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Global patient registry for influenza A/H5N1: strengthening results using multiple imputation

Wiku Adisasmito,1 Paul KS Chan,2 Nelson Lee,2 Ahmet Faik Oner,3 Viktor Gasimov,4 Faik Aghayev,5 Mukhtiar Zaman,6 Ebun Bamgboye,7 Nazim Dogan,8 Kathryn Starzyk,9 Nancy A Dreyer,9 Stephen Toovey10

Abstract

Background: Observational disease registries can provide very useful information about emergent infectious diseases such as influenza A/H5N1. Retrospective data collection is a key component of many registries. This analysis shows that patients obtain clinical benefit from the neuraminidase inhibitor oseltamivir when treatment is started as late as 6–8 days after symptom onset.

Methods: Retrospective observational data was collected on 231 laboratory-confirmed cases of influenza A/H5N1 from 22 countries during 2009–2010. Complete case analysis was performed on all cases, and then MI MCMC (SAS Institute, Inc., Cary, NC, USA) was used to multiple impute missing treatment data. Results were compared with those of the complete case analysis, which was reported by Adisasmito et al.1

Conclusions: MI is a useful tool for sensitivity analysis of the impact of missing data. In this example, using MI narrowed some CIs, but did not change the overall registry lessons about the benefit from antiviral treatment.

References


Figure 1. Available data from the Avian Flu Registry.

Table 1. Comparision between complete cases and MI analyses (RR of survival).

<table>
<thead>
<tr>
<th>Time from symptom onset (days)</th>
<th>Complete case analysis</th>
<th>MI analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–2</td>
<td>19/21 (90)</td>
<td>19/21 (90)</td>
</tr>
<tr>
<td>3–5</td>
<td>32/33 (97)</td>
<td>32/33 (97)</td>
</tr>
<tr>
<td>6–8</td>
<td>43/45 (96)</td>
<td>43/45 (96)</td>
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</tbody>
</table>

Figure 2. Complete case analysis: survival according to time of oseltamivir initiation in 325 laboratory-confirmed cases. Of these, 223 had complete information for all data needed for the complete case analysis (Figure 1).

Figure 3. Comparison between complete case and MI analyses of RR of survival (GG-1IC) according to time of oseltamivir initiation.

Conclusions

MI is a useful tool for reducing potential analytical bias and loss of precision due to missing data.

When applied to the Avian Flu Registry results, MI narrowed some CIs but did not change the overall findings relating to the benefit of antiviral treatment in influenza A/H5N1 infection.

Interpretation of study results was not changed in any category by the use of MI in place of complete case analysis. The benefit of oseltamivir when started as late as 6–8 days after symptom onset in patients with influenza A/H5N1 was confirmed.

Acknowledgement

The original complete case analysis showed increased survival in treated cases when treatment was started as late as 6–8 days after symptom onset (Figure 2).

Differences between oseltamivir-treated and untreated cases in percentage survival rates and the derived relative risks (RRs) were greatest when the treatment was initiated within 2 days of symptom onset. These differences narrowed as the interval from symptom onset to start of therapy increased. Very similar RRs were obtained when patients were treated from either 0–3 days or from 0–8 days after symptom onset (Table 1).

Use of the MI analysis yielded results very similar to those of the complete case analysis (Tables 2 and Figure 1). The largest change was seen in the analysis of survival in patients receiving treatment within 2 days of symptom onset; the estimated 95% confidence interval (CI) changed from 3.2 (2.7–4.5) to 3.0 (2.0–4.6). For the other time intervals, very small adjustments were noted, with narrowing of CIs (Figure 3).

The complete case analysis is summarized in Figure 1. Cases dropped from the analysis included those with missing symptom onset data, missing oseltamivir treatment start date, unknown date of first presentation or unknown date of death. The resulting dropout rate was 22% (284 cases).

To reflect the uncertainty surrounding the prediction of unknown values, MI replaces each missing data point with a set of plausible values that represent the uncertainty over the correct value to impute. The multiple sets can be analyzed by using the standard procedures used for complete data, and then combining the results from these analyses.

The MI method used to analyze the Avian Flu Registry data was SAS Proc MI (SAS Institute, Cary, NC, USA). Using this system, predictions are produced for each missing dataset treatment interval included country, gender, type of exposure (direct or indirect human, poultry, wild bird), outcome and symptoms.

The complete case analysis and MI analyses are presented in Table 1. Of the 223 cases with complete information for all data needed for the complete case analysis, 19/21 (90%) survived with oseltamivir treatment within 2 days of symptom onset, compared with 32/33 (97%) for all cases. The estimated RR (95% CI) for treatment within 2 days of symptom onset: the estimated RR (95% CI) changed from 3.0 (2.0–4.5) to 2.8 (1.9–4.1). For the other time intervals, very small adjustments were noted, with narrowing of CIs (Figure 3).

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