

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

Manuscript Number: THELANCETRM-D-14-00221R1

Title: Authors' response

Article Type: Correspondence

Corresponding Author: Prof. Jonathan S Nguyen-Van-Tam,

Corresponding Author's Institution: University of Nottingham

First Author: Stella Muthuri

Order of Authors: Stella Muthuri; Sudhir Venkatesan; Puja Myles; Jo Leonardi-Bee; Jonathan S
Nguyen-Van-Tam

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

Stella G Muthuri*, Sudhir Venkatesan*, Puja R Myles, Jo Leonardi-Bee, Tarig S A Al Khuwaitir, Abdullah Al Mamun, Ashish P Anovadiya, Eduardo Azziz-Baumgartner, Clarisa Báez, Matteo Bassetti, Bojana Beovic, Barbara Bertisch, Isabelle Bonmarin, Robert Booy, Victor H Borja-Aburto, Heinz Burgmann, Bin Cao, Jordi Carratala, Justin T Denholm, Samuel R Dominguez, Pericles A D Duarte, Gal Dubnov-Raz, Marcela Echavarría, Sergio Fanella, Zhancheng Gao, Patrick Gérardin, Maddalena Giannella, Sophie Gubbels, Jethro Herberg, Anjarath L Higuera Iglesias, Peter H Hoger, Xiaoyun Hu, Quazi T Islam, Mirela F Jiménez, Amr Kandeel, Gerben Keijzers, Hossein Khalili, Marian Knight, Koichiro Kudo, Gabriela Kuszniertz, Ilija Kuzman, Arthur M C Kwan, Idriss Lahlou Amine, Eduard Langenegger, Kamran B Lankarani, Yee-Sin Leo, Rita Linko, Pei Liu, Faris Madanat, Elga Mayo-Montero, Allison McGeer, Ziad Memish, Gokhan Metan, Auksė Mickiene, Dragan Mikić, Kristin G I Mohn, Ahmadreza Moradi, Pagbajabyn Nymadawa, Maria E Oliva, Mehpare Ozkan, Dhruv Parekh, Mical Paul, Fernando P Polack, Barbara A Rath, Alejandro H Rodríguez, Elena B Sarrouf, Anna C Seale, Bunyamin Sertogullarindan, Marilda M Siqueira, Joanna Skreć-Magierło, Frank Stephan, Ewa Talarek, Julian W Tang, Kelvin K W To, Antoni Torres, Selda H Törün, Dat Tran, Timothy M Uyeki, Annelies Van Zwol, Wendy Vaudry, Tjasa Vidmar, Renata T C Yokota, Paul Zarogoulidis, PRIDE Consortium Investigators†, Jonathan S Nguyen-Van-Tam

*SGM and SV are joint first-authors

†List of PRIDE Consortium Investigators' can be found on page 4

Conflicts of interest: Unchanged

Correspondence: Jonathan Van-Tam, DM, Room A28b, Clinical Sciences Building, University of Nottingham, City Hospital, Nottingham NG5 1PB, United Kingdom (jvt@nottingham.ac.uk).

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 comments¹⁻³ and address the key issues raised in a single response.

Potential datasets for the IPD analysis were identified via a systematic review⁴ 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 publication⁵ is part of a broader programme of study⁶ and only reports on one of the primary outcomes of interest, namely mortality.

Of the 44 published studies included in our earlier systematic review⁴, 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 protocol⁵. Some data contributors provided all their raw unprocessed data thus explaining why we have some missing values for NAI antiviral use. Figure 1⁵ 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 paper⁵.

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 review⁴ 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 publication⁵.

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 Schumacher¹ 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 model¹². 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.

PRIDE CONSORTIUM INVESTIGATORS

Maria De Lourdes Aguiar-Oliveira, Malakita Al Masri, Robed Amin, Wildo N Araújo, Elena Ballester-Orcal, Carlos Bantar, Jing Bao, Mazen M Barhoush, Ariful Basher, Edgar Bautista, Julie Bettinger, Roland Bingisser, Emilio Bouza, Ilkay Bozkurt, Elvira Čeljuska-Tošev, Kenny K C Chan, Yusheng Chen, Tserendorj Chinbayar, Catia Cilloniz, Rebecca J Cox, María R Cuzzo, Wei Cui, Simin Dashti-Khavidaki, Bin Du, Hicham El Rhaffouli, Hernan Escobar, Agnieszka Florek-Michalska, James Fraser, John Gerrard, Stuart Gormley, Sandra Götberg, Matthias Hoffmann, Behnam Honarvar, Jianmin Hu, Christoph Kemen, Gulam Khandaker, Evelyn S C Koay, Miroslav Kojic, Win M Kyaw, Leonard Leibovici, Hongru Li, Xiao-Li Li, Romina Libster, Tze P Loh, Deborah Macbeth, Efstratios Maltezos, Toshie Manabe, Débora N Marccone, Magdalena Marczynska, Fabiane P Mastalir, Mohsen Moghadami, Lilian Moriconi, Bulent Ozbay, Blaž Pečavar, Wolfgang Poeppel, Philippe G Poliquin, Mahmudur Rahman, Alberto Rascon-Pacheco, Samir Refaey, Brunhilde Schweiger, Fang G Smith, Ayper Somer, Thiago M L Souza, Payam Tabarsi, Chandrabhanu B Tripathi, Daiva Velyvyte, Diego Viasus, Qin Yu, Kwok-Yung Yuen, Wei Zhang, Wei Zuo.

References

1. Wolkewitz M, Schumacher M. Statistical concerns about the beneficial effect of neuraminidase inhibitors on mortality *Lancet Respiratory Medicine* 2014.
2. Jones M, Del Mar C, Hama R. Correspondence relating to Muthuri et al. (2014). *The Lancet Respiratory Medicine* 2014.
3. Antes G, Meerpohl J. Correspondence relating to Muthuri et al. (2014). *The Lancet Respiratory Medicine* 2014.
4. Muthuri SG, Myles PR, Venkatesan S, Leonardi-Bee J, Nguyen-Van-Tam JS. Impact of neuraminidase inhibitor treatment on outcomes of public health importance during the 2009-2010 influenza A(H1N1) pandemic: a systematic review and meta-analysis in hospitalized patients. *J Infect Dis* 2013; **207**(4): 553-63.
5. Muthuri SG, Venkatesan S, Myles PR, et al. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. *The Lancet Respiratory Medicine* 2014; **2**(5): 395-404.
6. Myles P, Leonardi-Bee J, Van-Tam J, Muthuri S, Venkatesan S. A systematic review of the impact of neuraminidase inhibitor antiviral use on outcomes of public health importance during the 2009/10 (swine) influenza A/H1N1v pandemic.
http://www.crd.york.ac.uk/IHR_PROSPERO/display_record.asp?ID=CRD42011001273#UvDWqFFNKW8(accessed Feb 4, 2014).
7. Kmietowicz Z. Study claiming Tamiflu saved lives was based on "flawed" analysis. *Bmj* 2014; **348**: g2228.
8. Jones M. Reply to Puja R Myles and Jo Leonardi-Bee. *Bmj* 2014; **2014**(348): g2990.
9. Myles PR, Leonardi-Bee J, Pride research consortium investigators. Authors' reply to Mark Jones's critique of the study by Muthuri and colleagues reported in The BMJ. *Bmj* 2014; **348**: g2990.
10. Myles P, Leonardi-Bee J. Further clarifications from the authors of the Muthuri et al. (2014) paper in response to Dr Jones' second critique. *Bmj* 2014; **348**: g2990.
11. Beyersmann J, Gastmeier P, Wolkewitz M, Schumacher M. An easy mathematical proof showed that time-dependent bias inevitably leads to biased effect estimation. *J Clin Epidemiol* 2008; **61**(12): 1216-21.
12. Wolkewitz M, Beyersmann J, Gastmeier P, Schumacher M. Modeling the effect of time-dependent exposure on intensive care unit mortality. *Intensive Care Med* 2009; **35**(5): 826-32.