



## **Estimation of the Serial Interval for Pandemic Influenza (pH1N1) in the Most Southern Province of Argentina**

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### **Abstract**

**Background:** A retrospective cohort study, in the context of household transmission, to estimate the serial interval (SI) of pH1N1 influenza in the island of Tierra del Fuego was carried out.

**Methods:** We collected data from the epidemiological surveillance system during disease outbreak in Ushuaia and Rio Grande, the two main cities of the southernmost province of Argentina. Only the records of patients and households with a positive result of RT-PCR assay for pH1N1 virus were used.

**Results:** A total of 283 laboratory confirmed cases were detected, from 550 samples analyzed. Hospitalizations were necessary in 13.8% of patients, yet no deaths were reported. Complete data of household contacts were available in 13 patients. We calculated an SI of 2.0 days (95% CI = 1.5 – 2.6 days), fitting to a log-normal distribution, the one that presented the best adjustment.

**Conclusion:** These results were consistent with estimates of SI calculated from Mexico, but lower than estimations from Canada, Germany and USA. We discuss these differences in relation to limitations of the current study design.

**Keywords:** Influenza A Virus, H1N1 subtype, Epidemiologic models, Argentina

### **Introduction**

In Argentina, the first imported cases of pandemic influenza H1N1 (pH1N1) were detected in April 2009, initiating the local transmission of the disease that widely spread in a few months (1). By August, 20 provinces of the country had reported deaths due to this disease. The first domestic cases in the island of Tierra del Fuego, the most southern province of Argentina, were detected in June in the cities of Ushuaia and Rio Grande. The transmission of the disease continued in both cities until October. A total of 6091 clinical cases were notified by the epidemiological surveillance system, and 281 cases were confirmed by serological tests for the novel influenza A virus (pH1N1). Control measures were implemented, including antiviral treatment for cases and post-exposure

prophylaxis for household contacts, isolation of symptomatic cases and school closures (2).

During H1N1 pandemics, mathematical models have been used to estimate the burden of disease, spread, and other health outcomes. These models depend on knowledge of key transmission parameters. One of the most important parameters estimated in the early stages of an epidemic is the serial interval. This parameter is defined as the time between successive cases in a single chain of transmission. The serial interval is generally calculated from the interval between clinical onsets (3). The aim of our study was to estimate the serial interval of pH1N1 influenza in Tierra del Fuego, particularly in household transmission, from empirical data.

## Materials and Methods

We analyzed the registries of influenza reported by the public health-care system of the cities of Ushuaia and Rio Grande, province of Tierra del Fuego, Argentina, between 1 June 2009 (date of symptoms onset of the first confirmed case of pH1N1 influenza in the province) and 10 November 2009 (date of symptoms onset of the last confirmed case). An influenza-like illness case was defined as temperature 38 degrees C or greater and either cough or sore throat. A confirmed case was defined by a positive result of a real-time polymerase chain reaction (RT-PCR) assay specific for pH1N1 virus. The laboratory tests was performed at the National Reference Laboratory, Servicio de Virosis Respiratorias del Instituto Nacional de Enfermedades Infecciosas, Buenos Aires, following the Centers for Disease Control and Prevention (CDC) protocol of real-time RT-PCR for influenza A (H1N1) of the USA, published by the World Health Organization (4).

The serial interval (SI) was estimated through a retrospective cohort design, using only the records of patients with a positive result of RT-PCR assay for pH1N1 virus in the entire province. The SI was calculated as the time in days between symptom onset in laboratory-confirmed index cases to symptom onset in corresponding household contacts. The pair index case-infected household contact were excluded if symptoms developed in both patients within the same day or with a difference greater than 7 days. When the disease developed in two or more household contacts, we only considered the difference found between the index case and the first household contact infected, and the other contacts were excluded. The serial intervals estimated were adjusted to three parametric models: Weibull, log-normal and gamma distributions (5). The three models were compared using the Akaike Information Criterion (AIC) for a better evaluation of adjustments. The preferred model is the one with the lowest AIC value. For the estimation of the serial interval and the 95% confidence intervals, we used a bootstrapping nonparametric resampling method

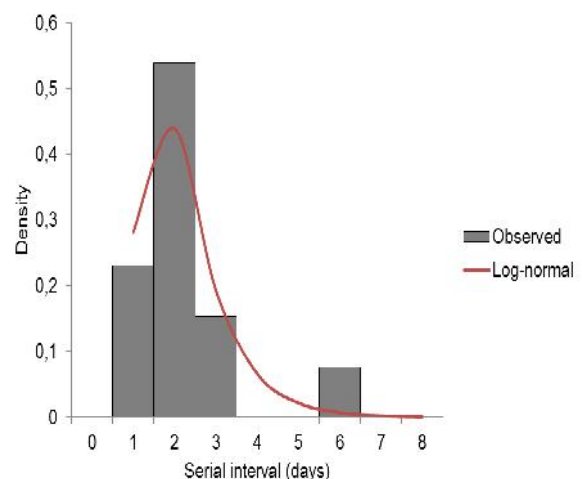
(6). Calculations were performed using R software version 2.10.1 (7) with the package fitdistrplus (8).

## Results

We detected 283 cases of pH1N1 influenza confirmed by laboratory tests from a total of 550 samples analyzed (51%). Hospitalizations were necessary in 13.8% of patients, yet no deaths were reported. Complete data of household contacts were available in 13 patients and all cases had clinical and serological confirmation. Thus, we obtained the estimates of the three distributions (Table 1).

**Table 1:** Parametric estimates of the serial interval for each probability distribution. Tierra del Fuego, Argentina, 2009

Probability distribution	Estimate	Standard error	Akaike Information Criterion (AIC)
Log-normal	Meanlog: 0.7 Sdlog: 0.5	0.1 0.1	39.4
Gamma	Shape: 4.2 Scale: 2.5	1.6 0.8	40.8
Weibull	Shape: 1.9 Scale: 2.5	0.4 0.4	43.1



**Fig.1:** Log-normal probability distribution (line) and observations (bars) for the influenza serial interval during 2009 outbreak in Tierra del Fuego, Argentina. According to the AIC, the log-normal distribution had the best adjustment. Using the results of the

1000 bootstrap resamplings, we estimated a mean SI of 2.0 days (95% CI = 1.5–2.6 days) (Fig.1).

## Discussion

Our estimation for the serial interval is consistent with the values estimated for the outbreak in La Gloria, Mexico: a SI of 1.91 days (9) or 2.09 days (10), but lower than other published values for Canada, Germany and USA, within the range of 2.5 and 5 days (11-15). As explained by White and Pagano (16), estimates of the serial interval are affected if the reporting fraction varies over time. This means that a decrease of the reporting fraction tends to underestimations of the serial interval. Thus, the study design may have influenced these estimates, since this was a retrospective study, and a decrease in the notification rates should be expected along the outbreak, especially in diseases with no specific treatment. Another interest point is that in our study, only secondary cases with laboratory confirmation by RT-PCR were considered. Some of the cited studies used the same criteria, while others have confirmed secondary cases if an epidemiological link to a laboratory-confirmed case could be demonstrated. Our study has several limitations. Nose and throat swabs were collected for laboratory confirmation of infection in a small number of patients. Not all patients sought medical care in health care centers, and we only considered medical consultations records within the public health care system. In consequence, these facts might have produced bias in our sample, as explained previously. Moreover, since this is a symptom-based design, selection bias might have occurred due to cases detected more than one day after symptoms onset, leading to a left truncation of infection status in household contacts. In addition, some secondary cases may be wrongly attributed to the household index and we may have misinterpreted some co-primary cases as secondary cases, leading us to underestimate the serial interval. Neither did we consider asymptomatic or sub-clinical infections. We performed the bootstrap technique to assess parameter uncertainty, but without a sensitivity analysis to evaluate the risk of community

transmission. This was due to the lack of information about other covariates that could allow the development of more complex statistical models, like the study by Cauchemez et al. (11). Despite the aforementioned limitations, we consider the estimation of the serial interval and other key parameters with empirical data very important for mathematical models of disease transmission.

## Ethical considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc) have been completely observed by the authors.

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## References

1. Raffo L (2009). Influenza A(H1N1) epidemic in Argentina. Experience in a National General Hospital (Hospital Nacional Alejandro Posadas). *Medicina (B Aires)*, 69(4):393-423.
2. Orellano PW, Grassi A, Reynoso JI, Palmieri A, Uez O, Carlino O (2010). Impact of school closings on the influenza A (H1N1) outbreak in Tierra del Fuego, Argentina. *Rev Panam Salud Publica*, 27(3):226-9.
3. Fine PE (2003). The interval between successive cases of an infectious disease. *Am J Epidemiol*, 158(11):1039-47.
4. World Health Organization WHO. CDC protocol of realtime RT-PCR for influenza A (H1N1). 2009; Available from: [http://www.who.int/csr/resources/publications/swineflu/CDCRealtimeRTPCR\\_SwineH1Assay-2009\\_20090430.pdf](http://www.who.int/csr/resources/publications/swineflu/CDCRealtimeRTPCR_SwineH1Assay-2009_20090430.pdf).
5. Cowling BJ, Fang VJ, Riley S, Malik Peiris JS, Leung GM. (2009). Estimation of the serial

- interval of influenza. *Epidemiology*, 20(3):344–7.
6. Efron B, Tibshirani RJ (1993). *An Introduction to the bootstrap*. Chapman and Hall. New York.
  7. Zuur AF, Ieno EN, Meesters EH (2009). *A beginner's guide to R*. Springer. New York.
  8. Delignette-Muller ML. Package 'fitdistrplus'. 2009; Available from: <http://cran.cnr.berkeley.edu/>.
  9. Fraser C, Donnelly CA, Cauchemez S, Hanage WP, Van Kerkhove MD, Hollingsworth TD, et al. (2009). Pandemic potential of a strain of influenza A (H1N1): early findings. *Science*, 324(5934):1557-61.
  10. White LF, Wallinga J, Finelli L, Reed C, Riley S, Lipsitch M, Pagano M (2009). Estimation of the reproductive number and the serial interval in early phase of the 2009 influenza A/H1N1 pandemic in the USA. *Influenza Other Respi Viruses*, (6):267-76.
  11. Cauchemez S, Donnelly CA, Reed C, Ghani AC, Fraser C, Kent CK et al. (2009). Household transmission of 2009 pandemic influenza A (H1N1) virus in the United States. *N Engl J Med*, 361(27):2619-27.
  12. Tuite AR, Greer AL, Whelan M, Winter AL, Lee B, Yan P et al. (2010). Estimated epidemiologic parameters and morbidity associated with pandemic H1N1 influenza. *CMAJ*, 182(2):131-6.
  13. Papenburg J, Baz M, Hamelin MÈ, Rhéaume C, Carbonneau J, Ouakki M et al. (2010). Household transmission of the 2009 pandemic A/H1N1 influenza virus: elevated laboratory-confirmed secondary attack rates and evidence of asymptomatic infections. *Clin Infect Dis*, 51(9):1033-41.
  14. Suess T, Buchholz U, Dupke S, Grunow R, an der Heiden M, Heider A et al. (2010). Shedding and transmission of novel influenza virus A/H1N1 infection in households—Germany, 2009. *Am J Epidemiol*, 171(11):1157-64.
  15. Sikora C, Fan S, Golonka R, Sturtevant D, Gratrix J, Lee BE et al. (2010). Transmission of pandemic influenza A (H1N1) 2009 within households: Edmonton, Canada. *J Clin Virol*, 49(2):90-3.
  16. White LF, Pagano M (2010). Reporting errors in infectious disease outbreaks, with an application to Pandemic Influenza A/H1N1. *Epidemiol Perspect Innov*, 7:12.