A preliminary estimation of the reproduction ratio for new influenza A(H1N1) from the outbreak in Mexico, March-April 2009

P Y Boëlle (boelle@u707.jussieu.fr)[1,2], P Bernillon[3], J C Desenclos[3]

1. INSERM, Institut national de la santé et de la recherche médicale (National Institute of Health and Medical Research), U707, Paris, France
2. Université Pierre et Marie Curie - Paris 6, UMR S 707, Paris, France
3. Institut National de Veille Sanitaire (Institute for Public Health Surveillance, InVS), Saint-Maurice, France

As of 12 May 2009, 5,251 cases of the new influenza A(H1N1) have been officially reported to the World Health Organization (WHO) from 30 countries, with most of the identified cases exported from Mexico where a local epidemic has been going on for the last two months. Sustained human-to-human transmission is necessary to trigger influenza pandemic and estimating the reproduction ratio (average number of secondary cases per primary case) is necessary for forecasting the spread of infection. We use two methods to estimate the reproduction ratio from the epidemic curve in Mexico using three plausible generation intervals (the time between primary and secondary case infection). As expected, the reproduction ratio estimates were highly sensitive to assumptions regarding the generation interval, which remains to be estimated for the current epidemic. Here, we suggest that the reproduction ratio was less than 2.2 – 3.1 in Mexico, depending on the generation interval. Monitoring and updating the reproduction ratio estimate as the epidemic spreads outside Mexico into different settings should remain a priority for assessing the situation and helping to plan public health interventions.

Introduction

As of 12 May 2009, 5,251 cases of the new influenza A(H1N1) have been officially reported to the World Health Organization (WHO) from 30 countries [1,2]. Two parameters must be estimated for this new virus using mathematical and computational models: the reproduction ratio (R), which measures the average number of secondary cases per primary case; and the generation interval, which measures the average time between infection in a primary case and its secondary cases. The larger the reproduction ratio, the higher the required efficacy of public health interventions [3]. Here we use two different methods to provide preliminary estimates of R for the outbreak in Mexico.

Methods

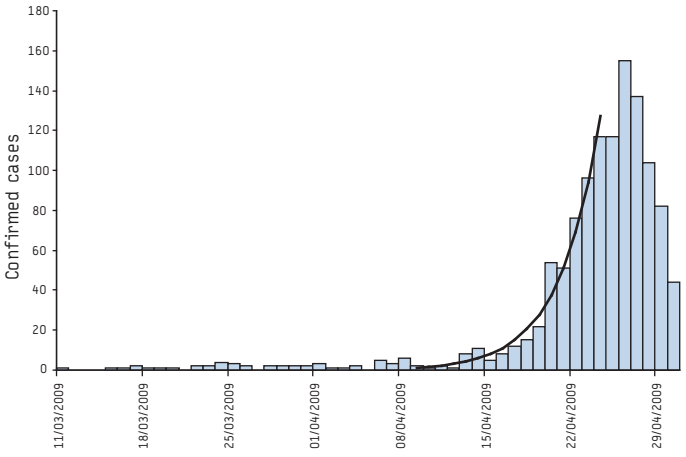
We used the daily incidence data from 11 March to 2 May 2009 as reported by the Mexican health authorities [4] (http://portal.salud.gob.mx/descargas/pdf/influenza/situacion_actual_de_la_epidemia_080509.pdf). The data consisted in 1,364 confirmed cases given as daily counts.

Two different approaches were used to estimate R:

- M1 - intrinsic growth rate [5]: the growth rate of the epidemic is estimated by Poisson regression over a given time interval and transformed to R using Laplace transform of the generation interval distribution. The assumptions are the exponential growth of the epidemic and known generation interval. After visual inspection of the epidemic curve, all periods starting before 20 April and ending after this date, more than five days long, were explored. Goodness of fit of the exponential model was judged by the deviance R–squared measure.
- M2 - real time estimation [6]: a daily reproduction ratio R(t) is determined by averaging the number of secondary cases over all possible chains of transmissions compatible with the epidemic curve. This approach assumes no imported cases, equiprobability of all chains of transmission compatible with the data and known generation interval.

Figure 1

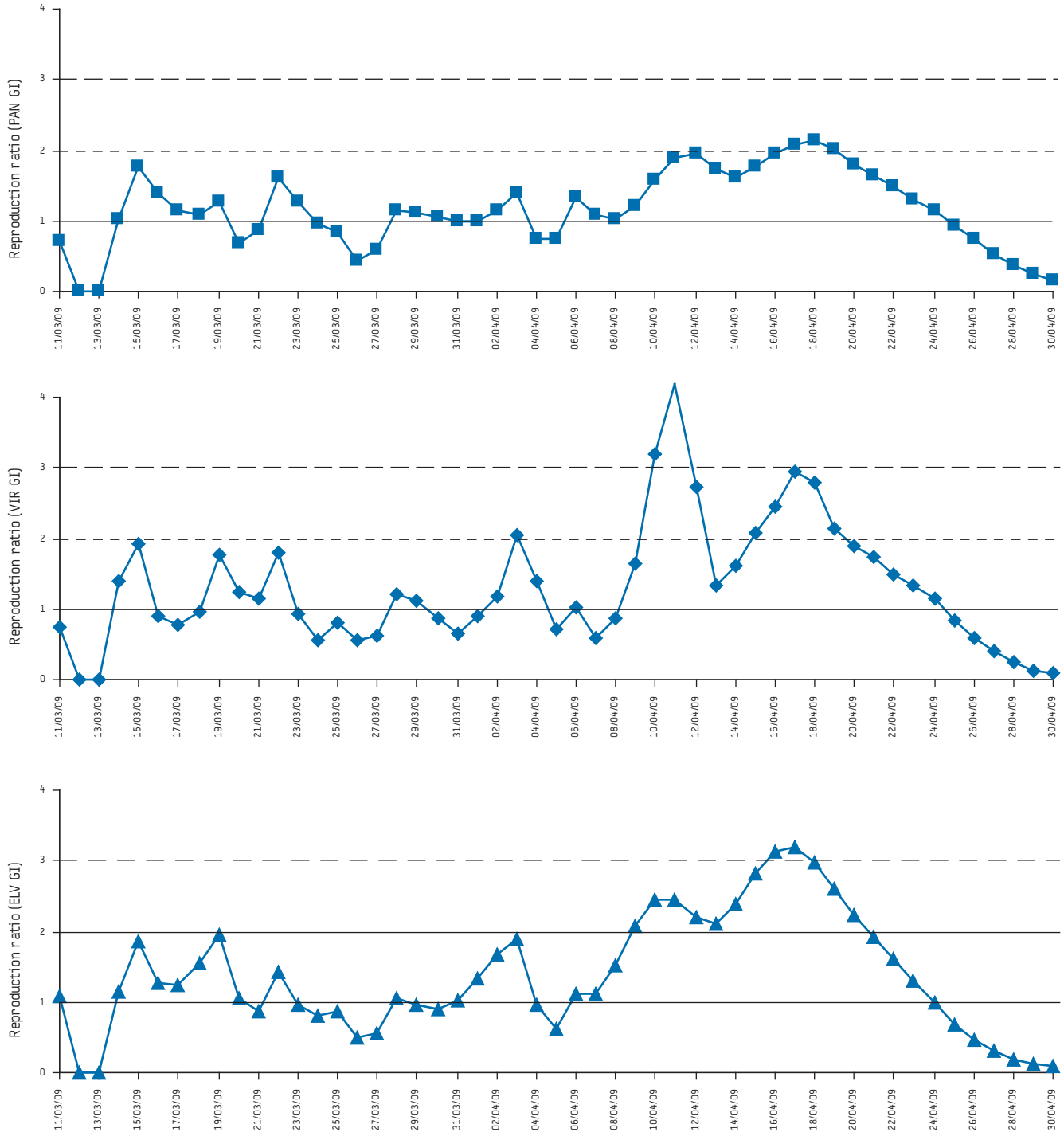
Epidemic curve of the outbreak of new influenza A(H1N1) in Mexico and fitted exponential growth over the period 9 to 24 April 2009



The two methods require full specification of the generation interval distribution. As no information regarding the actual generation interval in Mexico is available, we used three plausible candidate values of the generation interval (denoted GI) derived from different approaches: one (denoted as PAN) obtained from household studies from the 1957 and 1968 pandemics [7], one derived from viral excretion in experimental influenza infection (denoted as VIR) [8], and a hypothetical distribution introduced

Figure 2

Estimates of the daily reproduction ratio R(t) in the outbreak of new influenza A(H1N1) in Mexico, calculated with method M2 (see Methods) using three generation interval values: PAN GI (top), VIR GI (middle) and ELV GI (bottom)



in Elveback (denoted ELV) [9]. Their values with mean standard deviation (SD) were the following: PAN = 3.1 +/- 1.9 days; VIR = 2.6 +/- 1 day; ELV = 4.6 +/- 1.5 days.

Results

When using M1, the period starting on 9 April and ending on 24 April yielded the best fit for exponential growth, with daily rate r = 0.30 [CI95% 0.28-0.34] (Figure 1). The corresponding R was 2.2 [2.1, 2.4] for the PAN GI; 2.6 [2.4, 2.8] for the VIR GI; and 3.1 [2.9, 3.5] for the ELV GI. Overall, the differences in goodness of fit were small. The reproduction ratio decreased as the duration of the period used to estimate the growth rate increased: for the PAN GI, the maximum was 2.7 (8 days) and the minimum 2.0 (17 days).

With method M2, all three generation intervals led to similar profiles of R(t) with time: R(t) was around 1 up to 8 April then increased rapidly during the two following weeks (Figure 2). The magnitude of R depended on the generation interval: the maximum value was 2.1 (18 April) for the PAN GI; 4.0 (11 April) for the VIR GI; and 3.2 (17 April) for the ELV GI.

Discussion

Obtaining timely estimates of the reproduction ratio is crucial for deciding on public health interventions in case of a pandemic. In this respect, our analysis suggests that the maximum reproduction ratio was < 2.2 (for PAN GI); < 2.6 (for VIR GI) and < 3.1 (for ELV GI) during the outbreak in Mexico, subject to the following limitations.

Firstly, the epidemic curve was obtained by retrospective testing of samples, so that new cases may still be added. Indeed, for the same period (11 March to 26 April), there were 97 confirmed cases in the report published on 1 May, 682 in the 5 May report, and 803 in the 8 May report. With each new version of the epidemic curve, the reproduction ratio estimates grew smaller. The increase in the epidemic curve coincided with the setup of enhanced surveillance (starting from 16 April), suggesting improved case-finding with time. This notification/surveillance bias leads to overestimation of the reproduction ratio, as a larger number of late cases would be attributed to fewer earlier cases; on the other hand, however, the effect of public health interventions (closure of schools, restaurants and other public places, etc.) may affect the results in the opposite direction.

The assumptions required to estimate the reproduction ratio must also be taken into account. As already mentioned, the generation interval is unknown for the outbreak in Mexico, but of major importance for quantitative estimates. This illustrates the importance of estimating as soon as possible the generation time distribution to calibrate estimates of R [6]. As expected, longer generation time generally led to larger estimated R [3]. We believe the PAN GI should be favoured in the interpretation of the results, as it was determined from household data during past influenza pandemics.

A second limitation arises from arbitrary deciding which part of the epidemic curve displayed exponential growth, namely a minimum duration (five days), a starting and ending date. Stochastic variations, especially in small time series, may cause large uncertainties in the estimates [10]. Observing that the real time reproduction ratio M2, which does not rely on the exponential growth assumption, yielded smaller reproduction ratio estimates, suggests that method M1 yielded upper bound estimates.

A comprehensive analysis of all available data has independently led to the range 1.4-1.6 for the reproduction ratio [11]. At least two factors contribute to this substantially lower estimate: underreporting was explicitly taken into account and reduced the

Table

Epidemic growth rates estimated for the new influenza A(H1N1) epidemic in Mexico and corresponding reproduction ratio estimates calculated with method M1 (see Methods)

Period length (days)	Start date (m/d/y)	End date (m/d/y)	R^2	Growth rate (/day)	CI 95%	R (PAN GI)	R (VIR GI)	R (ELV GI)
5	04/19/09	04/23/09	0.8777	0.29	[0.29, 0.21]	2.2	2.5	3.0
6	04/19/09	04/24/09	0.9159	0.27	[0.27, 0.21]	2.1	2.4	2.8
7	04/16/09	04/22/09	0.9361	0.37	[0.37, 0.3]	2.6	3.1	3.9
8	04/15/09	04/22/09	0.9500	0.38	[0.38, 0.31]	2.7	3.2	4.0
9	04/15/09	04/23/09	0.9583	0.35	[0.35, 0.3]	2.5	2.9	3.6
10	04/15/09	04/24/09	0.9598	0.32	[0.32, 0.28]	2.3	2.7	3.3
11	04/14/09	04/24/09	0.9524	0.31	[0.31, 0.27]	2.3	2.6	3.2
12	04/13/09	04/24/09	0.952	0.3	[0.3, 0.26]	2.2	2.6	3.1
13	04/12/09	04/24/09	0.9537	0.3	[0.3, 0.27]	2.2	2.6	3.1
14	04/11/09	04/24/09	0.9585	0.3	[0.3, 0.27]	2.2	2.6	3.1
15	04/10/09	04/24/09	0.9619	0.31	[0.31, 0.28]	2.3	2.6	3.2
16	04/09/09	04/24/09	0.9643	0.3	[0.3, 0.28]	2.2	2.6	3.1
17	04/10/09	04/26/09	0.9564	0.26	[0.26, 0.24]	2.0	2.3	2.7
18	04/09/09	04/26/09	0.9596	0.26	[0.26, 0.24]	2.0	2.3	2.7
19	04/08/09	04/26/09	0.9544	0.26	[0.26, 0.24]	2.0	2.3	2.7
20	04/07/09	04/26/09	0.9554	0.25	[0.25, 0.24]	2.0	2.2	2.6

Note: Each line reports the best fitting period of given duration, as measured by the deviance R-squared measure.

reproduction ratio, and the generation interval, estimated from the actual epidemic, seems to have been much shorter than considered here (mean 1.9 days).

Although sensitive to all uncertainties discussed above, our early estimates show that the reproduction ratio in Mexico was in a range similar to that of past influenza pandemics [12,13].

Aknowledgements

The study was performed with the partial support of FP7 project FLUMODCONT (n° 20160)

References

1. World Health Organization. Influenza A(H1N1) - update 25. 12 May 2009. Available from: http://www.who.int/csr/don/2009_05_12/en/index.html
2. European Centre for Disease Prevention and Control. ECDC Situation Report. Influenza A(H1N1) infection. 12 May 2009. Available from: http://www.ecdc.europa.eu/en/files/pdf/Health_topics/Situation_Report_090512_0800hrs.pdf
3. Ferguson NM, Cummings DA, Fraser C, Cajka JC, Cooley PC, Burke DS. Strategies for mitigating an influenza pandemic. Nature. 2006;442(7101):448-52.
4. Ministry of Health of Mexico. Situación actual de la epidemia [Current epidemic situation]. 8 May 2009. Available from: http://portal.salud.gob.mx/descargas/pdf/influenza/situacion_actual_de_la_epidemia_080509.pdf
5. Wallinga J, Lipsitch M. How generation intervals shape the relationship between growth rates and reproductive numbers. Proc Biol Sci. 2007; 274(1609):599-604.
6. Cauchemez S, Boelle PY, Donnelly CA, Ferguson NM, Thomas G, Leung GM, et al. Real-time estimates in early detection of SARS. Emerg Infect Dis. 2006;12(1):110-3.
7. Ansart S, Boelle PY, Cauchemez S, Legrand J, Carrat F, Ferguson N, et al. Generation interval and reproduction number for influenza: a review. Technical report. Université Pierre et Marie Curie: Paris; 24 April 2009.
8. Carrat F, Vergu E, Ferguson NM, Lemaitre M, Cauchemez S, Leach S, et al. Time lines of infection and disease in human influenza: a review of volunteer challenge studies. Am J Epidemiol. 2008;167(7):775-85.
9. Elveback LR, Fox JP, Ackerman E, Langworthy A, Boyd M, Gatewood L. An influenza simulation model for immunization studies. Am J Epidemiol. 1976;103(2):152-65.
10. Chowell G, Nishiura H, Bettencourt LM. Comparative estimation of the reproduction number for pandemic influenza from daily case notification data. J R Soc Interface. 2007; 4(12):155-66.
11. Fraser C, Donnelly CA, Cauchelmes S, Hanage WP, Van Kerkhove MD, Hollingsworth TD, et al. Pandemic potential of a strain of influenza A (H1N1): early findings. Published 11 May 2009 on Science Express. DOI: 10.1126/science.1176062. Available from: http://www.sciencemag.org/cgi/content/abstract/1176062
12. Mills CE, Robins JM, Lipsitch M. Transmissibility of 1918 pandemic influenza. Nature. 2004; 432(7019):904-6.
13. Gani R, Hughes H, Fleming D, Griffin T, Medlock J, Leach S. Potential impact of antiviral drug use during influenza pandemic. Emerg Infect Dis, 2005;11(9):1355-62.

This article was published on 14 May 2009.

Citation style for this article: Boëlle PY, Bernillon P, Desenclos JC. A preliminary estimation of the reproduction ratio for new influenza A(H1N1) from the outbreak in Mexico, March-April 2009. Euro Surveill. 2009;14(19):pii=19205. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19205