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Review Article

Transmission parameters of the A/H1N1 (2009) influenza virus pandemic: a review

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Background The new influenza virus A/H1N1 (2009), identified in mid-2009, rapidly spread over the world. Estimating the transmissibility of this new virus was a public health priority.

Methods We reviewed all studies presenting estimates of the serial interval or generation time and the reproduction number of the A/H1N1 (2009) virus infection.

Results Thirteen studies documented the serial interval from household or close-contact studies, with overall mean 3 days (95% CI: 2·4, 3·6); taking into account tertiary transmission reduced this estimate to 2·6 days. Model-based estimates were more variable, from 1·9 to 6 days. Twenty-four studies reported reproduction numbers for community-based epidemics at the town or country level. The range was 1·2–3·1, with larger estimates reported at the beginning of the pandemic. Accounting for under-reporting in the early period of the pandemic and limiting variation because of the choice of the generation time interval, the reproduction number was between 1·2 and 2·3 with median 1·5.

Discussion The serial interval of A/H1N1 (2009) flu was typically short, with mean value similar to the seasonal flu. The estimates of the reproduction number were more variable. Compared with past influenza pandemics, the median reproduction number was similar (1968) or slightly smaller (1889, 1918, 1957).

Keywords Influenza pandemic, reproduction number, serial interval.

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Introduction

In April 2009, a new influenza virus A/H1N1 (2009) was isolated in Mexico and has rapidly spread over the world, being reported in 214 countries 1 year after its first identification.[1] The spread of the virus was extremely fast worldwide.[2] As soon as the new virus was identified, a major issue was to estimate the transmissibility of the new virus. In the guidance document 'Global surveillance during an influenza pandemic' released by the World Health Organization, three parameters were highlighted that should be documented quickly in this respect: the incubation period (time between infection and symptoms), the serial interval (time between symptoms onset in primary case and secondary case), and the reproduction ratio/number (average number of secondary cases per primary case).[3] These parameters are instrumental to assessing the feasibility and efficacy of intervention strategies against pandemic influenza.[4]

Information regarding the serial interval and the reproduction number from past pandemics has been limited. For the serial interval, the best information concerned seasonal influenza infections[5,6] and no information was available regarding past pandemics. There was comparatively more information regarding reproduction numbers, with estimates obtained in the last four pandemics (1889, 1918, 1957, 1968).[7–12] Estimates have ranged between 1 and 6 depending not only on place, time, wave, but also on the methods and assumptions used in estimation.

As we have now entered the post-pandemic period for H1N1(2009),[13] it is timely to review the results of all studies regarding the serial interval or generation time for the A/H1N1 flu, as well as the reproduction numbers, to allow comparison with previous pandemics and help in planning. Here, we present the results of a systematic review of published estimates concerning the first wave of A/H1N1 (2009) concerning the serial interval and the reproduction number.

Definitions

Generation time and Serial interval

The generation time (GT) is the time interval between the date of infection in one case and that in its infector.[14] It is

difficult to measure in practice, as the actual time of infection is not observed. The serial interval (SI), i.e., the time interval between the date of symptoms onset in one case and that in its infector, is therefore often considered instead of the GT because it has the same mean.[14] The GT or SI informs on the speed of transmission of the disease. It is not an intrinsic property of the disease, but a combination of biology (how much and when is a person infectious) and behavior (how many and when contacts leading to infection occur).[15]

A random sample of pairs of secondary case and their infector would allow unbiased estimation of the SI but is seldom available. In practice, various designs are used to observe pairs of infectee/infector, and this may impact the observed distribution.[16] For example, cases may be observed in households, where common exposure may have led to coprimary cases and ongoing transmission to an overlap of secondary and tertiary cases. Statistical modeling is therefore required to recover the true SI distribution.

Reproduction number

The reproduction number (or reproduction ratio), denoted R, is defined as the average number of secondary cases caused by one index case.[17] A reproduction number may be calculated at any time during an outbreak, a value larger than 1 corresponding to epidemic spread of the disease. In practice, additional qualifiers are often used when reporting a reproduction number: 'initial' in the beginning of an epidemic; 'basic' when the whole population is initially susceptible to the disease – R is in this case denoted R_0; 'effective' when the natural course of the outbreak is altered, for example, by interventions. Several methods are available to estimate reproduction numbers: using attack rates,[18] the exponential growth rate,[19] averaging over transmission chains.[20] An assumption regarding the GT distribution may be required to estimate the reproduction number; in this case, a shorter mean GT will likely lead to a smaller reproduction number estimate.

Methods

We systematically searched MEDLINE, Eurosurveillance (http://www.eurosurveillance.org), and Plos Currents Influenza (http://currents.plos.org/influenza) for published articles reporting estimates of the generation time/serial interval and reproduction numbers during the first wave of the A/H1N1 2009 flu pandemic. We used the following queries:

Q1 – (influenza OR flu) AND (H1N1 OR pandemic OR A/H1N1) AND (reproduction OR reproductive) AND (ratio OR rate OR number)

Q2 – (influenza OR flu) AND (H1N1 OR pandemic OR A/H1N1) AND ['serial interval' OR 'generation time' OR 'generation interval' OR ('onset' AND 'time')]

The search was performed on July 28, 2010, and was limited to publications in English after April 2009.

Query Q1 reported 101 hits in MEDLINE, and query Q2 reported 75 hits in MEDLINE. All publications were reviewed for relevance, and we finally retained 36 papers presenting original estimates of reproduction numbers, the serial interval, or the generation time.

For all studies, we abstracted the date of publication, the place and date where the data were collected, the estimate of the reproduction number and of the mean SI or GT and its confidence interval when reported; we summarized how the data were collected and the method for analysis. We focused on reproduction number estimates described as 'basic' or 'initial'. In studies where the reproduction number was estimated as a function of time, we reported the range of $R(t)$ values.

Results

Serial intervals and generation times

Seventeen independent estimates of the mean SI or GT during the 2009 H1N1 pandemic were reported in sixteen studies. Details are reported in Table 1 and Figure 1. The data were collected early in the pandemic, between April and August 2009.

In a first group of 13 studies, estimation was based on the analysis of observed time intervals between cases and their close contacts, especially in households. Cases and their households or contacts were included as part of the local health authorities response to the pandemic, except in one study where households had been included in a prospective clinical trial.[21] Whether the data were prospective or retrospective was not reported except in two retrospective cases.[22,23]

Household contacts only were used in eight studies,[21,23–29] yielding mean SIs in the range of 2·6–4·4 days. In all but one study, the index case was the first case in the household. Household observed serial intervals were defined as the difference in date of symptoms onset between incident cases and the index case. In the study where the index case could be different from the first, all cases after the index were considered as secondary cases of the index case.[27] The other five studies included contacts not limited to the household,[22,30–33] with mean SIs in the range of 2·5–3·5 days. Here, pairs of infector/infectee were identified where the infector was the only, or most probable, source of infection.

The largest estimate (4·4 days; range = [1,9]) was obtained from only five serial intervals observed in three

Table 1. Generation time or serial interval of A/H1N1 (2009) virus infection

Date published	Date collected	Country	*n*	Mean duration (days; 95% CI)	Data description	Method	Author
Model-based estimates							
May 2009	April 2009	Mexico	–	1·9 [1·3, 2·7]	Epidemic in La Gloria, Mexico	Mathematical modelling of the epi demic curve	Fraser[34]
October 2009	April–May 2009	Mexico	–	2·7 [2·6–2·9] 3·2 [2·9–3·4]	Dates of onset of laboratory-confirmed cases	Probabilistic modelling of the trans mission chain	Yang[29]
February 2010	April–June 2009	Canada	–	4·4	Laboratory-confirmed cases of pandemic H1N1 influenza with known date of onset	Mathematical modelling of the epidemic curve	Tuite[35]
September 2009	April 2009	USA	–	2·6 [1·9, 3·3]	Confirmed and probable cases reported to CDC	Probabilistic modelling of the transmission chain. Joint estimation with reproduction number	White[36]
Close-contacts estimates							
July 2009	June 2009	Netherlands	32	2·7 [2·3, 3·1]	Onset dates. Index cases: laboratory-confirmed cases; Other cases: 32 close contacts	Mean of empirical serial intervals	Hahné[32]
May 2009	May 2009	Spain	21	3·5 [1–6]**	Onset dates. Index cases: laboratory-confirmed cases; Other cases: 21 close contacts	Median of empirical serial intervals	SG-Spain[30]
October 2009	April 2009	USA	5	4·4 [1–7]*	Onset dates. Index cases: First in a household where ≥1 case was confirmed for H1N1 2009. Other cases: 5 clinical cases	Mean of empirical serial intervals	Yang[29]
October 2009	April–May 2009	Australia	37	2·9 [2·4, 3·3]	Onset dates. Index cases: laboratory-confirmed cases. Other cases: 37 cases with no other contact known	Mean of empirical SI distribution fitted by gamma distribution	McBryde[33]
November 2009	April–June 2009	UK	58	2·5 [2·1, 2·9]	Onset dates. Index cases: laboratory-confirmed cases. Other cases: 58 cases with no other contact known	Model fitting to empirical serial intervals, allowing tertiary cases	Ghani[31]
December 2009	May, 2009	USA	78	2·6 [2·2, 3·5]	Onset dates. Index cases: probable/confirmed H1N1 2009 flu reported to CDC. Other cases: 78 acute respiratory illnesses in household contacts	Probabilistic modelling accounting for out of household transmission and tertiary cases	Cauchemez[24]
December 2009	April–May 2009	USA	16	2·7 [2·0–3·5]	Onset dates. Index cases: laboratory-confirmed cases. Other cases: 16 laboratory-confirmed contacts with no other contact known	Fitting of parametric distribution to interval censored data (shortest/longest SI compatible with each pair)	Lessler[22]
January 2010	May–June 2009	Chile	54	3·6 (Median: 3)	Onset dates. Index cases: 57 laboratory-confirmed cases. Other cases: 54 household contacts with ILI	Mean of empirical serial intervals	Pedroni[27]
April 2010	April–May 2009	USA	32	3·4 [2·9, 4·0] (Median: 4)	Onset dates. Index cases: laboratory-confirmed cases; Other cases: 32 household contacts, laboratory confirmed, ILI or ARI	Mean of empirical serial intervals	Morgan[26]

Table 1. (*Continued*)

Date published	Date collected	Country	*n*	Mean duration (days; 95% CI)	Data description	Method	Author
April 2010	May 2009	USA	77	3·0 [2·5, 3·5] (Median: 3)	Onset dates. Index cases: Students in high school with ILI or laboratory confirmed. Other cases: 77 ILI in household contacts up to 1 month following index case	Mean of empirical serial intervals	France[23]
March 2010	April–August 2009	Germany	8	2·6 [1–3]*	Onset dates. Index cases: first with ILI in a household with ≥1 laboratory-confirmed infection. Other cases: 8 household members with ILI	Empirical mean of the time to the first non-index-case	Suess[28]
June 2010	July–August 2009	Hong Kong	8	3·2 [2·4, 4·0]	Onset dates. Index cases: laboratory-confirmed infections. Other cases: 8 household members with symptoms	Parametric fit of observed serial intervals, assuming all non-index-cases are secondary	Cowling[21]
June 2010	June 2009	Hong Kong	12	2·8 [2·1–3·4]	Onset dates. Index cases: students in secondary school with laboratory-confirmed infection. Other cases 12 household contacts	Mean of empirical serial intervals	Leung[25]

*Range.
**Median SI.

households.[29] One estimate (2·6 days, range = [1,3]) was based on eight observed household SI; however, only the first non-index-case in the household was used.[28] In four instances, only the median SI was reported,[22,23,26,30] and we computed the empirical mean of observed SI when the data were detailed enough: the mean SI was 3·5 days (CI 95% [2·9, 4·1])[26] and 3 days (95% CI [2·5–3·5]),[23] very similar to the reported medians. In these calculations, coprimary cases (same day as index case) and those occurring more than 7 days after the index case were excluded.

In all but two cases, the mean SI was calculated as the empirical mean of observed intervals, excluding the possibility of tertiary transmission. More sophisticated modeling allowing for several generations of transmission was carried out in the two other cases. In the first case, a household-based study, the empirical mean SI (excluding coprimary cases and cases >7 days after) was 2·9 days (95% CI [2·7, 3·1]).[24] After modeling, the reported mean SI decreased to 2·6 days (95% CI [2·2, 3·5]). In the second case, derived from the FF100 cohort in the UK, the empirical mean SI of observed serial intervals was 3·4 days (95% CI [2·9, 3·9]) and the reported mean SI decreased to 2·5 days (95% CI [2·1, 2·9]) after modeling.[31]

An overall estimate of the mean SI derived from these studies (excluding[28]), weighting by the number of observed SIs used for estimation in each study, was 3·0 days (CI 95% [2·4, 3·6]). No correlation was found between the reported SI and the size of the study ($P = 0·3$) or the date of report ($P = 0·3$). Household-based studies did not yield different estimates of the mean SI than close-contact studies ($P = 0·15$).

A second group of four studies reported the SI or GT estimated by modeling epidemic curves. These included the smallest estimate of all, a mean GT of 1·9 days (CI 95% [1·3, 2·7]) in a Mexican village,[34] and the largest, a mean GT of 4–5 days in Ontario.[35] The two other estimates used epidemic curves in the United States and Mexico, with results in the range of 2·6–3·2 days for the mean SI or GT. White estimated the mean SI at 2·6 days (CI 95% [1·9, 3·3]), but accounting for increased case ascertainment in time reduced this estimate to 2·2 days.[36] In Yang, the mean GT was 2·7 or 3·2 days depending on the assumed parametric form (Weibull or gamma).[29]

Reproduction numbers

Reproduction numbers were reported in 24 studies (see Table 2 and Figure 2) for 20 countries. All studies focused on the first few months of the pandemic, with data obtained between March and October 2009. Overall, the estimates at the community level (town, region or country) varied between 1·1 and 3·1, with a median value of 1·6. In the Netherlands, as in other European countries (except the UK), the reproduction number was smaller than 1

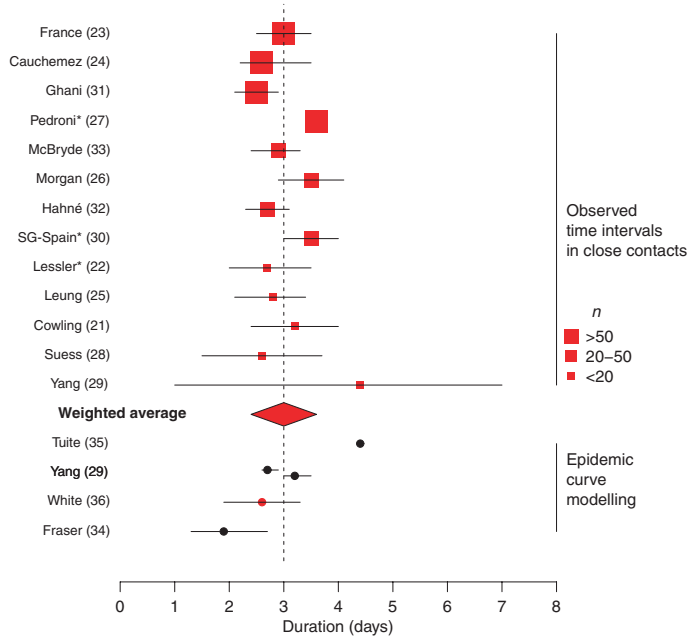

Figure 1. Mean serial intervals (red) or generation time (black) estimated for the A/H1N1 2009 pandemic, with 95% confidence interval. For serial intervals estimated in close contacts, the number of pairs infector/infectee *n* is coded by the size of the symbol. The dashed line is the weighted mean of mean SI in households and close-contacts studies; diamond shows the 95% confidence interval (*median SI).

(R = 0·5) in the period considered.[32,37] The largest estimate (R = 3·3) was obtained from the analysis of a school outbreak.[22] Ten papers qualified the reproduction number as 'basic', with a range from 1·3 to 2·3, all assuming that the whole population was susceptible at first; this range was not significantly different from that of the otherwise reported R values.

In 15 analyses, the exponential growth rate estimated from the initial epidemic curve was used to estimate the reproduction number, with a range of values between 0·5 and 3·1. The method for estimating the exponential growth rate was variable (for example, Poisson regression,[38] birth and death process,[39] least squares,[40] modified logistic growth[41]), as was the GT distribution (mean GT between 1·9 and 4·1) and the formula linking the exponential growth rate to the reproduction number. Other methods of estimation included fitting the output of transmission models to the data.[34,35,42] In two instances, the reproduction number was estimated using cases seen in tourists returning from Mexico, yielding 1·4 (95% CI [1·2, 1·8])[34] when comparing the number of cases in 9 countries to model predictions and 1·7 (CI 95% [1·6, 1·9]) using only the date of first introduction in 12 countries.[43]

No correlation was found in the reported reproduction number and the GT used in its computation (r = −0·04; P = 0·83). There was a decreasing trend in the reported values with time (r = −0·5, P = 0·004), large estimates being more frequent at first. A first explanation was the inclusion of correction for under-reporting: while no correction was applied for an early estimate in Mexico (R = 2·2[38]) and another analysis (R = 2·3[29]), accounting for an increasing trend in case reporting led to large differences, from 2·4 to 1·6 after such correction in Australia,[44] from 2·2 to 1·7 in the United States,[36] and from 2 to 1·4 in Mexico.[42] Another issue was the importance of school outbreaks in the early epidemic curve, so that the estimated reproduction number was not representative of transmission in the community. For example, the R estimate was 2·3 in Japan with a GT of 1·9 days,[39] but the reproduction number was approximately 1·3 when transmission was later established in the community.[45] Considering only estimates for which underdeclaration was taken into account and the generation time was close to 3 days, the reproduction number was between 1·2 and 2·3, with median value 1·5.

Discussion

Using all published information as of July 2010 regarding the A/H1N1 (2009) pandemic shows that the mean SI was <3 days and the reproduction number typically close to 1·5.

Serial intervals and generation times

A striking feature of the household/close-contact studies for the mean SI was that most estimates were in the range of 2·5–3·5 days, although the sampling as well as the meth-

Table 2. Reproduction number of A/H1N1 (2009) virus infection

Date published	Date collected	Country	Reproduction number	Mean GT (days)	Data description (type; spatial resolution; description)	Method	Author
North America							
May 2009	April–May 2009	Mexico	1·4 [1·2, 1·9] 1·2 [1·1, 1·6] 1·6 [1·3, 2·0]	2·6 1·9	Onset dates; country; cumulated cases in countries seeded from Mexico; cumulated cases by age class in local epidemic; gene sequences	Back calculation model based on passenger flows from Mexico; SEIR model maximum-likelihood fitting; Bayesian coalescent model	Fraser[34]
May 2009	April–May 2009	Mexico	2·2 [2·1, 2·4] 3·1 [2·9, 3·5]	3·1 4·1	Onset dates; country; daily confirmed cases	Best-fitting exponential growth rate	Boëlle[38]
July 2009	April–June 2009	Mexico	1·7	3	Onset dates; city; daily probable or confirmed cases	Exponential growth rate	Cruz-Pacheco[40]
August 2009	March–April 2009	Mexico	2·0 [1·8, 2·3] 1·4 [1·3–1·6]	>3	Onset dates; city; daily reported confirmed cases, corrected for under-declaration	Network-based statistical approach assuming on average 30 contacts per case	Pourbohloul[42]
September 2009	April–May 2009	Mexico	1·75 [1·6, 1·9]	3·6	Onset dates; country; time of onset of first H1N1 case in 12 countries	Maximum likelihood based on assumption of seeding from Mexico	Balcan[50]
September 2009	April–May 2009	USA	2·2 [1·4, 2·5] 1·7 [1·4, 2·1]	2·6 2·2	Onset dates; country; daily laboratory-confirmed cases	Maximum-likelihood estimation of R and GT based on Poisson assumption	White[36]
October 2009		US Mexico	1·0–2·1 [1·0, 3·7] 2·3 [2·1, 2·5]	3·5	Onset dates; households, schools, country; daily clinical or laboratory-confirmed cases	Weighted estimate of reproduction numbers in household, school, community	Yang[29]
December 2009	April–May 2009	USA	3·3 [3·0, 3·6]	2·8	Onset dates; school; daily incident cases in school students	Exponential growth rate	Lessler[22]
February 2010	April–June 2009	Canada (Ontario)	1·3 [1·2, 1·4]	6	Onset dates; province; daily confirmed cases	S/E/I/R fit to epidemic curve, accounting for imports	Tuite[35]
South America							
August 2009	June 2009	Peru	1·2–1·7	2·8	Onset dates; country; daily number of laboratory-confirmed cases	Exponential growth rate	Munayco[58]
January 2010	May–June 2009	Chile	1·8 [1·6, 2·0]	2·5	Onset dates; country; daily clinical and laboratory-confirmed H1N1 cases	Best-fitting exponential growth rate	Pedroni[27]
June 2010	June–August 2009	AR/CL/BZ/ NZ/AUS/SA	1·2–1·6	1·9	Onset dates; country; daily number of confirmed cases. daily number of hospitalizations for flu	Exponential growth rate (estimated using Richard's model)	Hsieh[41]
Asia							
June 2009	May–June 2009	Japan	2·3 [2·0, 2·6]	1·9	Onset dates; province; daily confirmed cases	Exponential growth rate	Nishiura[39]
August 2009	June 2009	Thailand	2·1 [1·9, 2·2] 1·8 [1·7, 1·9]	2·6 1·9	Onset dates; country; daily number of clinical cases	Best-fitting exponential growth rate	deSilva[59]

Table 2. (*Continued*)

Date published	Date collected	Country	Reproduction number	Mean GT (days)	Data description (type; spatial resolution; description)	Method	Author
March 2010	May–August 2009	Hong Kong	1·7 [1·6, 1·8]	3	Onset dates; city; daily number of cases in before June 11	S/E/I/R type model fit to initial epidemic curve	Wu[60]
May 2010	June–July 2009	VietNam	1·5 [1·5, 1·6] 2·0 [1·9,2·2]	1·9 3·6	Onset dates; country; daily confirmed cases	Exponential growth rate	Hien[61]
June 2010	September 2009	China	1·7 [1·5, 1·9]	4·3	Onset dates; province; daily number of hospitalized cases	S/E/I/R type model fit to initial epidemic curve	Tang[62]
Europe							
July 2009	May–June 2009	NL	0·5	3	Onset dates; country; daily confirmed cases	Average empirical growth rate	Hahné[32]
November 2009	May–June 2009	UK	1·4 [1·3, 1·6]	2·5	Onset dates; country; daily laboratory-confirmed cases	Exponential growth rate; transmission chain reconstruction	Ghani[31]
January 2010	June–October 2009	UK	1·3 [1·2, 1·5]	2·5	Onset dates; country; estimated weekly number of H1N1 cases by age class	SEIR model fitting using by maximum likelihood	Baguelin[47]
Oceania							
July 2009	June 2009	New Zealand	2·0 [1·8, 2·2]	2·8	Onset dates; country; daily confirmed or probable cases	Exponential growth rate	Nishiura[63]
July 2009	May–June 2009	Australia	2·4 [2·3, 2·4] 1·6 [1·5, 1·8]	2·9 3	Onset dates; province; daily laboratory-confirmed cases	Exponential growth rate; Model accounting for underreporting	McBryde[33]
January 2010	July–October 2009	Reunion Island	1·3 [1·1, 1·5]	1·9–2·8	Onset dates; province; weekly estimated number of A/H1N1 infections in general practice	Exponential growth rate	Renault[64]
June 2010	June–September 2009	New Zealand	1·6 [1·2, 1·9]	2·8	Onset dates; country; daily confirmed or probable cases	Bayesian sequential determination of R from epidemic curve	Paine[65]
June 2010	May 2009	Australia (Victoria)	1·5–2·5	2·8	Onset dates; province; daily number of laboratory-confirmed cases	Iterated Bayesian update of R value	Kelly[66]

GT, generation time.

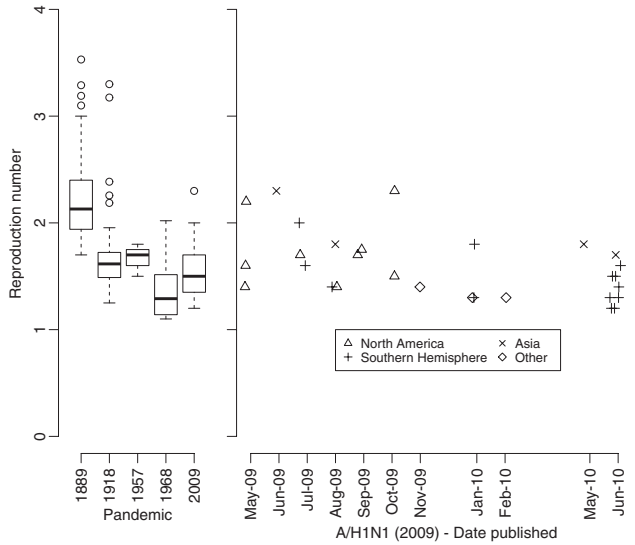

Figure 2. Reproduction number of pandemic influenza. (left) Estimates from the last five influenza pandemics (box plots show the first and third quartiles and median as thick line, see discussion for list of references). For 2009, only estimates corrected for under-reporting and mean GT approximately 3 days were shown (right) Estimates for the A/H1N1 (2009) pandemic according to location and date of publication.

ods of analysis was different. Overall, the weighted mean SI of all estimates was 3·0 days (CI 95% [2·7, 3·3]), but this reduced to 2·6 days in the studies where tertiary transmission was accounted for. Studies in households may have provided the best framework to estimate the SI, as potential contacts could be more easily identified. The only truly prospective study yielded little information (8 events),[21] so that the best evidence remains that from American households.[24]

The number of studies documenting the serial interval in the 2009 influenza pandemic contrasts with the relative absence of information for past pandemics or seasonal influenza. Indeed, before 2009, the two best documented values for the mean SI concerned seasonal influenza, with two estimates obtained in household-based studies: 2·6 days (CI 95% 2·1, 3·0)[6] and 3·6 days (CI 95% [2·9, 4·3])[5]; no information was available for past pandemics. The current estimate for A/H1N1 (2009) was somewhat closer to the first estimate; it was also in good agreement with the 2·8 days obtained by using the profile of viral excretion as a indicative of the GT distribution.[46]

As reported mean SIs are rather short, it is worth examining whether the mean SI could have been biased downwards. Changes in behavior and interventions may make long serial intervals unlikely. There was little information regarding behavior change and interventions in the reported studies: household members were, for example, instructed in simple hand-hygiene,[21] some index cases received antiviral treatment,[26] but neither isolation nor quarantine was reported. As all studies concerned the early phase of the pandemic, differences in attitude toward the A/H1N1 flu may have been limited. A second issue is that the combination of rapid transmission and limited number of contacts in households may lead to small intervals.[16] The secondary attack rates were modest (13%,[24] 11·2%,[31] 11·3%,[23] 8%[21]), arguing against a large effect in this respect because of susceptible depletion. A short follow-up could also limit the possibility of observing long serial intervals. In most studies when this was reported, the duration of follow-up in households was approximately 1 week so that few secondary cases should have been missed. Finally, some cases counted as secondary may have been attributed to common exposure (coprimary cases), leading to a downward bias. However, in most cases, cases occurring on the same date as the index case were excluded from the calculations, therefore limiting this bias.

Upward bias could occur because of successive generations of influenza overlapping in small time periods.[15] Indeed, some observed serial intervals in close-contact studies may be between primary and tertiary cases rather than secondary cases. Two studies used modeling to explicitly account for such phenomenon: in both approaches, the modeled mean SI was shorter than the empirical mean of observed values (2·6 vs. 2·9[24]; 2·5 vs. 3·4[31]). This suggests that tertiary transmission is always an issue for estimating the serial interval of influenza, and further implies that estimates reported in the other 11 studies could have been biased upwards.

The GT or SI estimates obtained by modeling epidemic curves were more variable. In such approaches, the mean GT depends on the structure of the model[14]: in the classical SEIR model, it is $L + I$, where L and I are the average durations of the latent and infectious period, so that the mean GT should have been 6 days instead of 4–5 days in Canada[35]; when the E and I stages are split into two (as in [34,46]), the mean GT is $L + 3/4 \times I$, so that it should have been 1·6 days rather than 1·9 days in the La Gloria epidemic in Mexico.[34] The two other modeling approaches yielded estimates similar to those in households/close-contact studies.

Reproduction numbers

Reproduction numbers for the A/H1N1 2009 pandemic varied according to place, methods, and hypotheses, with a reported range from 1·1 to 3·3. While the most used approach relied on determining the initial exponential growth, the formulas and fitting methods changed with authors and how the initial exponential growth period was chosen was little documented. When provided, the sensitivity analyses illustrated that somewhat arbitrary hypotheses (choice of the GT, correction for under-reporting, exponential growth period,…) had a large effect on the reported

value. In Mexico alone, estimates ranged between 1·2 and 3·1 during the same period.[29,34,38,40,42] Factors explaining these differences were numerous. The first is differences in data, either by nature (travelers back from Mexico *or* suspected/confirmed cases in Mexico *or* local epidemics *or* genetic sequence) or by collection time. For example, cases were added to the epidemic curve in retrospect, so that early estimates were biased upwards.[38] A second factor was the choice of the GT distribution, shorter mean GTs leading to smaller reproduction number estimates: from 3·1 (mean GT = 4 days) to 2·2 (mean GT = 3 days),[38] from 3·4 (mean GT = 5·5 days) to 1·9 (mean GT = 2·3 days; supplementary material[29]), and from 2·0 (mean GT = 2·6 - days) to 1·4 (mean GT = 1·9 days[34]). When similar mean GTs were allowed (approximately 3 days), less variability was present (2·2,[38] 2·0,[34] 2·3[29]). A third factor was underdeclaration in the initial period of the pandemic, leading to smaller estimates: from 2 to 1·4[42] and from 2·6 to 2·4.[29] Methods less dependent on the completeness of the data (genetic sequences, travelers out of Mexico) consistently led to lower estimates, from 1·2 to 1·7.

The short mean GT (1·9 days[34]) estimated early in Mexico may have led to underestimation when it was used to estimate the reproduction number in later studies. The impact was moderate: for example, the reproduction number in several countries from the southern hemisphere ranged between 1·2 to 1·6 using a GT of 1·9 days[41] and increased by approximately 10% when a mean GT of 2·8 days was used. In practice, collecting data that allow the joint estimation of the serial interval and reproduction ratio should be encouraged to limit these uncertainties.[48]

In approximately one report of two, the authors described the estimated reproduction ratio as 'basic' (i.e., R_0), while others used 'initial', 'effective', several qualifiers or none. Estimating R_0 requires an additional assumption on the initial susceptibility of the population, and all authors reporting R_0 assumed, often implicitly, that the whole population was initially susceptible. It is now known that adults over 50 years of age were less susceptible to the disease,[24,49] making this assumption incorrect. Practically, this means that it is unlikely that any of the reported estimates were truly 'basic' and that accounting for differential susceptibility will be required to obtain R_0 estimates. For public health purposes, however, it is the initial R which is the most relevant estimates as it informs on the required strength of interventions and is useful to calibrate mathematical models. In this respect, the reproduction number may have been poorly estimated at the start of the pandemic, as a result of poor case ascertainment; how imported cases in the course of the outbreak were accounted for in estimation; and the over-representation of places like schools where transmission was large.[45] Several new methods have been proposed to estimate the reproduction number during the pandemic,[34,36,42,50,51] which should now be compared in terms of data requirements, applicability, and how they deal with the issues listed earlier to help select best practice.

Overall, the initial reproduction number estimates of A/H1N1 (2009) pandemic ranged from 1·2 to 2·3 with median value 1·5 when correction for underdeclaration was applied and the mean GT was approximately 3 days. This was lower than the median for 1889, 1918, and 1957, but compared with 1968 (see Figure 2). For example, the reproduction number (using a mean GT of 2·8 days) was between 1·7 and 3·0 (median 2·1) in 96 cities in 1889,[7] between 1·3 and 2·5 in 1918 (using estimates obtained with GTs approximately 3 days),[8,11,12,52–54] lower than 2 in 1957,[10,55–57] and in the range of 1–2 in 1968.[9,57]

A large number of studies have documented transmission parameters for the A/H1N1 (2009) pandemic almost in real time. Short generation times and low reproduction number were characteristic in the first year of introduction of the virus. The A/H1N1 (2009) pandemic led to less mortality than previous pandemics, compared with past flu pandemics regarding transmission.

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