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Systematic Reviews and Meta- and Pooled Analyses

Serial Intervals of Respiratory Infectious Diseases: A Systematic Review and Analysis

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The serial interval of an infectious disease represents the duration between symptom onset of a primary case and symptom onset of its secondary cases. A good evidence base for such values is essential, because they allow investigators to identify epidemiologic links between cases and serve as an important parameter in epidemic transmission models used to design infection control strategies. We reviewed the literature for available data sets containing serial intervals and for reported values of serial intervals. We were able to collect data on outbreaks within households, which we reanalyzed to infer a mean serial interval using a common statistical method. We estimated the mean serial intervals for influenza A(H3N2) (2.2 days), pandemic influenza A(H1N1)pdm09 (2.8 days), respiratory syncytial virus (7.5 days), measles (11.7 days), varicella (14.0 days), smallpox (17.7 days), mumps (18.0 days), rubella (18.3 days), and pertussis (22.8 days). For varicella, we found an evidence-based value that deviates substantially from the 21 days commonly used in transmission models. This value of the serial interval for pertussis is, to the best of our knowledge, the first that is based on observations. Our review reveals that, for most infectious diseases, there is very limited evidence to support the serial intervals that are often cited.

generation interval; generation time; respiratory infectious diseases; serial interval

Abbreviations: ICC, index case–to–case; RSV, respiratory syncytial virus; SARS, severe acute respiratory syndrome.

A key epidemiologic variable that characterizes the spread of an infectious disease is the mean serial interval. It represents the average time between the time of symptom onset of a primary case and that of a secondary case. This interval is widely used in infectious disease surveillance and control. Its importance is illustrated by the efforts to rapidly determine the serial intervals for severe acute respiratory syndrome (SARS) when it emerged in 2003 (1), as well as for influenza A(H1N1)pdm09 when this strain emerged in 2009 (2). The serial interval plays an essential role in outbreak studies because it allows investigators to identify epidemiologic links between cases and to diagnose new cases that have such epidemiologic links with laboratory-confirmed cases. It is relevant to the surveillance of infectious disease because it sets the natural interval for reporting new notifications. The serial interval is an essential ingredient in predictive epidemic transmission models used to evaluate the impact of interventions and to inform policy makers on how to control or mitigate emerging outbreaks.

Typical values for the serial interval of an infectious disease are often difficult to find, are imprecisely reported, or lack references to the original data. The original observations underlying the reported typical values for the serial interval cannot always be identified, the statistical procedures to infer the typical values from the observations vary, and as a result, the range of plausible values is sometimes impractically large. For a well-studied infection, such as pertussis, we find that plausible values for the serial interval used in epidemiologic analyses range from 14 to 28 days (3–6), and often-cited references present ranges of 28–33 days (6) and 5–35 days (7, 8). These ranges for pertussis, as well as for other infections, are given without reference to a source with observations upon which the estimated ranges are based; therefore, they do not comply with the modern standard of evidence in medicine. Without a firmly established evidence base, it is difficult to use serial intervals to make adequate clinical or infection control decisions.

We reviewed the literature on reported values of serial intervals of the following respiratory pathogens selected for their clinical and public health importance: influenza, respiratory syncytial virus (RSV), SARS, measles, mumps, varicella, rubella, smallpox, pertussis, and tuberculosis. We analyzed published data on these infections using a common statistical method. In doing so, we aimed to find consensus in the medical literature on serial intervals, to assess the strength of evidence underlying this consensus, and to provide improved estimates of serial intervals whenever evidence is weak or absent. Previous reviews have shown the importance of the serial interval to the epidemiology of influenza (9). We are not aware of reviews that reexamine published data and that use a common method for analyzing, estimating, and reporting the serial interval for a broad range of respiratory infections.

METHODS

Search strategy and selection criteria

For each infection, we searched PubMed for publications, written in English, that contained estimates of the serial interval (last search on October 1, 2013). We used the search terms "serial interval" and disease name, "generation interval" and disease name, or "generation time" and disease name. The diseases we studied were influenza, RSV, SARS, measles, varicella, smallpox, mumps, rubella, pertussis, and tuberculosis. When common variations of the disease name existed, we also included these. All abstracts were reviewed once to identify relevant articles; if necessary, the article received a full-text review. Articles were excluded from further analysis if they did not contain an estimate of the serial interval, did not discuss the serial interval in the context of disease transmission, or did not contain data on time of symptom onset of cases within households or other small, well-defined populations. Furthermore, we reviewed relevant citations from the included articles, articles from our own collections, and widely used infectious disease references (Table 1).

Systematic analysis of the mean serial interval

There is confusing terminology regarding the serial interval, with the terms "generation interval" and "generation time" often used to distinguish between duration from primary to secondary infection as measured by times of infection instead of by symptom onset. Focusing on the mean value avoids this discussion; both the serial interval and the mean generation time have the same mean value, provided the incubation times of the infectee and infector are independent and identically distributed (10). However, as a result of our analyses, the complete distribution of the serial interval is also estimated, providing us knowledge about the serial intervals likely to be observed.

The serial interval. The serial interval is the duration between symptom onset of a secondary case and that of its primary case. For infections in which cases can be infectious before symptom onset, it is possible that the serial interval attains negative values because some of the secondary cases might develop symptoms before their primary case did so (11).

Table 1. Range of Typical Values of the Serial Intervals for Common Respiratory Infectious Diseases From 2 Widely Used Infectious Disease References

Disease	Serial Interval, days[a]	
	Anderson and May, 1991 (6)	Vynnycky and White, 2010 (8)
Influenza A	3–6	2–4
Measles	12–16	7–16
Mumps	16–26	8–32
Pertussis	28–33	5–35
Rubella	18–26	7–28
Smallpox	10–14	9–45
Varicella	18–23	

[a] Values were obtained by summing the latent and infectious periods presented by Anderson and May (6); or they were taken from the range of serial intervals presented by Vynnycky and White (8), which was adapted from Fine (7).

The index case–to–case interval. We used data on times of symptom onset of successive cases in households or other small populations, such as boarding schools. We refer to the case with the first onset of symptoms in a household as the index case. For all other cases in the household, we observed the duration between their times of symptom onset and that of the index case. We refer to such observed intervals as index case–to–case (ICC) intervals. The ICC intervals may result from different transmission paths between 2 cases in 1 household. For example, the 2 cases could be coprimary cases, a primary case and its secondary case, a primary case and a tertiary case, a primary case and a quaternary case, and so on (Figure 1). We consider transmission paths up to primary-quaternary cases, because longer paths are unlikely in household settings.

Statistical model. We estimate the serial interval distribution using the distribution of ICC intervals. These 2 distributions are not the same: ICC intervals are, by definition, always positive, whereas the corresponding serial interval can be negative, and the ICC interval may reflect transmission pairs other than primary-secondary. Building on earlier work, we develop a likelihood function for ICC intervals by using a mixture model (12, 13) in which we identify the mixture components with transmission paths (14) as follows:

$$f(x \mid \mu, \sigma^2) = w_1 f_1(x \mid \sigma^2) + w_2 f_2(x \mid \mu, \sigma^2) + w_3 f_3(x \mid \mu, \sigma^2) + w_4 f_4(x \mid \mu, \sigma^2). \quad (1)$$

Here, $f_i(x)$ is the component density of the i'th transmission route, and w_i is the weight of the i'th component density, such that $\sum_{i=1}^{4} w_i = 1$. Each mixture component corresponds to a transmission path as described before and illustrated in Figure 2. The serial interval X is assumed to follow a normal distribution with unknown mean and standard deviation. The ICC interval for primary-secondary pairs results from folding the negative values of the serial interval distribution onto the positive axis. In this model we assume, as in previous work (12, 13), that the ICC intervals reflect observations of

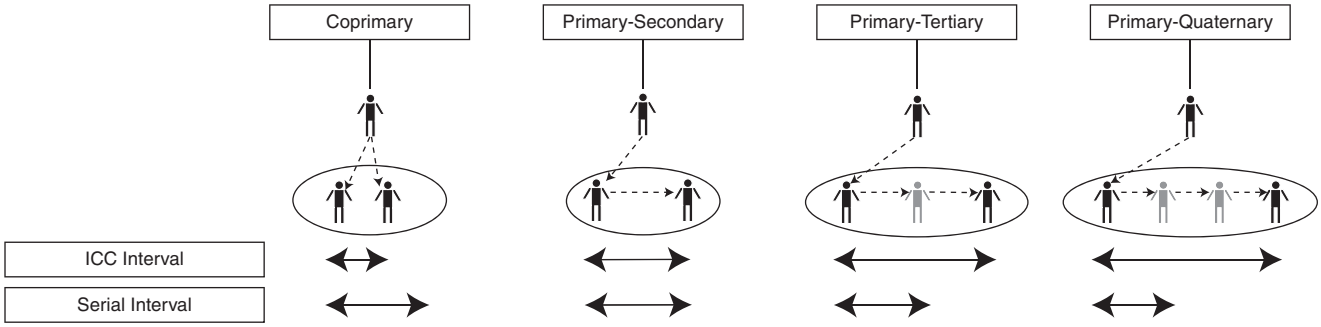

Figure 1. Inferring the mean serial interval from observed outbreaks in a household. An observed interval between symptom onset of 2 cases (black figures) in a household can result from different transmission paths within this household. From left to right: 2 cases were both infected by the same person (coprimary cases); the index case infected the other observed case (primary-secondary); the index case infected an asymptomatic case (grey figure) that infected the other observed case (primary-tertiary); the index case infected the other observed case via 2 asymptomatic cases (primary-quaternary). ICC, index case–to–case.

independent events. All other transmission paths are related to this distribution by sums or differences of the serial interval in the following way:

- Coprimary transmission, f_1. Household members 1 and 2 are, independently of each other, infected by the same person outside the household. Each of the 2 persons has a serial interval, X_1 and X_2 (with X_1 and X_2 independent identical copies of X). The observed ICC interval follows the distribution of $|X_1 - X_2|$, the half-normal distribution.
- Primary-secondary transmission, f_2. Household member 1 infects person 2. The serial interval X follows a normal distribution with mean μ and variance σ^2. The observed ICC interval follows the distribution of $|X|$, a folded normal distribution with parameters μ and σ^2.
- Primary-tertiary transmission, f_3. Household member 1 infects person 2, and person 2 infects person 3. The time between symptom onset of person 1 and that of person 2 is X_1. The time between symptom onset of person 2 and person 3

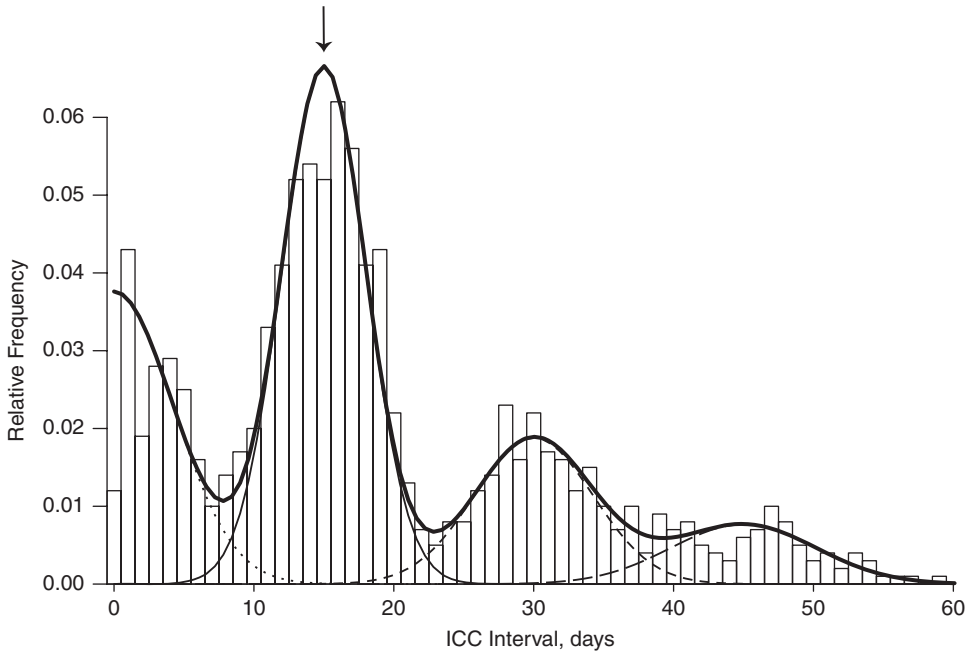

Figure 2. Distribution of observed index case–to–case (ICC) intervals. The histogram of intervals from the index case to other cases in a household consists of a mixture of distributions (smooth bold solid line). Each of the mixture components corresponds to a transmission path as described in Figure 1. From left to right: coprimary path (dotted line), primary-secondary path (solid line), primary-tertiary path (dashed line), and primary-quaternary path (large-dashed line). The mean serial interval is indicated by the arrow and is inferred both from the location of the second peak and from the distance between the successive peaks.

is X_2. The observed ICC interval between person 1 and person 3 follows the distribution of $|X_1 + X_2|$, a folded normal distribution with parameters 2μ and $2\sigma^2$.

- Primary-quaternary transmission, f_4. Household member 1 infects person 2, person 2 infects person 3, and person 3 infects person 4. The observed interval between symptom onset of person 1 and that of person 4 follows the distribution of $|X_1 + X_2 + X_3|$, a folded normal distribution with parameters 3μ and $3\sigma^2$.

Discretization of the ICC interval. Most data sets give only the day of symptom onset, leading to discretized observed ICC intervals, commonly referred to as doubly interval-censored data (for example, in the work of Reich et al. (15)). We assume that the actual moment of symptom onset is equally likely to be any moment during the day (i.e., uniformly distributed over a day from 0:00 to 24:00 hours). The interval between symptom onset in 2 persons is then distributed according to a triangular distribution. Hence, the probability density of observing an ICC interval T that lasts exactly t days is given by

$$P(T = t) = \int_{t-1}^{t+1} f(x)g(x)dx, \qquad (2)$$

where $f(x)$ is the mixture density as in equation 1, and $g(x)$ is the triangular distribution function.

Parameter estimation. The probability of observing person i with an ICC interval of t_i days, $P(t_i; w_1, w_2, w_3, \mu, \sigma^2)$, was taken as described in equation 2. We estimate the 5 unknown parameters using a likelihood-based method. The likelihood is given by

$$L(w_1, w_2, w_3, \mu, \sigma^2 \mid \mathbf{x}) = \prod_{i=1}^{N} P(t_i; w_1, w_2, w_3, \mu, \sigma^2).$$

For each disease, we fit the mixture model to the household data. We estimate the parameters with a robust expectation-maximization algorithm.

Expectation-step. For a given μ and σ^2,

- calculate the probability for each mixture component of observing interval x_i;
- calculate the relative probability of the data point x_i to belong to 1 of the components;
- calculate the mixture weights w_i.

Maximization step. For the given weights w_i,

- calculate the mean μ as the weighted mean of the data using the weights of the second mixture component only;
- calculate the variance σ^2 as the weighted variance of the data using weights of the second mixture component only.

Repeat the procedure until the estimates have converged.

Each individual contributes to the likelihood only an amount proportional of belonging to the second mixture component (primary-secondary transmission route). As a result, the method is more robust to observed ICC intervals in the tail of the distribution. We used several starting values for the expectation-maximization algorithm to ensure we found a global and not a local maximum. The method was verified by fitting the model to simulated data, which gave good results (Web Appendix 1, available at http://aje.oxfordjournals.org/). Data analysis was repeated assuming the serial interval to follow a gamma distribution rather than a normal distribution. All analyses were done using the R statistical package, version 2.13.1 (R Foundation for Statistical Computing, Vienna, Austria). The R code and all data sets are provided in Web Appendix 2 and Web Appendix 3, respectively.

Confidence intervals for the mean serial interval were computed under the assumption that this mean follows a Student's t distribution. For each data set, we present the estimated serial interval distribution. When several data sets were available for 1 infection, we also fit our model to the pooled data to obtain a pooled serial interval distribution. We compared this result with the estimate obtained from a random-effects meta-analysis.

RESULTS

From the literature search in PubMed, we obtained 98 articles, 93 of which were written in English. We found 51 articles suitable for full-text review. Of these, 36 contained estimates of serial intervals. These included 23 articles with estimates of the serial interval for pandemic influenza A(H1N1)pdm09 and 9 articles with estimates of the serial intervals for other influenza A subtypes. We found only 2 articles with estimates for the serial interval of measles, 1 with an estimate of the serial interval for smallpox, and 1 with an estimate of the serial interval for tuberculosis. In addition to the PubMed search, we collected 26 other articles from follow-up and from our collections, which contained estimates of serial intervals. All estimates from the combined literature search are presented in Table 2.

We found 18 articles that presented ICC intervals, from which we could estimate serial intervals using our statistical method. The estimates of the serial interval distribution are presented in Table 3. For each data set, we estimated the mean serial interval with its 95% confidence interval (Figure 3A). These confidence intervals are small, but there is substantial variation between data sets. When the serial interval is used to identify epidemiologic links between cases during an outbreak, it is more relevant to know the variability of the serial interval than the typical value. The distribution of the serial intervals, after pooling the data sets for each infection, reveals that, although the range from the 2.5th percentile to the 97.5th percentile for serial intervals may be quite large (Figure 3B), the 25th and 75th percentiles capture the estimated mean serial interval of the individual data sets in almost all cases. Similar results for the pooled mean serial interval were obtained using a random-effects meta-analysis (Web Table 1). The statistical model accurately captures the serial interval distribution from the observed dates of symptom onset within households, as illustrated by the model fits for the largest data set for each infection in Figure 4. Similar results were obtained when data were analyzed assuming the serial interval followed a gamma distribution rather than a normal distribution (Web Table 2 and Web Figure 1).

Table 2. Estimates of the Serial Intervals for Common Respiratory Infectious Diseases in the Scientific Literature

First Author, Year (Reference No.)	Infection	Estimated Serial Interval, days
Wallinga, 2007 (42)	Influenza A(H1N1)	2.85
Lessler, 2007 (43)	Influenza A(H1N1)	1.9
Carrat, 2008 (44)	Influenza A(H1N1)	2.3
White, 2008 (45)	Influenza A(H1N1)	2.83, 3.31, 3.33, 3.81, 4.01, 4.66, 8.28
Levy, 2013 (46)	Influenza A(H1N1)	3.3
Cowling, 2009 (12)	Influenza A(H1N1)	3.6
Fraser, 2009 (2)	Influenza A(H1N1)pdm09	1.91
Asiedu-Bekoe, 2012 (47)	Influenza A(H1N1)pdm09	2
Orellano, 2012 (48)	Influenza A(H1N1)pdm09	2
te Beest, 2013 (39)	Influenza A(H1N1)pdm09	2.1, 2.3, 2.7, 3.4
Hens, 2012 (49)	Influenza A(H1N1)pdm09	2.2
Cauchemez, 2011 (40)	Influenza A(H1N1)pdm09	2.3, 3.7
Kelso, 2010 (50)	Influenza A(H1N1)pdm09	2.3
Archer, 2012 (51)	Influenza A(H1N1)pdm09	2.3
Barakat, 2012 (52)	Influenza A(H1N1)pdm09	2.3
Roberts, 2011 (53)	Influenza A(H1N1)pdm09	2.38
White, 2009 (54)	Influenza A(H1N1)pdm09	2.5–2.6, 2.2–2.3
Ghani, 2009 (55)	Influenza A(H1N1)pdm09	2.51
Cauchemez, 2009 (16)	Influenza A(H1N1)pdm09	2.6
Suess, 2010 (56)	Influenza A(H1N1)pdm09	2.6
Yang, 2009 (57)	Influenza A(H1N1)pdm09	2.6–3.2
Lessler, 2009 (58)	Influenza A(H1N1)pdm09	2.7
Hahné, 2009 (17)	Influenza A(H1N1)pdm09	2.7
Archer, 2012 (59)	Influenza A(H1N1)pdm09	2.78
Leung, 2011 (60)	Influenza A(H1N1)pdm09	2.8
Petrie, 2013 (61)	Influenza A(H1N1)pdm09	2.8
Donnelly, 2011 (13)	Influenza A(H1N1)pdm09	2.9
McBryde, 2009 (62)	Influenza A(H1N1)pdm09	2.9
Katriel, 2011 (63)	Influenza A(H1N1)pdm09	2.92
Roll, 2011 (64)	Influenza A(H1N1)pdm09	2.92
France, 2010 (18)	Influenza A(H1N1)pdm09	3
Boëlle, 2011 (9)	Influenza A(H1N1)pdm09	3
Savage, 2011 (19)	Influenza A(H1N1)pdm09	3
Levy, 2013 (46)	Influenza A(H1N1)pdm09	3.1
Cowling, 2010 (65)	Influenza A(H1N1)pdm09	3.2
Papenburg, 2010 (20)	Influenza A(H1N1)pdm09	3.2, 3.9
Park, 2010 (66)	Influenza A(H1N1)pdm09	3.4
Sikora, 2010 (67)	Influenza A(H1N1)pdm09	3.4
Janjua, 2012 (68)	Influenza A(H1N1)pdm09	3.5
Surveillance Group, 2009 (69)	Influenza A(H1N1)pdm09	3.5
Morgan, 2010 (21)	Influenza A(H1N1)pdm09	4
Tuite, 2010 (70)	Influenza A(H1N1)pdm09	4–5
Carrat, 2008 (44)	Influenza A(H3N2)	3.1
Petrie, 2013 (61)	Influenza A(H3N2)	3.2
Cowling, 2010 (65)	Influenza A(H3N2)	3.4
Levy, 2013 (46)	Influenza A(H3N2)	3.5
Ferguson, 2005 (71)	Influenza A(H5N1)	2.6
White, 2008 (72)	Influenza A(H5N1)	3.37
Carrat, 2008 (44)	Influenza B	3.4
Levy, 2013 (46)	Influenza B	3.7
Petrie, 2013 (61)	Influenza B	4.9
Simpson, 1948 (73)	Measles	9, 10, 10.5, 13
Fraser, 2007 (74)	Measles	10.5
Klinkenberg, 2011 (14)	Measles	11.1, 11.2, 11.9, 12.2
Simpson, 1952 (23)	Measles	12
Paterson, 2013 (75)	Measles	12.3
Meyer, 1962 (33)	Mumps	18.3
Simpson, 1952 (23)	Mumps	20
Stocks, 1933 (35)	Pertussis	7
Crowcroft, 2008 (22)	RSV	7
Aycock, 1946 (34)	Rubella	15–23
Lipsitch, 2003 (1)	SARS	8.4
Chelsky, 1977 (31)	Smallpox	18.6
ten Asbroek, 1999 (37)	Tuberculosis	29.5[a]
Borgdorff, 2011 (38)	Tuberculosis	1.44[b]
Simpson, 1954 (27)	Varicella	13.8, 14, 15.1
Simpson, 1952 (23)	Varicella	14

Abbreviations: RSV, respiratory syncytial virus; SARS, severe acute respiratory syndrome.

[a] Value is expressed in weeks.

[b] Value is expressed in years.

Influenza

The reported values of the mean serial interval of influenza A(H1N1) and pandemic influenza A(H1N1)pdm09 ranged from 1.9 to 5 days (Table 2). For influenza A(H1N1)pdm09, we identified 6 data sets that contained information on symptom onset dates in households (16–21). Estimates of the mean serial interval for influenza A(H1N1)pdm09 from these data sets ranged from 1.7 to 3.7 days (pooled mean = 2.8 days; Figure 3A). We found substantial variation among the estimates for the serial interval for different data sets, even when 1 common method was used. The spread of the pooled serial interval distribution (Figure 3B) captured the values for the serial interval that are commonly reported.

Table 3. Estimated Serial Interval Distributions From Available Data Using a Common Method

First Author, Year (Reference No.)	Infection	Country	Collection Years	No. of ICC Intervals	Normal Distribution Serial Interval	95% CI of Mean Serial Interval
Hahné, 2009 (17)	Influenza A(H1N1)pdm09	Netherlands	2009	50	$N(1.7, 1.2^2)$	1.3, 2.0
Cauchemez, 2009 (16)	Influenza A(H1N1)pdm09	United States	2009	78	$N(2.1, 1.2^2)$	1.8, 2.4
Savage, 2011 (19)	Influenza A(H1N1)pdm09	Canada	2009	56	$N(2.8, 0.8^2)$	2.6, 3.0
Papenburg, 2010 (20)	Influenza A(H1N1)pdm09	Canada	2009	48	$N(2.9, 1.2^2)$	2.5, 3.2
France, 2010 (18)	Influenza A(H1N1)pdm09	United States	2009	77	$N(3.0, 0.9^2)$	2.8, 3.2
Morgan, 2010 (21)	Influenza A(H1N1)pdm09	United States	2009	32	$N(3.7, 1.1^2)$	3.3, 4.1
Viboud, 2004 (76)	Influenza A(H3N2)	France	1999–2000	131	$N(2.2, 0.8^2)$	2.1, 2.4
Aaby, 1990 (24)	Measles	Kenya	1974–1981	431	$N(9.9, 2.4^2)$	9.7, 10.2
Bailey, 1954 (25)	Measles	England	1947–1951	219	$N(10.9, 1.9^2)$	10.6, 11.1
Simpson, 1952 (23)	Measles	England	1947–1951	203	$N(10.9, 2.0^2)$	10.6, 11.2
Chapin, 1925 (26)	Measles	United States	1917–1923	5,659	$N(11.9, 2.6^2)$	11.8, 12.0
Fine, 2003 (11)	Measles	England	1932	28	$N(13.7, 1.5^2)$	13.1, 14.3
Fine, 2003 (11)	Measles	United States	1934	105	$N(13.8, 2.5^2)$	13.3, 14.3
Simpson, 1952 (23)	Mumps	England	1947–1951	142	$N(18.0, 3.5^2)$	17.4, 18.6
de Greeff, 2010 (36)	Pertussis	Netherlands	2006–2008	315	$N(22.8, 6.5^2)$	22.1, 23.5
Crowcroft, 2008 (22)	RSV	England	1998–1999	59	$N(7.5, 2.1^2)$	7.0, 8.1
Aycock, 1946 (34)	Rubella	Unknown	Unknown	126	$N(18.3, 2.0^2)$	18.0, 18.6
Fine, 2003 (11)	Smallpox	Germany	1970	19	$N(16.7, 3.3^2)$	15.1, 18.3
Fine, 2003 (11)	Smallpox	Kosovo	1972	174	$N(17.3, 1.9^2)$	17.0, 17.6
Ministry for Social Affairs, 1953 (32)	Smallpox	Netherlands	1951	45	$N(18.9, 4.0^2)$	17.7, 20.1
Vally, 2007 (28)	Varicella	Australia	2002	43	$N(13.1, 2.2^2)$	12.4, 13.8
Simpson, 1952 (23)	Varicella	England	1947–1951	184	$N(14.1, 2.4^2)$	13.7, 14.4
Lai, 2011 (29)	Varicella	Taiwan	2007	15	$N(14.2, 1.3^2)$	13.5, 14.9

Abbreviations: CI, confidence interval; ICC, index case–to–case; RSV, respiratory syncytial virus.

The reported values for the mean serial interval of influenza A(H3N2) are 3.1 and 3.4 days (Table 2). For this influenza subtype, we identified 1 data set that contained information on symptom onset dates in households. The estimate of the mean serial interval for this data set was 2.2 days (Table 3, Figure 3), which is 1 day shorter than the reported values found in the literature.

The reported values for influenza A(H5N1) and influenza B were between 2.6 and 4.9 days (Table 2). We did not have any data sets to estimate the serial interval for these types.

Respiratory syncytial virus

For RSV, we found a reported estimate of the mean serial interval of 7 days (Crowcroft et al. (22), Table 2). We reanalyzed the data from this article and obtained an estimate of the mean serial interval of 7.5 days (Table 3). The resulting estimate is close to the original reported value.

Severe acute respiratory syndrome

For the outbreak of SARS in Singapore in 2003, the mean serial interval was estimated at 8.4 days (1). We could not find data on time of symptom onset in households that would allow us to estimate the mean serial interval.

Measles

For measles, we found reported serial intervals in the range of 9–13 days in the literature (Table 2). We identified 6 usable data sets for measles (11, 23–26) and estimated the mean serial interval to be between 9.9 days and 13.8 days, with a pooled mean of 11.7 days (Figure 3). The range of estimated values captured the range of reported values, as shown in Table 2.

Varicella

For varicella, we found reported values of the serial interval ranging from 13 to 15 days (27), which differs substantially from the range of 18 to 23 days that is often cited (Anderson and May (6); Table 1). We identified 3 usable data sets for varicella (23, 28, 29) (Table 3, Figure 3) and estimated the pooled mean serial time to be 14.0 days. This corresponds with the value as originally reported by Simpson (23) but is substantially shorter than the typical value of 21 days used in some mathematical transmission models of varicella (30).

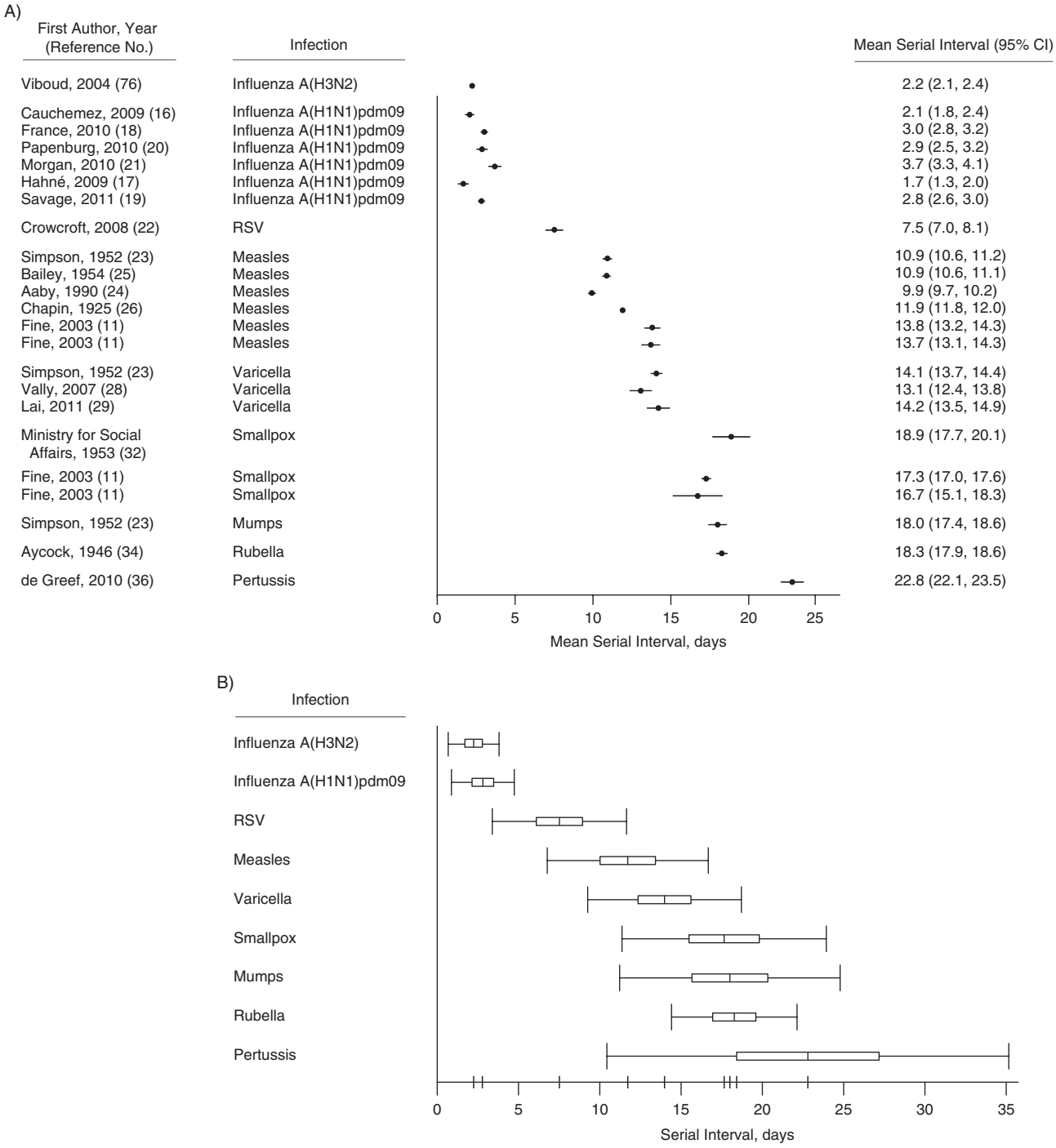

Figure 3. Estimated serial intervals. A) Mean serial interval (dots) and 95% confidence intervals (CIs) (bars) for each data set found in the literature. B) Distribution of serial interval for each infection in which the data sets are pooled. The box-and-whisker plot denotes the 2.5th, 25th, 50th, 75th, and 97.5th percentiles of the serial interval distribution. RSV, respiratory syncytial virus.

Smallpox

For smallpox, we found a reported serial interval of 18.6 days (31). We identified data sets from 3 outbreaks of smallpox in towns (11, 32). For each outbreak, we treated the population as if it were a household and inferred the values of the mean serial intervals as 16.7, 17.3, and 18.9 days. We did not find a statistically significant difference between those values. The results for the outbreak of smallpox in

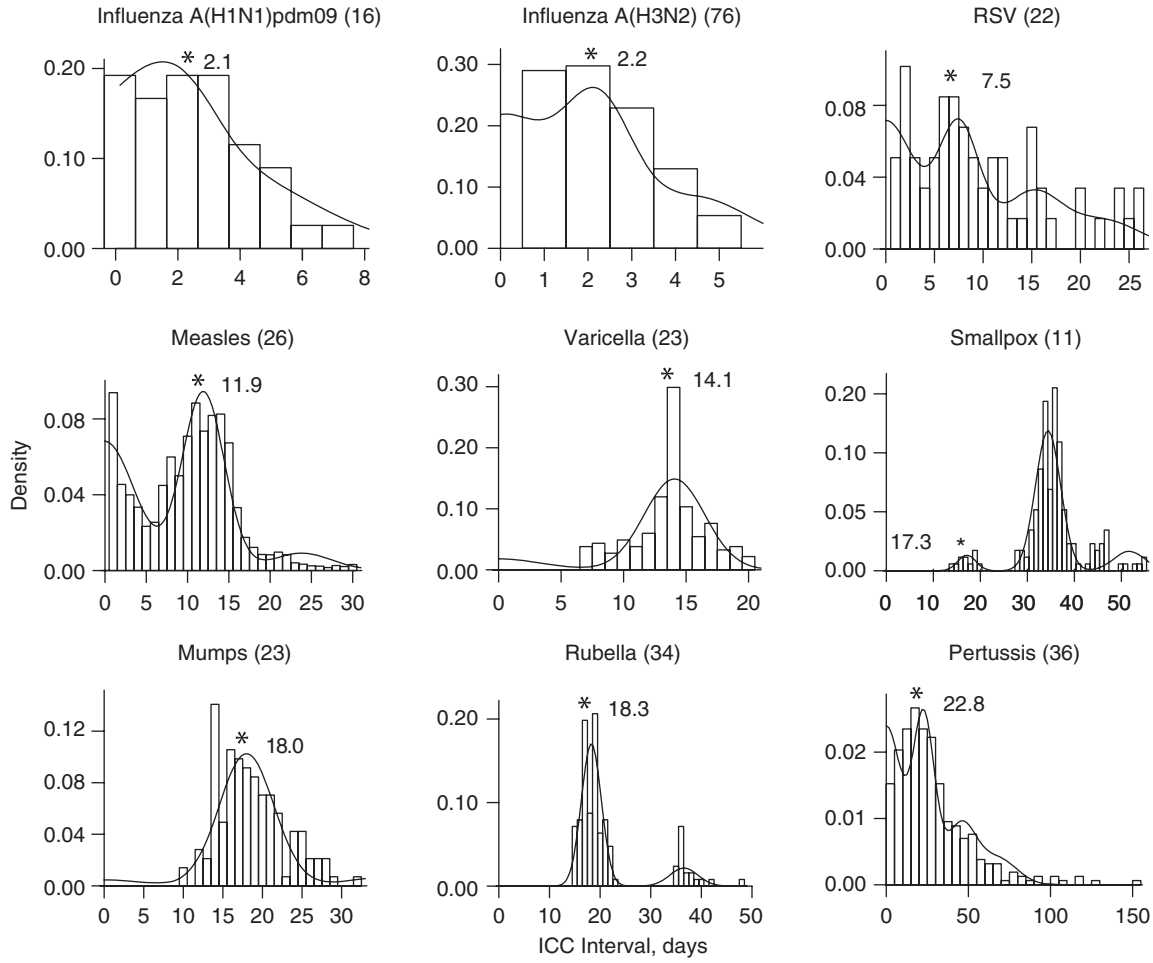

Figure 4. Model fit of the serial interval to index case–to–case (ICC) interval data. Mean serial interval (asterisk) inferred from observed ICC data (histogram) and the estimated mixture density (solid line) for each infection. RSV, respiratory syncytial virus.

Kosovo (11) are shown in Figure 4. The pooled mean serial interval for smallpox was 17.7 days, which is 1 day shorter than the typical value reported in the literature (Table 2).

Mumps

For mumps, we found reported serial intervals of 20 days (23) and 18.3 days (33). We identified 1 usable data set for mumps (23) and estimated the mean serial interval for mumps to be 18.0 days. This is lower than the original reported value for this data set and closer to the value reported by Meyer (33).

Rubella

For rubella, we found an estimate of the serial interval of 18 days (range, 15–23 days) (34). This estimate was based on a rubella outbreak in a boarding school; it was the only suitable data set for rubella that we identified. We used the boarding school data as if it were from 1 household. Reanalysis of these data confirmed the estimated mean serial interval for rubella of 18.3 days (Figure 4).

Pertussis

For pertussis, we found no reported estimates of the serial interval except for 1 very old observation that stated that the serial interval for pertussis was most frequently 1 week, but with a wide range of 4 to 56 days (35). We found 1 relevant data set (36) from which we estimated the mean serial interval to be 22.8 days. The serial interval distribution has a large variance, leading to a wide range of values that the serial interval may attain (Figure 3B). We note that this is, to the best of our knowledge, the first estimate of the mean serial interval of pertussis.

Tuberculosis

For tuberculosis, we found 2 reported estimates of the mean serial interval: 29.5 weeks (37) and 1.4 years (38)

(Table 2). We did not identify a data set that we could use to estimate the mean serial interval for tuberculosis.

DISCUSSION

Our study shows that the evidence supporting reported serial intervals is minimal for many diseases. For influenza and measles, several data sets allowed us to confirm the estimated values of the serial intervals. Using the same methodology, we were able to confirm the existing estimates of the serial intervals for smallpox and varicella, for which 3 data sets were available, as well as for RSV, mumps, and rubella, for which only 1 data set was available. For pertussis, we found no previous estimates that were based on original data, but we identified a data set that allowed us to infer a serial interval for pertussis of 22.8 days.

Several factors may account for the observed differences among studies. The duration of the serial interval depends on the nature of contacts (39, 40), and this can vary among studies conducted at different times in different places. The serial interval also depends on the incidence of infection (10, 41), which may have differed among studies, although none of the studies reported the incidence of infection at the time of observation. The definition of symptom onset might influence the serial interval; varying the definition of the onset of measles symptoms from "onset of conjunctivitis" to "onset of illness" in the data set of Simpson (23) results in a change of the mean serial interval from 9 to 13 days—approximately the range in mean serial intervals observed among all measles studies. Lastly, the estimated duration of the serial interval will depend on the inclusion criteria for cases; for example, for varicella, very short durations for ICC intervals were excluded by Simpson (23) but not in more recent studies (28, 29). We checked informally for differences between studies by plotting the estimates (Figure 3), and we checked formally by testing for statistically significant differences between studies; for smallpox, we found no such differences.

The 95% confidence intervals of the most likely values for the serial intervals in an outbreak, as presented in Figure 3B, are useful for outbreak control to establish epidemiologic links between cases and to characterize how the risk of new cases varies as a function of time since the onset of symptoms. The precise ranges for serial intervals can be improved further when more data become available, or when more detailed data on who-infected-whom in household outbreaks become available. Such detailed data would allow us to account for dependencies in the observed ICC intervals because these may have affected the precision of the estimated mean values presented here.

We focused on a common methodology for analyzing, estimating, and reporting serial intervals from observations of symptom onset dates in households for different infections. By dropping the constraint of using 1 validated methodology, we could use a range of methods and include data sets other than those of households. This allowed us to investigate whether serial intervals are affected by the setting of the infectious contact, such as schools, workplaces, or households. Although we acknowledge that factors specific to household contacts may have affected our results, we note that, for each infection, the typical observed range of serial intervals (Table 2) covers our household estimates.

The presented estimates of the mean serial interval are restricted to published data sets for a range of important respiratory infections. We found few articles by using standard key words in PubMed and many articles by searching through the citations. This indicates that it is very difficult for an infectious disease expert to find the evidence underlying often-cited values for serial intervals. It also suggests that any literature review on this topic, including ours, is likely to miss useful data sets that provide more evidence for the duration of serial intervals. Therefore, we have made our code available in the hope of inspiring researchers to collect new data sets or to use existing unpublished data. The statistical method we used here is not restricted to the respiratory transmission route; we have successfully estimated the mean serial intervals of norovirus and hepatitis A, which are 2 infections that spread by contaminative contact (Web Appendix 1). Future work will focus on assessing the evidence for serial intervals, such as vector-based infections (e.g., dengue) in a household or village or sexually transmitted infections (e.g., human immunodeficiency virus, syphilis, and chlamydia) in a relationship. When the statistical approach to estimate the mean serial interval proves to be successful for infections irrespective of the transmission route, it has the potential to be used when facing an outbreak of a new pathogen with an unknown transmission route.

We have reanalyzed published data to provide estimates of the serial interval for important respiratory diseases. Whereas previously published estimates generally provided new data sets for 1 specific disease and reported some summary measure for the serial interval, the aspect of interest here is the mean serial interval. This is the crucial factor in relating the growth rate of an epidemic to the reproduction number (42) and the required control effort to interrupt the transmission chains in that epidemic. Knowledge of the mean serial interval also helps identify the most likely source of infection in outbreak investigations. It helps in planning for the duration of isolation of cases whose dates of exposure are known. Our comprehensive review bases the mean serial interval directly on observed times of symptom onset, which makes it useful in research, clinical practice, and public health policy.

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