Elsevier Editorial System(tm) for The Lancet Respiratory Medicine
Manuscript Draft

Manuscript Number: THELANCETRM-D-14-00221R1

Title: Authors' response

Article Type: Correspondence

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Manuscript Region of Origin: UNITED KINGDOM

EFFECTIVENESS OF NEURAMINIDASE INHIBITORS IN REDUCING MORTALITY IN HOSPITALISED INFLUENZA A(H1N1)pdm09 PATIENTS: AN INDIVIDUAL PARTICIPANT DATA META-ANALYSIS

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Conflicts of interest: Unchanged

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Current word count: 856 (not including Tables and legends)

Authors' response

We thank Drs Wolkewitz, Schumacher, Jones, Del Mar, Hama, Antes and Meerpohl for their comments [1-3] and address the key issues raised in a single response.

Potential datasets for the IPD analysis were identified via a systematic review[4] of published papers investigating the association between neuraminidase inhibitor (NAI) antiviral use and public health outcomes in hospitalised A(H1N1)pdm09 patients. This included quality assessment of studies using the Newcastle Ottawa Scale (NOS); median score 6 (range: 4-9). Studies were scored lower primarily because of failure to adjust for confounders.

To ensure that we included as many datasets as possible in the subsequent IPD analysis, we contacted authors of any publications (including letters) suggesting that they may have access to pandemic patient surveillance datasets including data on NAI antiviral use and patient outcomes. Our current publication[5] is part of a broader programme of study [6] and only reports on one of the primary outcomes of interest, namely mortality.

Of the 44 published studies included in our earlier systematic review[4], we were unable to obtain 37 datasets that included data on NAI antiviral use and mortality (median NOS score 6; range 4-9). Of these, 9 reported results significantly in favour of NAI antiviral treatment, none reported results significantly against NAI antiviral treatment and 28 did not find significant associations between treatment and mortality. The majority of our data were from unpublished surveillance studies that met our minimum dataset criteria and were then standardised according to an agreed protocol[5]. Some data contributors provided all their raw unprocessed data thus explaining why we have some missing values for NAI antiviral use. Figure 1[5] shows missing data on mortality and NAI antiviral use for transparency. We are unable to comment on unpublished datasets that are not included in our analysis or the extent to which these could bias our findings; this is clearly acknowledged in our paper[5].

Industry-sponsored trials involving A(H1N1)pdm09 patients would have met our inclusion criteria. We actively searched trials registers and contacted both NAI manufacturers for such studies during the conduct of our previous systematic review [4] but no data pertaining to the pandemic virus were identified.

With regard to the datasets included in the IPD analysis, all data contributors (co-authors) were asked to declare conflicts of interest including industry-sponsorship for their datasets, using the standard ICJME proforma. None of the datasets were declared as being industry-sponsored. A statement of declaration of interests can be found in the publication[5].

We have acknowledged in our paper that there are inherent limitations in a retrospective IPD analysis of observational data and our propensity score adjustment cannot completely eliminate selection bias or confounding by indication. Our conclusions that early NAI antiviral treatment is associated with a reduction in mortality are based on the results of the generalised linear mixed models.

Jones has already queried the validity of our time-dependent analysis elsewhere[7, 8] and we have submitted a detailed response[9, 10] explaining that we have used standard methods for modelling NAI antiviral use as a time-dependent covariate by splitting survival time in treated patients into untreated and treated time to account for immortal time bias. While, the publication by Beyersmann et al. [11] provided mathematical proof that accounting for time-dependent exposures should diminish the treatment effect, it did not focus on shared frailty models (to account for clustering nature of

our data) or the effect of other time-dependent biases and competing risks. Therefore, it is difficult to predict the shift in direction of the treatment effect when shared frailty models are considered.

Wolkewitz and Schumacher[1] make a valid point that patients who are discharged alive from hospital (competing risk for death) are presumably in a better health condition than patients who remain in hospital and we thank them for suggesting the Fine and Gray subdistribution hazard regression model[12]. However, accounting for all these biases in a single model with shared frailty is complex and standard statistical software packages cannot currently deal with them. Moreover, whether shared frailty models allowing for competing risks are appropriate is a controversial topic that needs to be resolved before they can be applied to clinical questions of such importance.

The accompanying table presents results from a series of models with advantages and disadvantages listed for each. In addition we include the hazard ratio for being discharged alive within 30 days of illness onset to illustrate the potential impact of discharge as a competing risk for the outcome death; this suggests patients who received antivirals were more likely to be discharged. Even though we are unable to quantify this effect at present using a single model which accounts for all the complexities mentioned above, it is unlikely that accounting for the competing risk will shift the effect of NAI antiviral treatment on the hazard of death towards the null.

Comparison of findings from various models (NAI treatment at any time versus none)

Model used (outcome)	**Adjusted† Ratio (95% CI)**	**Main advantages and disadvantages**
Odds ratio (in-patient death): generalized linear mixed model with study fitted as a random intercept	0·81 (0·70–0·93)[1]	Accounts for competing events and clustering; ignores time dependency of exposure and outcome
Hazard ratio (in-patient death): standard Cox regression model	0.36 (0.32-0.41)[2]	Antiviral use modelled as a time constant exposure; does not take into account clustering or immortal time bias
Hazard ratio (in-patient death): time-dependent Cox regression model	0.53 (0.48-0.59)[2]	Antiviral use modelled as a time dependent exposure to account for immortal time bias; does not take into account clustering
Hazard ratio (in-patient death): Cox regression shared frailty model	0.94 (0.80-1.10)[2]	Antiviral use modelled as a time constant exposure; does not take into account immortal time bias; takes into account clustering
Hazard ratio (in-patient death): time-dependent Cox regression shared frailty model	0·51 (0·45–0·58)[1]	Antiviral use modelled as a time dependent exposure to account for immortal time bias; takes into account clustering
Hazard ratio (in-patient death): Hazard ratio (discharge): time-dependent Cox regression shared frailty model	0.54 (0.47-0.62)[2*] 1.09 (1.05-1.13)[2*]	Antiviral use modelled as a time dependent exposure to account for immortal time bias; takes into account clustering; HR for discharge illustrates the potential impact of discharge as a competing risk for the outcome death

† Adjusted for propensity score quintile and treatment with corticosteroids and antibiotics

*A subset of the sample used for the survival analysis (99%) presented in Muthuri et al. (2014) where dates of discharge were known

[1] Findings presented in Muthuri et al. (2014); [2] New results from additional analyses conducted in response to Wolkewitz and Schumacher (2014)

In summary, we hope we have provided an adequate clarification on the issues raised in the correspondence and demonstrated how various biases and assumptions affect the results. This highlights the importance of a consensus in the scientific community regarding how to model shared frailty with competing risks and time dependent analyses to account for immortal time bias and time varying effects.

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