Author's response: influenza-associated mortality oseltamivir: beware of misstepping into stepwise procedures

Mark Reacher^{1,2}, Neville Q. Verlander³, Maria Zambon⁴, on behalf of the authors of the original article⁵

1. Public Health England Field Service, Cambridge Institute of Public Health, Cambridge, United Kingdom

2. Public Health England and Cambridge Universities Hospitals NHS Foundation Trust Cambridge, Cambridge, United Kingdom

3. Statistics Unit, Statistics, Modelling and Economics Department, National Infection Service – Data and Analytical Sciences, Public Health England, London, United Kingdom

4. National Infection Service, Public Health England, London, United Kingdom

5. The authors are acknowledged at the end of the article

Correspondence: Mark Reacher (Mark.Reacher@phe.gov.uk)

Citation style for this article:

Reacher Mark, Verlander Neville Q., Zambon Maria, on behalf of the authors of the original article. Author's response: influenza-associated mortality oseltamivir: beware of misstepping into stepwise procedures. *Euro Surveill.* 2019;24(46):pii=1900692. <https://doi.org/10.2807/1560-7917.ES.2019.24.46.1900692>

Article submitted on 14 Nov 2019 / accepted on 14 Nov 2019 / published on 14 Nov 2019

We thank Lytras et al. [1] for the comments on our recent article assessing risk factors for mortality in inpatients with influenza and the effect of oseltamivir [2]. For this study, the authors are confident that the identification and adjustment for confounding variables have been done in a systematic and objective manner using stepwise logistic regression. We note the concerns on the methods we have used, but we do not see how these concerns are specific to our work. Rather the concerns relate in general to the application of these methods.

We observed evidence of a protective association of full course 5 days treatment with oseltamivir against inpatient mortality, which emerged following adjustment for the confounding variables we identified. We believe this is plausible, given that risk of death is widely recognised to be associated with comorbidities and age, and that oseltamivir is licensed as an effective medication for seasonal influenza with a rational drug design against a viral target.

It is the case that multiple testing using regression analysis has occurred and the authors agree that accounting for this could result in an upper limit exceeding 1. However, it would still be the case that evidence of an association between standard course of oseltamivir and protection against inpatient mortality was demonstrated in a relatively large historic cohort of hospitalised patients receiving routine clinical care.

Lytras et al. [1] write that the final multivariable model contained nine predictors in a dataset with just 32 outcome events (deaths), that our model was severely overfitted suggesting that the low prevalence of several risk factors in the data hints at potential multicollinearity problems and that, both during the stepwise

procedure and in the final model, Variance Inflation Factors for the covariates should have been included (i.e. in Table 2 of the article [2]). In response, we note there were only seven variables in the final model of Table 2 with a total of nine parameters and do not agree that there is universal acceptance of the 10 events per variable recommendation [3]. In any situation, the required number of observations could be more or less than this number. An over fitted model would be manifested in extreme estimates and confidence intervals. All the estimates and confidence intervals presented are proportionate, with the wide confidence interval for 'excessive alcohol use' reflecting the few individuals with that factor. The nonlinear link function used in the logistic regression has meant that collinearity would have needed to have been severe for it to have caused difficulties, which would have been manifested in the estimates and confidence intervals.

With regard to delay in Table 3 of our study [2], for those not receiving oseltamivir, the delay was coded as zero. A binary variable defined to be one if antiviral given and zero otherwise was created in order to assess the impact of delay on mortality by interacting it with delay whenever delay was to be analysed.

Acknowledgements

The following authors of the original article are acknowledged: Ben Warne, Lucy Reeve, Nicholas K. Jones, Kyriaki Ranellou, Silvana Christou, Callum Wright, Saher Choudhry, Clare Sander, Hongyi Zhang and Hamid Jalal. All authors of the original article approved the response.

Conflict of interest

None declared.

Authors' contributions

Mark Reacher, Neville Verlander and Maria Zambon wrote the response letter.

References

1. Lytras T, Bonovas S, Nikolopoulos GK, Tsiodras S. Letter to the editor: influenza-associated mortality and oseltamivir: beware of misstepping into stepwise procedures. *Euro Surveill.* 2019;24(46):1900678. <https://doi.org/10.2807/1560-7917.ES.2019.24.46.1900678>
2. Reacher M, Warne B, Reeve L, Verlander NQ, Jones NK, Ranellou K, et al. Influenza-associated mortality in hospital care: a retrospective cohort study of risk factors and impact of oseltamivir in an English teaching hospital, 2016 to 2017. *Euro Surveill.* 2019;24(44):1900087. <https://doi.org/10.2807/1560-7917.ES.2019.24.44.1900087> PMID: 31690364
3. van Smeden M, de Groot JAH, Moons KGM, Collins GS, Altman DG, Eijkemans MJC, et al. No rationale for 1 variable per 10 events criterion for binary logistic regression analysis. *BMC Med Res Methodol.* 2016;16(1):163. <https://doi.org/10.1186/s12874-016-0267-3> PMID: 27881078

License, supplementary material and copyright

This is an open-access article distributed under the terms of the Creative Commons Attribution (CC BY 4.0) Licence. You may share and adapt the material, but must give appropriate credit to the source, provide a link to the licence and indicate if changes were made.

Any supplementary material referenced in the article can be found in the online version.

This article is copyright of the authors or their affiliated institutions, 2019.