claims data
• Limitation: cohorts were defined by ICD-9/10-CM diagnoses and were not confirmed by laboratory tests
• Limitation: BiPAP rates were lower than expected, likely due to billing practices

Acknowledgements and Disclosures
The Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223201400030I. Many thanks to the Data Partners that provided data used in the analysis. The authors have no conflicts of interest to disclose. 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.

*Rate of ECMO after ILI, P&I, and MAARI cohort entry < 2/10,000

Figure 1. Baseline characteristics per cohort, July 2016

Figure 2. Rates of influenza testing in the 30 days after ILI cohort entry / 10,000, by influenza season and age group

Figure 3. Rates of ordinal endpoints in the 30 days after cohort entry / 10,000, July 1, 2016 – June 30, 2017, by cohort

Figure 4. Rates of ordinal endpoints in the 30 days after ILI cohort entry / 10,000, July 2016 – June 2017, by age group

Figure 5. Rates of ordinal endpoints in the 183 days prior to cohort entry diagnosis

*Rate of ECMO after ILI, P&I, and MAARI cohort entry < 2/10,000