Bangladesh and Rwanda: a case for a high burden of influenza in tropical countries?

Wladimir J. Alonso[1], André Ricardo Ribas Freitas[2], Cynthia Schuck-Paim[3]

[1] Laboratory for Human Evolutionary and Ecological Studies, Department of Genetics and Evolutionary Biology, University of São Paulo, São Paulo, Brazil

[2] Department of Epidemiology, São Leopoldo Mandic Medical School, Campinas, São Paulo, Brazil

[3] Origem Scientifica, São Paulo, Brazil

Corresponding Author:

Wladimir J. Alonso[1]

Email address: wladimir.j.alonso@wolfson.oxon.org

PeerJ Preprints | https://doi.org/10.7287/peerj.preprints.26705v1 | CC BY 4.0 Open Access | rec: 15 Mar 2018, publ: 15 Mar 2018

Bangladesh and Rwanda: a case for a high burden of influenza in tropical countries?

Wladimir J. Alonso
Laboratory for Human Evolutionary and Ecological Studies, Department of Genetics and Evolutionary Biology, University of São Paulo, São Paulo, Brazil
Corresponding author (wladimir.j.alonso@wolfson.oxon.org)

André Ricardo Ribas Freitas
São Leopoldo Mandic Medical School
Campinas, SP, Brazil

Cynthia Schuck-Paim
Origem Scientifica, São Paulo, Brazil

Two articles published recently conclude that influenza is associated with a significant mortality and morbidity burden in Bangladesh(Ahmed et al., 2018)and Rwanda(Nyamusore et al., 2018) . This is a matter of high relevance for public health, as it brings into consideration the introduction of annual influenza immunization campaigns in countries with severe competing priorities in public health. Bangladesh and Rwanda are both tropical countries, with mild winters. This is often good news as far as influenza burden is concerned, as there are indications that not only is influenza seasonality different in tropical regions(Alonso et al., 2015), but also associated with a considerably lower burden. Recently, the 2009 pandemic provided us with an additional opportunity to put this hypothesis on trial as, different from other years, the fraction of respiratory mortality attributable to the influenza relative to co-circulating pathogens could be identified much more clearly (given anomalies in the timing and amplitude in the temporal signal of deaths and hospitalizations caused by the pandemic). That hypothesis had support first in Brazil, a country with a relatively homogeneous public health system and immunization policies, yet spanning a wide range of latitudes and climates: while in non-equatorial regions of Brazil H1N1pdm was clearly associated with excess mortality rates (mainly in the southernmost states)(Freitas, Francisco & Donalisio, 2013; Freitas & Donalisio, 2018), the pandemic produced no noticeable anomalies in equatorial regions of Brazil (the poorest)(Schuck-Paim et al., 2012). Additionally, and contrary to what was

claimed, our analyses showed that H1N1pdm also did not affect mortality rates in Madagascar at that time(Alonso & Schuck-Paim, 2013). WHO's updates on the pandemic and subsequent studies also failed to detect a higher flu burden during the pandemic in other tropical regions (World Health Organization, 2010; Nzussouo et al., 2012) .

So we analyzed with great interest the recent claim of a relatively high influenza-associated mortality burden in Bangladesh (of 6 and 11 deaths per 100,000 population, respectively, in 2010-11 and 2011-12) and hospitalization burden in Rwanda. While doing so, we detected a poor match between the temporal signature of influenza virus detection and ARI cases(Alonso et al., 2012)Figure 2 of the Bangladeshi paper(Ahmed et al., 2018) shows that influenza circulation is out of phase with ARI-associated deaths; the lack of a match is particularly pronounced in the population older than 60 years, for which peaks in mortality (Dec-Feb) happen when influenza activity was at its lowest. In the case of the Rwandan study, no data on the seasonal patterns of influenza activity and hospitalization rates is provided (the authors "used annual influenza virus detection rate because the number of SARI cases enrolled did not display seasonal variations (data not shown)" (Nyamusore et al., 2018)A similar situation had been previously observed in an equatorial city in Brazil: when the timing of events was dissected closely, influenza circulation was found to be out of phase - by five weeks - with pneumonia & influenza attributed deaths(Alonso et al., 2012). The absence of respiratory syncytial virus (RSV) tests in these two studies from Bangladesh and Rwanda may have also contributed to distortions, as RSV has been shown to be associated with a substantial disease burden in all age groups(Fleming & Cross, 1993; Fleming et al., 2015). This may have been particularly accentuated in Rwanda where there was an estimate of disproportionately high hospitalization among younger children who are usually the most affected by this virus. We must also consider the more general difficulties associated with the attribution of disease burden to a specific pathogen when many of the deaths were in fact of patients with severe chronic conditions. Should the death of a terminal cancer patient who was infected with influenza be attributed to influenza or cancer? For public health policy

considerations, would the introduction of influenza vaccines spare a high number of lives in this context, particularly in light of the observation that it would not have prevented most (e.g. 87% in Bangladesh) ARI and SARI cases? These observations make us reluctant about the claim of a "heavier burden of influenza-associated severe illness on the continent" (Nyamusore et al., 2018) or the "substantial burden of seasonal influenza in the population of Bangladesh" (particularly in light of the 25-fold difference in the estimated seasonal mortality burden between this study and that of previous approach - 0.23 deaths/100,000 population – i.e. that does consider the problem of competing attributions of disease burden(Institute for Health Metrics and Evaluation (IHME), 2017)). We congratulate the authors of those studies for bringing more data into this relevant discussion, but suggest that the issues discussed here are considered in a putative recommendation of seasonal influenza vaccines in tropical settings.

Bibliography

Ahmed M., Aleem MA., Roguski K., Abedin J., Islam A., Alam KF., Gurley ES., Rahman M., Azziz-Baumgartner E., Homaira N., Sturm-Ramirez K., Danielle Iuliano A. 2018. Estimates of seasonal influenza-associated mortality in Bangladesh, 2010-2012. *Influenza and other Respiratory Viruses* 12:65–71. DOI: 10.1111/irv.12490.

Alonso WJ., Laranjeira BJ., Pereira S a R., Florencio CMGD., Moreno EC., Miller M a., Giglio R., Schuck-Paim C., Moura FE a. 2012. Comparative dynamics, morbidity and mortality burden of pediatric viral respiratory infections in an equatorial city. *The Pediatric infectious disease journal* 31:e9-14. DOI: 10.1097/INF.0b013e31823883be.

Alonso WJ., Schuck-Paim C. 2013. What can the 2009 influenza outbreak teach us about the risk of a severe pandemic? The Madagascar experience. *Epidemiology and Infection* 141:2454–2455. DOI: 10.1017/S0950268812003068.

Alonso WJ., Yu C., Viboud C., Richard SA., Schuck-Paim C., Simonsen L., Mello WA., Miller MA. 2015. A global map of hemispheric influenza vaccine recommendations based on local patterns of viral circulation. *Scientific Reports* 5:17214. DOI: 10.1038/srep17214.

Fleming D., Cross K. 1993. Respiratory syncytial virus or influenza? *The Lancet* 342:1507–1510. DOI: 10.1016/S0140-6736(05)80082-0.

Fleming DM., Taylor RJ., Lustig RL., Schuck-Paim C., Haguinet F., Webb DJ., Logie J., Matias G., Taylor S. 2015. Modelling estimates of the burden of Respiratory Syncytial virus infection in adults and the elderly in the United Kingdom. *BMC Infectious Diseases* 15:443. DOI: 10.1186/s12879-015-1218-z.

Freitas ARR., Donalisio MR. 2018. Excess of Mortality in Adults and Elderly and Circulation of Subtypes of Influenza Virus in Southern Brazil. *Frontiers in Immunology* 8:1903. DOI: 10.3389/fimmu.2017.01903.

Freitas ARR., Francisco PMSB., Donalisio MR. 2013. Mortality Associated with Influenza in Tropics, State of São Paulo, Brazil, from 2002 to 2011: The Pre-Pandemic, Pandemic, and Post-Pandemic Periods. *Influenza Research and Treatment* 2013:1–9. DOI: 10.1155/2013/696274.

Institute for Health Metrics and Evaluation (IHME). 2017.IHME Bangladesh Influenza, Both sexes, All ages. GBD Compare Data Visualization. *Available at http://ihmeuw.org/4cj5* (accessed December 20, 2017).

Nyamusore J., Rukelibuga J., Mutagoma M., Muhire A., Kabanda A., Williams T., Mutoni A., Kamwesiga J., Nyatanyi T., Omolo J., Kabeja A., Koama JB., Mukarurangwa A., Umuringa J d'Arc., Granados C., Gasana M., Moen A., Tempia S. 2018. The national burden of influenza-associated severe acute respiratory illness hospitalization in Rwanda, 2012-2014. *Influenza and Other Respiratory Viruses* 12:38–45. DOI: 10.1111/irv.12494.

Nzussouo NT., Michalove J., Diop OM., Njouom R., Monteiro M de L., Adje HK., Manoncourt S., Amankwa J., Koivogui L., Sow S., Elkory MB., Collard J-M., Dalhatu I., Niang MN., Lafond K., Moniz F., Coulibaly D., Kronman KC., Oyofo BA., Ampofo W., Tamboura B., Bara AO., Jusot J-F., Ekanem E., Sarr FD., Hwang I., Cornelius C., Coker B., Lindstrom S., Davis R., Dueger E., Moen A., Widdowson M-A. 2012. Delayed 2009 Pandemic Influenza A Virus Subtype H1N1 Circulation in West Africa, May 2009–April 2010. *The Journal of Infectious Diseases* 206:S101–S107. DOI: 10.1093/infdis/jis572.

Schuck-Paim C., Viboud C., Simonsen L., Miller M a., Moura FE a., Fernandes RM., Carvalho ML., Alonso WJ. 2012. Were equatorial regions less affected by the 2009 influenza pandemic? The Brazilian experience. *PloS one* 7:e41918. DOI: 10.1371/journal.pone.0041918.

World Health Organization. 2010.WHO | Situation updates - Pandemic (H1N1) 2009. *Available at http://www.who.int/csr/disease/swineflu/updates/en/* (accessed March 4, 2017).