Published in final edited form as:
Epidemiology. 2013 November ; 24(6): . doi:10.1097/EDE.0b013e3182a67448.

Case fatality risk of influenza A(H1N1pdm09): a systematic review

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Abstract

Background—During the 2009 influenza pandemic, uncertainty surrounding the seriousness of human infections with the H1N1pdm09 virus hindered appropriate public health response. One measure of seriousness is the case fatality risk, defined as the probability of mortality among people classified as cases.

Methods—We conducted a systematic review to summarize published estimates of the case fatality risk of the pandemic influenza H1N1pdm09 virus. Only studies that reported population-based estimates were included.

Results—We included 77 estimates of the case fatality risk from 50 published studies, about one-third of which were published within the first 9 months of the pandemic. We identified very substantial heterogeneity in published estimates, ranging from less than 1 to more than 10,000 deaths per 100,000 cases or infections. The choice of case definition in the denominator accounted for substantial heterogeneity, with the higher estimates based on laboratory-confirmed cases (point estimates= 0–13,500 per 100,000 cases) compared with symptomatic cases (point estimates= 0–1,200 per 100,000 cases) or infections (point estimates=1–10 per 100,000 infections). Risk based on symptomatic cases increased substantially with age.

Conclusions—Our review highlights the difficulty in estimating the seriousness of infection with a novel influenza virus using the case fatality risk. In addition, substantial variability in age-specific estimates complicates the interpretation of the overall case fatality risk and comparisons among populations. A consensus is needed on how to define and measure the seriousness of infection before the next pandemic.

In April 2009 the World Health Organization declared a formal “public health emergency of international concern,” marking the start of an international public health response to the first influenza pandemic of the 21st Century. One of the immediate priorities was to quantify the transmissibility of the new pandemic influenza A(H1N1pdm09) virus (denoted H1N1pdm09 hereafter) and the seriousness of infection with this virus, because these two

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CONFLICTS OF INTEREST

The authors report no other potential conflicts of interest.

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epidemiologic measures in combination determine the severity of the pandemic in the absence of control measures. [1, 2] Whereas a number of transmissibility estimates, based on the reproduction number R, were published with broad agreement from the early stages of the pandemic, [3] there was far greater difficulty in estimating the seriousness of infections. In the report of the World Health Organization's Review Committee on the functioning of the 2005 International Health Regulations in relation to H1N1pdm09, Fineberg et al. [4] identified "the absence of a consistent, measurable and understandable depiction of severity of the pandemic" as one of the major shortcomings of the international public health response.

One measure of the seriousness of infection is the "CFR," classically the case fatality rate or ratio.[5] We prefer "risk" to describe this probability, namely the conditional probability of mortality among classified "cases." Strictly speaking, the case fatality risk is neither a rate (because there is no unit of time in the denominator) nor a ratio, which applies principally to a relationship between two measures of the same kind (for example, an odds ratio). There are complications in defining and estimating the case fatality risk, associated with both the numerator (deaths) and the denominator (persons classified as cases).[1, 6] We reviewed published estimates of the case fatality risk of H1N1pdm09 to identify technical challenges in its estimation and to offer recommendations for estimating this measure in the future.

METHODS

Search Strategy

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. [7] Studies reporting estimates of the case fatality risk of H1N1pdm09 were retrieved from Medline (PubMed) and Embase on 26 April 2013. We searched for articles using the following free search terms in 'All fields':

#1 'fatalit*' OR 'case-fatality*' OR 'severity' OR 'mortality' OR 'death' OR 'lethal*' OR 'virulence'

#2 'influenza' OR 'flu' OR 'H1N1*' OR 'pH1N1*' OR 'pdmH1N1*' OR 'nH1N1*'

#3 #1 AND #2

The search was limited to studies published after 1 April 2009 (subsequent to the emergence of H1N1pdm09) through 26 April 2013. Additional relevant studies identified by the authors were manually retrieved from the database.

Study Selection

The titles of all papers identified by the search strategy were independently screened by two authors (J.Y.W. and B.J.C.). Abstracts of potentially relevant papers and the full text of manuscripts were reviewed for eligibility. Articles in all languages were selected for assessment if at least one statistical estimate of the case fatality risk for H1N1pdm09 was presented and described in the article. Eligible articles reported one or more population-based estimates of the case fatality risk. We excluded studies that reported only estimates in hospitalized patients or in population subgroups such as pregnant women or those at higher risk of severe illness if infected (e.g. persons with chronic health conditions).

Definition of Case Fatality Risk

We defined the case fatality risk as the conditional probability of death associated with H1N1pdm09 for cases that met a specified case definition. The case fatality risk for a population is estimated as the number of H1N1pdm09-associated deaths divided by the number of H1N1pdm09 cases in that population. The numerator could be counts or

estimates of the number of deaths among laboratory-confirmed cases, the number of deaths among symptomatic cases, or indirect estimates of the total number of deaths associated with H1N1pdm09. The denominator could be counts or estimates of the number of laboratory-confirmed H1N1pdm09 cases, the number of symptomatic H1N1pdm09 cases, or the number of infections. We classified the denominator of the CFR as the estimated number of infections only when it was estimated based on serologic surveillance or included explicit adjustment for asymptomatic infections.

Data Extraction

All data were extracted onto a standardized form. The primary data were the estimates of the case fatality risk, the estimates or counts of the number of H1N1pdm09-associated deaths (numerator), and the estimates or counts of the number of H1N1pdm09 cases (denominator). Whenever available, we extracted case fatality risks stratified by age group. Although age groupings differed across studies, we defined children as those up to age 19, adults as those 20–64 and elderly as those 65 years or older.

Statistical Analysis

Statistical heterogeneity was assessed by the I^2 statistic, with higher values signifying a greater degree of variation.[8] Due to very substantial heterogeneity, we did not make pooled estimates of the case fatality risk. All analyses were conducted with R version 2.15.1 (R Foundation for Statistical Computing, Vienna, Austria) and the *metafor* package.[9]

RESULTS

Of the 12,197 papers initially identified, we examined 120 full-length articles, of which 70 were subsequently excluded (eTable, http://links.lww.com/EDE/A708) (Figure 1).[6, 10–58] The 50 articles we included, reporting a total of 77 case fatality risk estimates, are summarized in the Table. One-third (16/50) of the studies were published within the first nine months of the pandemic (Figure 2). The lag time between the end of the particular study period and the publication date increased over time (median = 236 days) (eFigure 2, http://links.lww.com/EDE/A708). In total, our analysis was based on reports from 32 countries or regions, specifically Abu Dhabi, Argentina, Australia, Canada, Chile, Colombia, European Union (EU), French Guiana, Germany, Greece, Guadeloupe, Hong Kong, India, Japan, Korea, Martinique, Mauritius, Mexico, New Zealand, Nepal, Netherlands, New Caledonia, Peru, Pacific Island countries, Reunion Island, Singapore, Spain, St. Martin, Taiwan, Thailand, United Kingdom (UK) and the United States (including metropolitan Atlanta). In addition, three publications estimated the case fatality risk worldwide,[54] for 45 specified countries,[43] and for developed countries.[57] Illustrating one of the potential sources of heterogeneity, the number of cases or infections adopted as denominators ranged from 172 to 61,000,000 (eFigure 1, http://links.lww.com/EDE/A708).

Overall, the case fatality risk estimates based on laboratory-confirmed cases were higher than the other estimates and published earlier (Figure 3). Estimates based on laboratory-confirmed cases ranged from 0 to 13,500 deaths per 100,000 cases, with very substantial heterogeneity [I^2=99.97%]. Most (25/29) of the risk estimates in this category fell within the range of 100 to 5,000 deaths per 100,000 cases.

There was also substantial heterogeneity among the 37 risk estimates based on symptomatic cases, ranging from 0 to 1,200 deaths per 100,000 [I^2=99.98%]. Most of the estimates in this category fell in the range of 5 to 50 deaths per 100,000 cases. In age-stratified analyses, risk estimates rose monotonically with age, from approximately one death per 100,000 symptomatic cases in children to approximately 1,000 deaths per 100,000 symptomatic

cases in the elderly, although with substantial variation in the estimates within each age group (Figure 4).

In 14% (11/77) of the case fatality risk estimates, the denominator was based on an estimated number of infections. Among those 11 studies, 8 used denominators based on population serological studies, while the others used modelling or multiplier approaches. Those risks tended to remain stable over time, although no such estimates were published within the first year of the pandemic (Figure 3). Estimates ranged from 1 to 10 deaths per 100,000 infections, with substantial heterogeneity [I^2=94.46%]. The majority of studies adopted laboratory-confirmed deaths as the numerator (Table), while one study estimated that the number of "excess" deaths attributable to H1N1pdm09 was higher than the number of deaths of laboratory-confirmed cases, leading to a generally higher case fatality risk based on the excess-deaths numerator compared with the confirmed-deaths numerator.[6] The increase in age-specific risk estimates by age based on infection were similar to those based on symptomatic cases (data not shown).

The highest case fatality risk estimates were observed in Argentina,[30, 42] Mexico,[20, 42] and Colombia.[18] All of these studies reported case fatality risks among laboratory-confirmed cases. Apart from differences in case definition, it is not clear why estimates during the early stage of the pandemic were so high in Mexico (ranging from 100 to 5,580 deaths per 100,000).[20, 26, 28, 29, 42, 55]

DISCUSSION

There is very substantial heterogeneity in published estimates of case fatality risk for H1N1pdm09, ranging from <1 to >10,000 per 100,000 infections (Figure 3). Large differences were associated with the choice of case definition (denominator). Because influenza virus infections are typically mild and self-limiting, and a substantial proportion of infections are subclinical and do not require medical attention, it is challenging to enumerate all symptomatic cases or infections.[2, 45] In 2009, some of the earliest available information on fatality risk was provided by estimates based primarily on confirmed cases. However, because most H1N1pdm09 infections were not laboratory-confirmed, the estimates based on confirmed cases were up to 500 times higher than those based on symptomatic cases or infections (Figure 3). The consequent uncertainty about the case fatality risk — and hence about the severity of H1N1pdm09 — was problematic for risk assessment and risk communication during the period when many decisions about control and mitigation measures were being made.

Whereas our review has focused on the case fatality risk, there are other measures of seriousness of infection that can be useful in assessing the risk associated with pandemic and seasonal influenza viruses. For example, the outbreak of H1N1pdm09 in a New York school in April–May 2009 was informative because none of the more than 800 students and staff with influenza-like illness had severe illness,[59] implying a low risk of hospitalization among infected cases. At the other end of the spectrum of disease, a description of the risk of mortality among hospitalized patients could be affected by flexible thresholds for admission depending on demand and capacity. A comprehensive seriousness profile could include age-specific estimates of the risks of illness, hospitalization and mortality on a per-infection basis. In addition, while transmissibility and seriousness profiles can allow prediction of the number of serious illnesses, the availability of health care resources would also affect the likely impact of an epidemic or pandemic.[60]

Arguably one of the ideal estimates of seriousness of infection is the infection fatality risk,[6] i.e. the case fatality risk based on infections as denominator. This risk estimate can be

compared across populations without concerns over differences in symptom perceptions and reporting, health-care seeking behaviors, or laboratory-testing capacity.[61] Estimates of the infection fatality risk can also be used in combination with estimates of transmissibility to directly inform predictions of population impact.[62] The use of the term "infection fatality" differentiates this risk estimate from the case fatality risk since the asymptomatic, undetected and undiagnosed infections included in the denominator would not appear as "cases" under typical case definitions. However, few estimates of the infection fatality risk were available for H1N1pdm09, and none was available early in the pandemic (Figure 3). Serologic studies,[63] or estimates of the cumulative incidence of symptomatic infections in a population adjusted for the proportion of infections that are asymptomatic,[52, 64] can be used to estimate the denominator for the infection fatality risk. However, one has to define how to estimate infection rates from serologic data, and there is not yet consensus on the best approach.

Given that estimates of the infection fatality risk are unlikely to be available early enough for decision-making in a pandemic, a more feasible solution may be to measure the case fatality risk among symptomatic cases. One obvious limitation is that differences in the definition of a symptomatic case are likely to affect comparability and limit generalizability. In our review the case fatality risk estimates for symptomatic cases covered a wide range (eFigure 1, http://links.lww.com/EDE/A708). In practice, estimation of fatality risk among symptomatic cases could be based on outpatient surveillance data in combination with laboratory data, and with adjustment for the proportion of symptomatic cases not presenting for medical attention. These may vary by age, sex, location, and other factors.[13, 17, 24, 44, 45, 49, 52] Such estimates based on symptomatic cases may provide timely but imprecise estimates of seriousness for risk assessment.

In addition to differences in case fatality risk estimates due to the differences in case definition (denominator), the definition of the numerator is also an important issue. Almost all of the studies in our review based the numerator on deaths among patients with laboratory-confirmed influenza infection. In contrast, most estimates of the population impact of seasonal influenza epidemics have been based on estimation of the number of excess deaths associated with influenza (i.e. estimated deaths), with the greatest annual impact in the elderly — despite influenza virus infections rarely being confirmed in this age group.[65, 66] The use of excess deaths rather than laboratory-confirmed deaths in the numerator of the infection fatality risk would theoretically be justified because the denominator includes all infections and not only those with a positive laboratory result. For a similar reason, deaths of patients with laboratory-confirmed infection might be a more appropriate numerator for the case fatality risk based on symptomatic case denominators.

In addition to the differences in risk estimates due to differences in numerators and denominators, our review also identified substantial variability by age, ranging from approximately one death per 100,000 symptomatic cases in children to 1,000 deaths per 100,000 symptomatic cases in the elderly (Figure 4). This variability complicates the interpretation of the overall risk and the comparison of risk among countries, because overall risk would depend on the age structure of the population and the age distribution of infections.[67, 68] Age-standardization is an accepted method for comparing incidence rates among the populations of various countries,[69] but no similar approach has yet been discussed or recommended for comparison of case fatality risks.

Further limitations of our review are that most of the included estimates corresponded to the initial epidemics of H1N1pdm09 in 2009 (Figure 2). Fewer data are available on possible changes in the case fatality risk after that period, although there have been reports of up to four epidemic waves in some countries.[20, 70] We excluded studies that focused on specific

risk groups (e.g. those with underlying diseases) to improve consistency among studies. There was also substantial heterogeneity among estimates of the case fatality risk, depending particularly on case definition (eFigure 1, http://links.lww.com/EDE/A708). We could not determine whether these differences were artefactual or real, perhaps related to differences in the prevalence of underlying risk factors for severe illness in various populations.[71, 72] Further work could attempt to identify additional factors that explain this heterogeneity, for example by exploring very different estimates of risk apparently based on the same case definition (e.g., from Argentina,[30, 42] Mexico[20, 26, 28] and the United States[29, 41, 42]).

Results of this review point to possible improvements in future studies of the case fatality risk. First, there is a problem in using confirmed cases as the denominator of CFR for influenza, given that most infections are mild and do not present for medical attention. Because it is not feasible to diagnose all suspected cases with laboratory testing except at the very beginning of a pandemic,[2] it is unrealistic that risk estimates based on confirmed cases can be consistently calculated and remain directly comparable over time, age groups, and location. We suggest avoiding entirely the use of case fatality risk based on confirmed cases. The case fatality risk based on symptomatic cases would provide a more reliable early assessment of seriousness for seasonal influenza or the next influenza pandemic. Second, estimation of seriousness in real-time is complicated by delays in reporting and analysis. Estimation of the case fatality risk based on confirmed deaths and symptomatic cases may be possible if relevant models can be prepared in advance and quickly fitted to available data during the pandemic. We have previously discussed real-time estimation of the cumulative incidence of infection based on serologic data.[73] This would form the denominator of the infection fatality risk, but, as noted previously, this is unlikely to be available early in the pandemic.

In preparation for the next influenza pandemic, it is essential to reach a consensus on how to define and measure the seriousness of infection (an important indicator of the severity of the pandemic), and whether the analysis can be based entirely on estimates of age-specific risk of death among cases. The consistent estimates of the infection fatality risk at around 1 to 10 deaths per 100,000 infections identified in our review (Figure 3) may represent the seriousness of H1N1pdm09 in developed countries where data were available. Similar estimates for seasonal influenza viruses, however, are not available for comparison, and neither are estimates from less developed countries in which the seriousness profile would likely be higher.[74]

An alternative assessment of seriousness of infection may be to compare an absolute value of case fatality risk against an arbitrarily defined threshold value.[1] In either case, the experience from 2009 indicates that explicit and consistent definitions are required to permit comparisons. As highlighted by the Fineberg report,[4] updated pandemic plans must clarify how severity will be estimated and interpreted. Improvements in measuring seriousness of infection, perhaps within a multidimensional metric not limited to the case fatality risk, could be a valuable objective of the new World Health Organization Pandemic Influenza Preparedness Framework. Our review also identified substantial delays between study completion dates and publication dates. A mechanism for early sharing of data that does not interfere with subsequent publication would be welcome.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

DKMI receives research funding from F. Hoffman-La Roche. BJC has received research funding from MedImmune Inc., and consults for Crucell NV.

SOURCES OF FUNDING

This work received financial support from the Harvard Center for Communicable Disease Dynamics from the National Institute of General Medical Sciences (grant no. U54 GM088558), the Research Fund for the Control of Infectious Disease, Food and Health Bureau, Government of the Hong Kong SAR (grant no. HK-12-04-02), and the Area of Excellence Scheme of the University Grants Committee of Hong Kong (grant no. AoE/M-12/06).

We thank Vicky Fang and Lincoln Lau for technical support. We thank Eric Lau and Peng Wu for helpful discussions.

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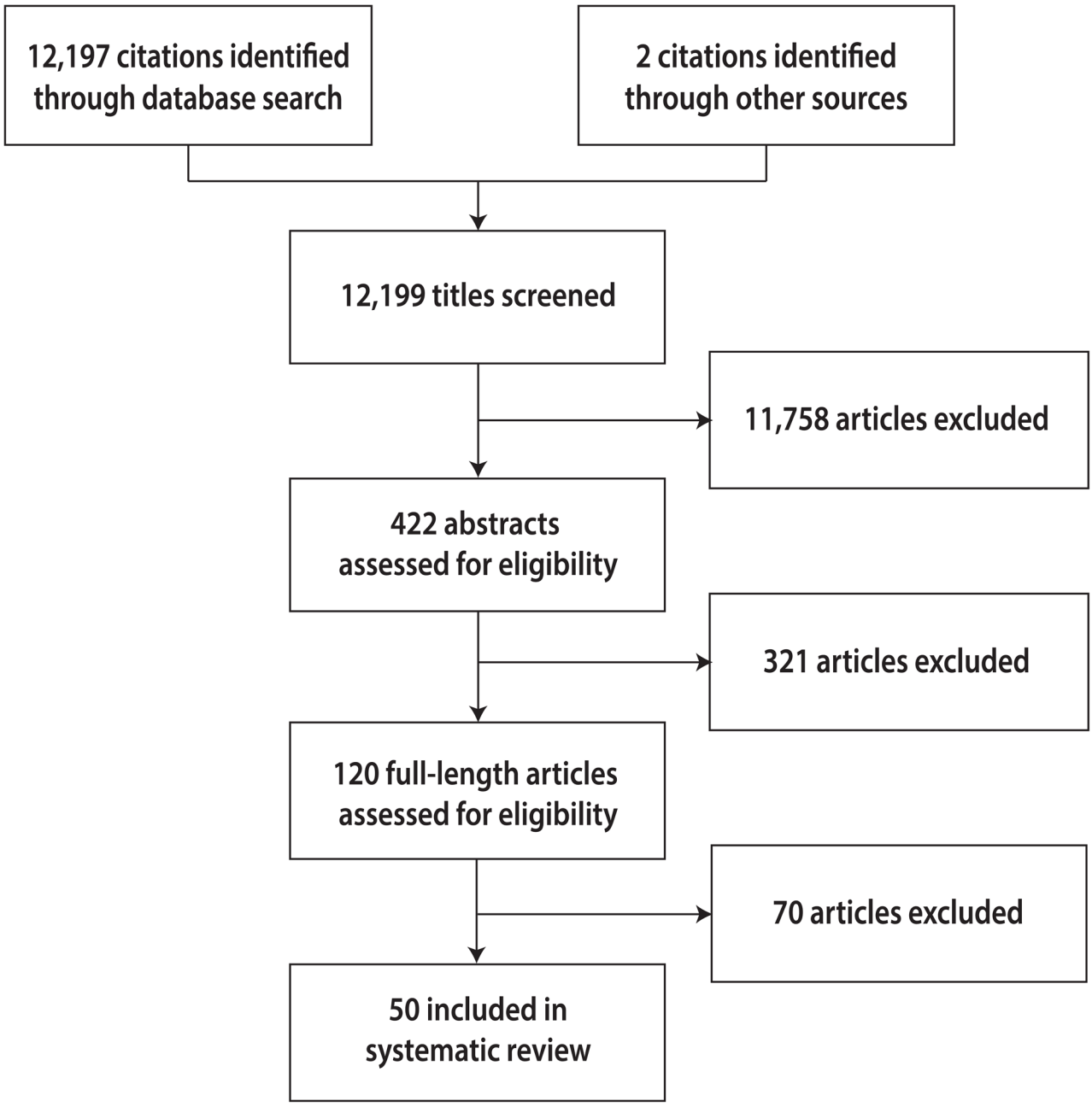

Figure 1.
Flow diagram of study selection.

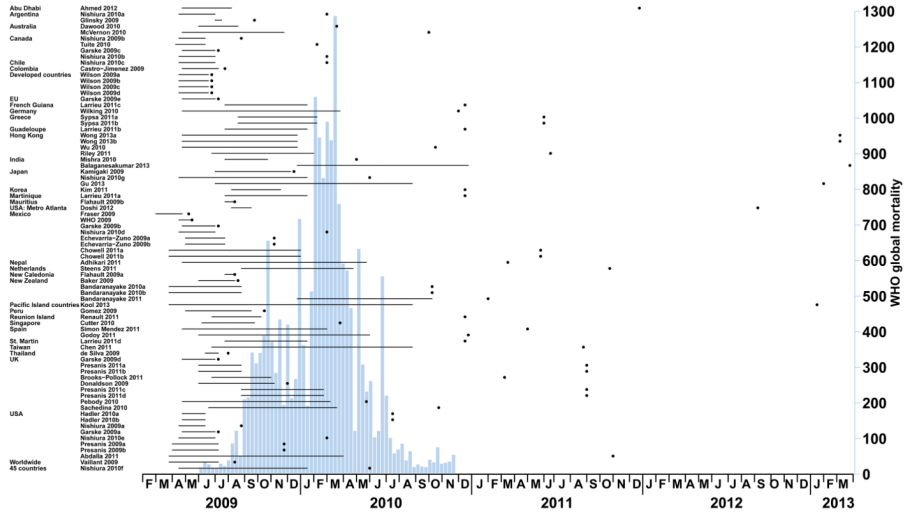

Figure 2.

Study dates (solid horizontal lines), eventual publication dates of the studies included in the review (points) compared with the histogram of confirmed H1N1pdm09 deaths reported to the World Health Organization (underlying histogram). See Table for details of each study.

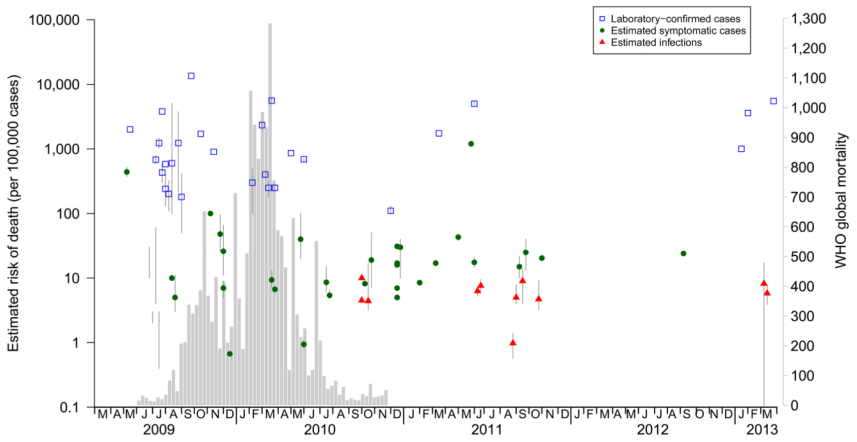

Figure 3.

Estimated risk of death by eventual publication dates of the studies included in the review (points with 95% CI) compared with the histogram of confirmed H1N1pdm09 deaths reported to the World Health Organization (underlying histogram).

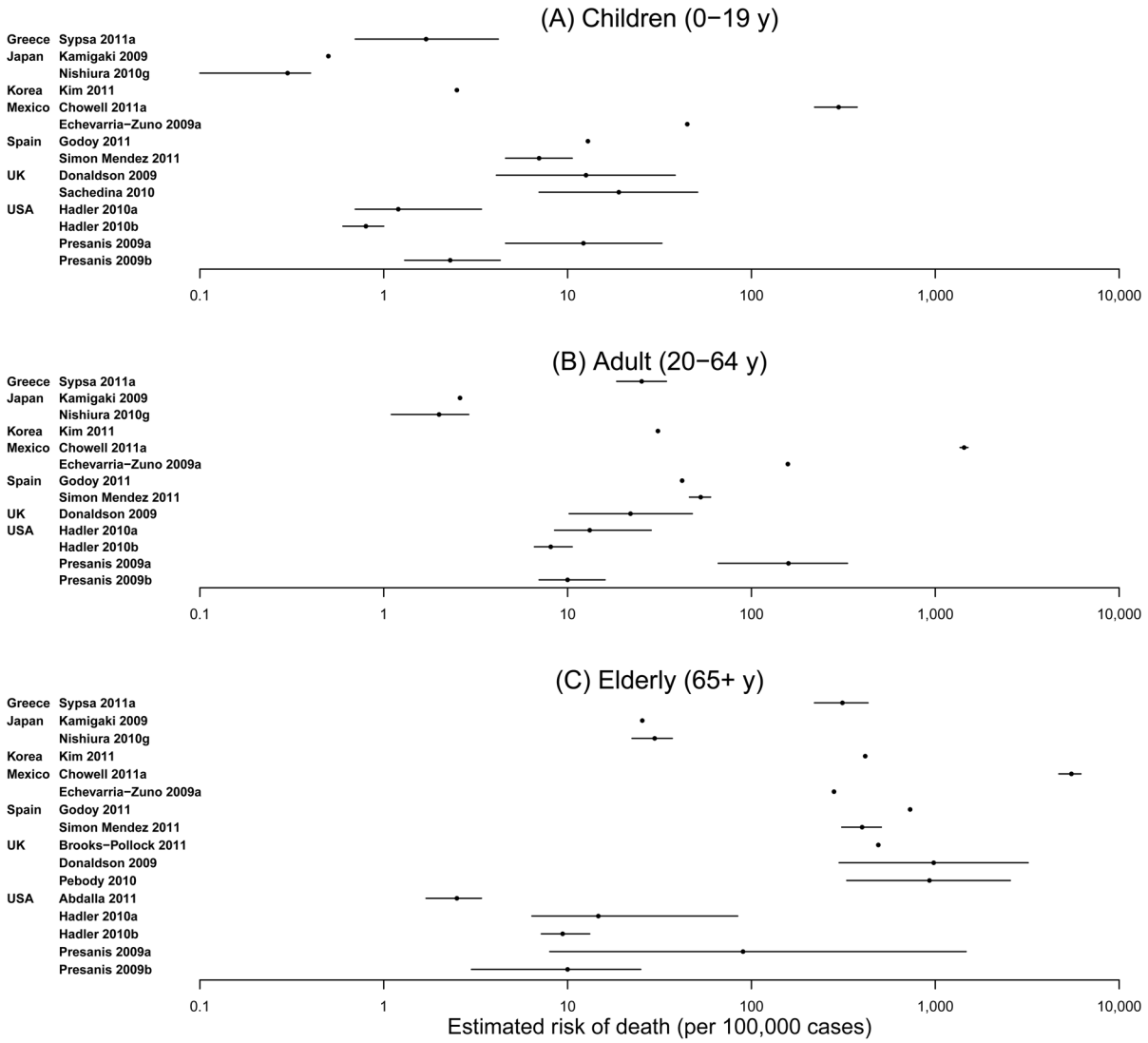

Figure 4.
Age-specific estimated risk of death.

Table 1

Table Summary of case fatality risk studies of influenza A (H1N1-2009) included in the systematic review.

References[a]	Country	Study period	Death definition	Case definition	Case fatality risks[b]	(95% CI)
Estimated infections as denominator[c]						
Bandaranayake 2010a [15]	New Zealand	Apr 09 – Sep 09	Confirmed deaths	Serology	4.5	na
Chen 2011 [19]	Taiwan	Jul 09 – Aug 10	Confirmed deaths	Serology	1	(0.6–1.4)
McVernon 2010 [39]	Australia	Apr 09 – Dec 09	Confirmed deaths	Serology	10	na
Presanis 2011a [46]	UK	Jun 09 – Aug 09	Confirmed deaths	Deaths to hospitalizations × hospitalizations to symptomatic cases × symptomatic cases to infection	5	(4–8)
Presanis 2011c [46]	UK	Sep 09 – Feb 10	Confirmed deaths	Deaths to hospitalizations × hospitalizations to symptomatic cases × symptomatic cases to infection	9	(4–14)
Riley 2011 [48]	Hong Kong	Jul 09 – Feb 10	Confirmed deaths	Serology	7.6	(6.2–9.5)
Steens 2011 [51]	Netherlands	Sep 09 – Apr 10	Confirmed deaths	Serology	4.7	(3.2–9.2)
Sypsa 2011b [52]	Greece	Aug 09 – Feb 10	Confirmed deaths	ILI × LAB, adjusting for the sensitivity of LAB test and proportion of infections that are asymptomatic	6.3	(5.3–7.5)
Wong 2013a [6]	Hong Kong	May 09 – Dec 09	Excess deaths	Serology	8.2	(0.1–17.3)
Wong 2013b [6]	Hong Kong	May 09 – Dec 09	Confirmed deaths	Serology	5.8	(3.9–7.8)
Wu 2010 [58]	Hong Kong	Apr 09 – Dec 09	Confirmed deaths	Serology	4.4	(3.2–17)
Estimated symptomatic cases as denominator[d]						
Abdalla 2011 [10]	USA	Apr 09 – Apr 10	Confirmed deaths	ILI	20.4	na
Baker 2009 [13]	New Zealand	Jun 09 – Aug 09	Confirmed deaths	ILI × LAB, adjusting for health-care seeking behaviour	5	(3–11)
Bandaranayake 2010b [15]	New Zealand	Apr 09 – Sep 09	Confirmed deaths	Serology, scaling down to include only individuals with symptoms	8.2	na
Bandaranayake 2011 [16]	New Zealand	Jan 10 – Oct 10	Confirmed deaths	Serology, scaling down to include only individuals with symptoms	8.5	na

References[a]	Country	Study period	Death definition	Case definition	Case fatality risks[b]	(95% CI)
Brooks-Pollock 2011 [17]	UK	Jul 09 – Nov 09	Confirmed deaths	ILI × LAB, adjusting for health-care seeking behaviour	17	na
Chowell 2011a [20]	Mexico	Apr 09 – Dec 09	ILI deaths	ILI	1200	(1100–1200)
Cutter 2010 [21]	Singapore	Jun 09 – Oct 09	Confirmed deaths	ILI of ARI cases × LAB + non-ILI of ARI cases × LAB	6.7	na
Dawood 2010 [22]	Australia	Jun 09 – Aug 09	Confirmed deaths	ILI × LAB	9.4	(7.1–13.2)
Donaldson 2009 [24]	UK	Jun 09 – Nov 09	Confirmed deaths	ILI × LAB + ANTIVIRAL service × LAB, adjusting for health-care seeking behaviour	26	(11–66)
Doshi 2012 [25]	USA	Aug 09 – Sep 09	P&I deaths	ILI	24	na
Echevarria-Zuno 2009a [26]	Mexico	Apr 09 – Jul 09	Confirmed deaths	ILI	100	na
Flahault 2009a [27]	New Caledonia	Aug 09	Confirmed deaths	Estimated cases, adjusting for health-care seeking behaviour	10	na
Flahault 2009b [27]	Mauritius	Aug 09	Confirmed + suspected deaths	Estimated cases, adjusting for health-care seeking behaviour	10	na
Fraser 2009 [28]	Mexico	Mar 09 – Apr 09	Confirmed + suspected deaths	Confirmed cases among tourists, backcalculating from confirmation to infection	440	(370–520)
Godoy 2011 [31]	Spain	Jun 09 – May 10	Confirmed deaths	ILI	30	(10–40)
Hadler 2010a [34]	USA	May 09 – Jun 09	Confirmed deaths	ILI, adjusting for background ILI using LAB and emergency department visit data	8.6	(6.1–15.1)
Hadler 2010b [34]	USA	May 09 – Jun 09	Confirmed deaths	ILI, adjusting for background ILI using emergency department visit data	5.4	(4.7–6.5)
Kamigaki 2009 [35]	Japan	Jul 09 – Dec 09	Confirmed deaths	ILI, adjusting by medical institutions proportion	0.7	na
Kim 2011 [36]	South Korea	Aug 09 – Nov 09	Confirmed deaths	ILI × LAB, adjusting by medical institutions proportion	16	na
Larrieu 2011a [38]	Martinique	Aug 09 – Jan 10	Confirmed deaths	ILI	5	na
Larrieu 2011b [38]	Guadeloupe	Aug 09 – Jan 10	Confirmed deaths	ILI	31	na
Larrieu 2011c [38]	French Guiana	Aug 09 – Jan 10	Confirmed deaths	ILI × LAB	17	na
Larrieu 2011d [38]	St. Martin	Aug 09 – Jan 10	Flu-related deaths	ILI × LAB	0	na

References[a]	Country	Study period	Death definition	Case definition	Case fatality risks[b]	(95% CI)
Nishiura 2010g [43]	Japan	Jul 09 – Jan 10	Confirmed deaths	ILI	0.94	(0.8–1.08)
Pebody 2010 [44]	UK	Apr 09 – Mar 10	Confirmed deaths	ILI × LAB + ANTIVIRAL service × LAB, adjusting for health-care seeking behaviour	40	(20–100)
Presanis 2009a [45]	USA	Apr 09 – Jul 09	Confirmed deaths	Deaths to hospitalizations × hospitalizations to medically attended cases × medically attended cases to symptomatic cases + deaths to medically attended cases × medically attended cases to symptomatic cases	48	(26–96)
Presanis 2009b [45]	USA	Apr 09 – Jul 09	Confirmed deaths	ILI	7	(5–9)
Presanis 2011b [46]	UK	Jun 09 – Aug 09	Confirmed deaths	Deaths to hospitalizations × hospitalizations to symptomatic cases	15	(10–22)
Presanis 2011d [46]	UK	Sep 09 – Feb 10	Confirmed deaths	Deaths to hospitalizations × hospitalizations to symptomatic cases	25	(13–40)
Renault 2011 [47]	Reunion Island	Jul 09 – Oct 09	Confirmed deaths	ARI × LAB, adjusting for health-care seeking behaviour	7	na
Sachedina 2010 [49]	UK	Jun 09 – Mar 10	Confirmed deaths	ILI × LAB + ANTIVIRAL service × LAB, adjusting for health-care seeking behaviour	19	(7–51)
Simon Mendez 2011 [50]	Spain	May 09 – Mar 10	Confirmed deaths	ILI × LAB	43	(38–48)
Sypsa 2011a [52]	Greece	Aug 09 – Feb 10	Confirmed deaths	ILI × LAB, adjusting for the sensitivity of LAB test	17.5	(14.6–20.8)
Wilson 2009a [57]	Developed countries	Apr 09 – Jun 09	Confirmed deaths	Confirmed cases, adjusting by a multiplier of 10–30	10–30	na
Wilson 2009b [57]	Developed countries	Apr 09 – Jun 09	Confirmed deaths	ILI x LAB	2–3	na
Wilson 2009c [57]	Developed countries	Apr 09 – Jun 09	Excess deaths	5%–10% of the US population <65y	4–60	na
Wilson 2009d [57]	Developed countries	Apr 09 – Jun 09	Confirmed deaths	5%–30% of the Canadian population	0.4–3	na
Laboratory-confirmed cases as denominator[e]						
Adhikari 2011 [11]	Nepal	Apr 09 – May 10	Confirmed deaths	Confirmed cases	1740	na
Ahmed 2012 [12]	Abu Dhabi	May 09 – Aug 09	Confirmed deaths	Confirmed cases	0	na
Balaganesakumar 2013 [14]	India	Jan 10 – Dec 10	Confirmed deaths	Confirmed cases	5500	na

Epidemiology. Author manuscript; available in PMC 2014 November 01.

References[a]	Country	Study period	Death definition	Case definition	Case fatality risks[b]	(95% CI)
Castro-Jimenez 2009 [18]	Colombia	May 09 – Jul 09	Confirmed deaths	Confirmed cases	3800	na
Chowell 2011b [20]	Mexico	Apr 09 – Dec 09	ILI deaths	Confirmed cases	5000	(4700–5300)
de Silva 2009 [23]	Thailand	Jun 09 – Jul 09	Confirmed deaths	Confirmed cases	580	na
Echevarria-Zuno 2009b [26]	Mexico	Apr 09 – Jul 09	Confirmed deaths	Confirmed cases	900	na
Garske 2009a [29]	USA	Apr 09 – Jul 09	Confirmed deaths	Confirmed + probable cases, adjusting for delay from onset to death	680	(590–780)
Garske 2009b [29]	Mexico	Apr 09 – Jul 09	Confirmed deaths	Confirmed cases, adjusting for delay from onset to death	1230	(1030–1470)
Garske 2009c [29]	Canada	Apr 09 – Jul 09	Confirmed deaths	Confirmed cases, adjusting for delay from onset to death	430	(300–580)
Garske 2009d [29]	UK	Apr 09 – Jul 09	Confirmed deaths	Confirmed cases, adjusting for delay from onset to death	240	(130–410)
Garske 2009e [29]	EU	Apr 09 – Jul 09	Confirmed deaths	Confirmed cases, adjusting for delay from onset to death	200	(110–320)
Glinsky 2009 [30]	Argentina	Jul 09	Confirmed deaths	Confirmed cases	13500	na
Gomez 2009 [32]	Peru	May 09 – Sep 09	Confirmed deaths	Confirmed cases	1710	na
Gu 2013 [33]	Japan	Jul 09 – Aug 10	Influenza-associated encephalopathy deaths	Influenza-associated encephalopathy cases	3600	na
Kool 2013 [37]	Pacific Island countries	Apr 09 – Aug 10	Confirmed deaths	Confirmed cases	1000	na
Mishra 2010 [40]	India	Aug 09 – Oct 09	Confirmed deaths, adjusting by hospitalization rate	Confirmed cases	860	na
Nishiura 2009a [41]	USA	Apr 09 – Jun 09	Confirmed deaths	Confirmed cases, adjusting for delay from onset to death	1230	(210–3760)
Nishiura 2009b [41]	Canada	Apr 09 – Jun 09	Confirmed deaths	Confirmed cases, adjusting for delay from onset to death	180	(50–410)
Nishiura 2010a [42]	Argentina	Apr 09 – Jul 09	Confirmed deaths	Confirmed cases, adjusting for delay from onset to death	2330	(1970–2720)
Nishiura 2010b [42]	Canada	Apr 09 – Jul 09	Confirmed deaths	Confirmed cases, adjusting for delay from onset to death	400	(330–470)
Nishiura 2010c [42]	Chile	Apr 09 – Jul 09	Confirmed deaths	Confirmed cases, adjusting for delay from onset to death	250	(180–330)
Nishiura 2010d [42]	Mexico	Apr 09 – Jul 09	Confirmed deaths	Confirmed cases, adjusting for delay from onset to death	5580	(5150–6020)

References[a]	Country	Study period	Death definition	Case definition	Case fatality risks[b]	(95% CI)
Nishiura 2010e [42]	USA	Apr 09 – Jul 09	Confirmed deaths	Confirmed cases, adjusting for delay from onset to death	250	(220–290)
Nishiura 2010f [43]	45 countries	Jul 09 – Jan 10	Confirmed deaths	Confirmed cases	690	(650–730)
Tuite 2010 [53]	Canada	Apr 09 – Jun 09	Confirmed deaths	Confirmed cases	300	(100–500)
Vaillant 2009 [54]	Worldwide	Apr 09 – Jul 09	Confirmed deaths	Confirmed cases	600	(100–5100)
WHO. 2009 [55]	Mexico	Apr 09 – May 09	Confirmed deaths	Confirmed cases	2000	na
Wilking 2010 [56]	Germany	Apr 09 – Mar 10	Confirmed deaths	Confirmed + suspected cases	110	(100–130)

na indicates not available; ILI, influenza-like illness consultations; LAB, laboratory specimens positive for influenza; ARI, acute respiratory infection consultations; ANTIVIRAL, antiviral dugs authorizations.

[a] Letters following the year of publication (e.g., Bandaranayake 2010a) indicate one of multiple analyses, which are described in this table.

[b] Case fatality risks are expressed as number of deaths per 100,000 cases or infections.

[c] Overall: point estimates ranged from 1 to 10 deaths per 100,000 infections

[d] Overall: point estimates ranged from 0 to 1,200 deaths per 100,000 cases

[e] Overall: point estimates ranged from 0 to 13,500 deaths per 100,000 cases