

Estimated global mortality associated with the first 12 months of 2009 pandemic influenza A H1N1 virus circulation: a modelling study



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Summary

Background 18 500 laboratory-confirmed deaths caused by the 2009 pandemic influenza A H1N1 were reported worldwide for the period April, 2009, to August, 2010. This number is likely to be only a fraction of the true number of the deaths associated with 2009 pandemic influenza A H1N1. We aimed to estimate the global number of deaths during the first 12 months of virus circulation in each country.

Methods We calculated crude respiratory mortality rates associated with the 2009 pandemic influenza A H1N1 strain by age (0–17 years, 18–64 years, and >64 years) using the cumulative (12 months) virus-associated symptomatic attack rates from 12 countries and symptomatic case fatality ratios (sCFR) from five high-income countries. To adjust crude mortality rates for differences between countries in risk of death from influenza, we developed a respiratory mortality multiplier equal to the ratio of the median lower respiratory tract infection mortality rate in each WHO region mortality stratum to the median in countries with very low mortality. We calculated cardiovascular disease mortality rates associated with 2009 pandemic influenza A H1N1 infection with the ratio of excess deaths from cardiovascular and respiratory diseases during the pandemic in five countries and multiplied these values by the crude respiratory disease mortality rate associated with the virus. Respiratory and cardiovascular mortality rates associated with 2009 pandemic influenza A H1N1 were multiplied by age to calculate the number of associated deaths.

Findings We estimate that globally there were 201 200 respiratory deaths (range 105 700–395 600) with an additional 83 300 cardiovascular deaths (46 000–179 900) associated with 2009 pandemic influenza A H1N1. 80% of the respiratory and cardiovascular deaths were in people younger than 65 years and 51% occurred in southeast Asia and Africa.

Interpretation Our estimate of respiratory and cardiovascular mortality associated with the 2009 pandemic influenza A H1N1 was 15 times higher than reported laboratory-confirmed deaths. Although no estimates of sCFRs were available from Africa and southeast Asia, a disproportionate number of estimated pandemic deaths might have occurred in these regions. Therefore, efforts to prevent influenza need to effectively target these regions in future pandemics.

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Introduction

Influenza pandemics are typically characterised by higher, but widely varying, number of deaths than are seasonal epidemics.¹ The emergence of pandemic influenza A H1N1 in April, 2009, led WHO to request that countries report all laboratory-confirmed deaths associated with it. For the period up to August, 2010, 18 500 deaths associated with laboratory-confirmed 2009 pandemic influenza A H1N1 have been reported.² This number is likely to be an underestimate because diagnostic specimens are not always obtained from people who die with influenza and the viruses might no longer be detectable by the time of death in some people.

Estimation of the 2009-pandemic-associated mortality presents several challenges. First, data for influenza in many countries are sparse and obtained through

virological surveillance without standardised case reporting or population denominators needed to estimate incidence. Second, the level and timing of the circulation of the pandemic virus might vary by region and country.^{3–5} Third, the severity of influenza might vary by region and country due to differences in access to and quality of health care, nutritional status, prevalence of underlying chronic disorders, age distribution of the populations, and the use of influenza vaccines and antiviral drugs.^{6–10}

Influenza-associated mortality is often estimated indirectly, by use of statistical models, as the number of excess deaths during periods of circulation of the virus.^{11–13} Influenza-associated deaths that might be missed by direct counts of only laboratory-confirmed deaths are taken into account with the use of these indirect approaches. However, indirect estimation might not be

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See Online for appendix

as easy to apply in settings where influenza viruses circulate perennially without a clearly defined season or where data for circulation with other respiratory viruses are not available. Additionally, methods to estimate excess mortality require the availability of vital statistics data that are sparse in some regions of the world and not always available in aggregate until 2–3 years after deaths are reported in countries that do have data. Thus, new methods are needed to produce timely and representative estimates of worldwide influenza-associated mortality.

A global estimate of the mortality associated with the 2009 pandemic influenza A H1N1 is needed to document the effect of the pandemic on the world's population and to help guide allocation and delivery of prevention and treatment measures during future pandemics. So far, most reported estimates of mortality associated with 2009 pandemic influenza A H1N1 are from high-income, temperate countries.^{14–17} We developed a new approach to estimate global mortality and the number of years of life lost (YLL) associated with the first year of circulation of the 2009 pandemic influenza A H1N1 virus in each country.

Methods

Estimation of respiratory mortality rate

To calculate the base respiratory mortality rate associated with the 2009 pandemic influenza A H1N1 (unadjusted for differences between regions in risk of death) for each country, we estimated the 12 month cumulative symptomatic attack rate (sAR) with data from high-income, middle-income, and low-income countries and multiplied it by the estimated symptomatic case fatality ratio (sCFR) from select high-income countries. sAR was defined as the percentage of the population who developed a symptomatic respiratory illness associated with laboratory-confirmed 2009 pandemic influenza A H1N1. sCFR was defined as the percentage of individuals with symptomatic respiratory illness associated with laboratory-confirmed 2009 pandemic influenza A H1N1 who died.

We stratified the estimates of sAR and sCFR into three age groups: 0–17 years (paediatric age group), 18–64 years, and greater than 64 years. We did not further stratify the paediatric age group largely because estimates for smaller strata lack precision. In previous pandemics, risk of death due to influenza has varied between countries,⁹ possibly because of differences in the underlying chronic diseases and co-infections and access to antibiotics and intensive care. Therefore, to adjust sCFR estimates for differences in risk of death from respiratory disease in low-income versus high-income countries, we stratified countries into three risk groups. We adjusted the estimated base mortality in each risk group using a risk-group-specific respiratory mortality multiplier (RMM). The RMM was calculated by use of WHO's estimates of mortality rate for lower respiratory tract infection.¹⁸ Thus, for each of the nine age–risk strata, we built a Monte Carlo probability model using SAS (version 9.2) with probability distributions defined according to the range

of estimates of each parameter. We then estimated the number of respiratory deaths associated with 2009 pandemic influenza A H1N1 for each age and country-risk group by multiplying sAR, sCFR, RMM, and age group population.

Because pandemic H1N1 introduction was delayed in some countries by up to 8 months after the emergence of the virus in the Americas,³ our approach implicitly estimates the mortality attributable to the pandemic virus during the first 12 months of circulation with yearly cumulative attack rates in each country and not a contemporaneous complete calendar year.

Estimates of the cumulative sAR for the first 12 months after virus introduction in each country were obtained from 17 sites in 13 countries—Bangladesh, Cambodia, Denmark, Germany, India, Kenya, the Netherlands, New Zealand, Nicaragua, Peru, the UK (England), the USA, and Vietnam. Data from the site in Cambodia were only gathered during 5 months and therefore were not included in the final model. For most sites, sARs were calculated with raw data gathered with a standard template. Most sAR estimates were calculated from rates of outpatient visits for influenza-associated influenza-like illness divided by the proportion of individuals seeking medical care according to surveys of the use of health-care patterns for respiratory illness during the pandemic; or from prospective, active community-based surveillance of respiratory illness with respiratory specimens that were obtained and tested for influenza viruses (detailed description of data sources and calculation methods is provided in appendix p 1).^{14,19–28} Estimates of the sARs were 4–33% for the paediatric age group, 0–22% for people aged 18–64 years, and 0–4% for those older than 64 years (table 1). We assumed that the true sAR of the 2009 pandemic influenza A H1N1 virus in all age groups was greater than zero; therefore, we set the lower bound of the sAR for people aged 18–64 years and older than 64 years as 1% in our model. Because of the huge variation in sARs within and between countries, we defined the probability of any particular sAR value in the model with a uniform distribution (ie, an equal probability of any sAR value in the range).

We obtained all available age-stratified estimates of the 2009 pandemic influenza A H1N1 sCFR from six studies in Denmark, the Netherlands, New Zealand, the UK, and the USA (two estimates).^{14,23–26} Sites in the UK, the USA, and Denmark were each adjusted for under-reporting of deaths according to their own methods, whereas sites in the Netherlands and New Zealand estimated sCFR based on laboratory-confirmed, reported deaths only. sCFR estimates were 0.002–0.013% for the paediatric age group, 0.018–0.159% for people aged 18–64 years, and 0.090–0.308% for those older than 64 years (table 1). Because the estimates of sCFR had wide and overlapping 95% CIs, we first built a triangular distribution for each sCFR by setting the median of the triangular distribution as being equal to the point

estimate and the minimum and maximum values were set as the fifth and 95th percentiles (tenth and 90th percentiles for US estimates), respectively. We then sampled each triangular distribution an equal number of times to produce a sample of 10 000 points from which the final model was sampled. As a sensitivity analysis, we repeated the same procedure using a uniform distribution for each sCFR estimate (results shown in appendix p 5).

RMM

To adjust for differences in risk of death from respiratory complications between countries, we developed an RMM for all age groups with WHO's 2008 country-specific estimated mortality rates for lower respiratory tract infection¹⁸ and WHO's classification of member states into five mortality strata—very low child and adult mortality; low child and adult mortality; low child and high adult mortality; high child and adult mortality; and high child and very high adult mortality.²⁹ We defined the RMM for countries in the lowest WHO mortality stratum as equal to 1. We then calculated mortality rate ratios for all other countries as the mortality rate associated with lower respiratory tract infection in a given country divided by the median mortality associated with lower respiratory tract infection from the lowest WHO mortality stratum (24 per 100 000 individuals).

Mortality rate ratios are shown by country in appendix p 6. To minimise the effect of individual mortality rate ratios calculated with data of variable quality, we plotted the median mortality rate ratio for lower respiratory tract infection by WHO region and all-cause mortality stratum (appendix p 11). We then assigned countries to one of three risk groups on the basis of the resulting distribution and used the median mortality rate ratio from each group as the RMM for that group (with uncertainty defined by the IQR for the mortality rate ratios). These risk groups were all-African countries, non-African countries with high child and adult mortality, and all other countries (table 2). Non-African countries with high child and adult mortality included Afghanistan, Bangladesh, Bhutan, Bolivia, Burma, Djibouti, Ecuador, Egypt, Guatemala, Haiti, India, Iraq, Maldives, Morocco, Nepal, Nicaragua, North Korea, Pakistan, Peru, Somalia, Sudan, Timor-Leste, and Yemen.

Population estimates

We used the UN's projected population estimates³⁰ for 2010 when available, and the US Census Bureau mid-year population estimates³¹ for 2010 for all remaining countries. Kosovo, Niue, and Vatican City were excluded from this analysis because no available age-stratified population estimates were available.

Estimated respiratory mortality

We ran our Monte Carlo model 10 000 times to estimate mortality for each of the nine age-risk strata (a total of 90 000 iterations). We then applied each of the resulting

	0–17 years	18–64 years	>64 years
Countries with data inputs for symptomatic attack rate			
Cambodia (Kapong Cham) ^{28*†}	1%
Bangladesh (Dhaka) ^{21*}	4%	0%	0%
Denmark ^{23‡§}	13%	4%	1%
Germany¶	32%	12%	2%
India (Ballabgarh)*	7%	4%	2%
Kenya (Kibera)*	11%	6%	0%
Kenya (Lwak)*	22%	22%**	0%
Netherlands ^{26††}	13%	1%	0%
New Zealand ^{20††}	20%	7%	1%
Nicaragua (Managua) ^{22*}	19%
Peru (Cusco) ^{19,27*}	4%	1%	0%
Peru (Lima) ^{19,27*}	23%	7%	3%
Peru (Madre de Dios) ^{19,27*}	12%	2%	0%
Peru (Tumbes) ^{19,27*}	33%	5%	2%
UK (England) ^{25‡}	10%	3%	0%
USA ^{14‡}	32%	12%	4%
Vietnam (Hanoi)*	5%	2%	0%
Countries with data inputs for symptomatic case fatality ratio‡‡			
USA ¹⁴	0.005% (0.004–0.008)	0.027% (0.019–0.040)	0.092% (0.066–0.136)
Denmark ^{23§}	0.005% (0.002–0.013)	0.031–0.077%§§	..
Netherlands ²⁶	0.004% (0.003–0.006)	0.019–0.051%§§	..
New Zealand	0.002% (0.0003–0.005)	0.018% (0.012–0.024)	0.122% (0.024–0.220)
UK (England) ²⁵	0.008% (0.004–0.013)	0.028% (0.012–0.047)	0.308% (0.057–1.069)
USA (WI and NY) ^{24§}	0.013% (0.005–0.033)	0.159% (0.066–0.333)	0.090% (0.008–1.471)

References are for the general methods used for data gathering but might not include estimates for the period reported in this table. *Based on population-based surveillance or cohort study of respiratory illness with laboratory confirmation of 2009 pandemic influenza A H1N1 virus infection. †Data from Kampong Cham were only gathered over 5 months; therefore, estimates of symptomatic attack rates from this site were not included in the final model. ‡Based on statistical modelling by use of multiple data sources (see appendix p 1 for details). §Data were available for the following age groups: 0–14 years, 15–64 years, and greater than 64 years. ¶Derived from population-based surveillance for medically attended respiratory illness adjusted with the estimated proportion of people who sought care for respiratory illness. ||No available reference. **Outlier estimate excluded from the final model. ††Based on estimate of seroprevalence of 2009 pandemic influenza A H1N1 virus infection adjusted with the estimated proportion of people who were seropositive and had symptoms of respiratory illness. ‡‡90% CI reported for USA and 95% CI for all other estimates. §§Only 95% CI used.

Table 1: Data inputs for estimation of mortality associated with 2009 pandemic influenza A H1N1 by age group

10 000 estimates for each age-risk stratum to population estimates for each country in the RMM stratum to calculate the number of deaths by age in each country. The distribution of mortality-rate estimates for each age-risk stratum was highly right skewed with the lower 75% of the estimates clustered within a narrow range of values and the upper 25% of estimates dispersed across a wide range of values (appendix p 12 shows an example of the distribution of estimates from one Monte Carlo simulation). We summed the median and 25% and 75% estimates for each country and age group to calculate a global point estimate and range, respectively, by age group and WHO region.

Estimated cardiovascular mortality

Since influenza deaths can arise from respiratory or cardiovascular complications, we also estimated

cardiovascular deaths due to 2009 pandemic H1N1 in people older than 17 years (influenza-associated cardiovascular deaths are rare in children). First, we calculated ratios of estimated cardiovascular to respiratory deaths associated with 2009 pandemic influenza A H1N1 using estimates of excess circulatory

and respiratory deaths attributed to the virus in five high-income and middle-income countries stratified by age 64 years and younger and older than 64 years. To calculate the ratio of cardiovascular to respiratory deaths associated with the 2009 pandemic influenza A H1N1 virus, we used estimates of excess deaths attributable to this strain for Argentina, Brazil, Chile, Mexico, and the USA. The estimated ratios were 0.3–1.6 (median 0.7) in people aged 64 years and younger and 1.3–2.0 (1.8) in those older than 64 years (appendix p 14).

Second, we multiplied the median estimate of the ratio of cardiovascular to respiratory deaths for each age group by the base respiratory mortality rate in each country for people aged 18–64 years and older than 64 years to calculate the base cardiovascular mortality rate associated with 2009 pandemic influenza A H1N1 (unadjusted for differences between regions in risk of cardiovascular death). We then assessed differences in risk of death from cardiovascular disease between countries by calculating mortality rate ratios from WHO's¹⁸ estimates of cardiovascular disease mortality rate based on the same method as for the RMM. Because the median mortality rate ratios for each region–mortality stratum were 1–2 (appendix p 13), we did not use a mortality multiplier for cardiovascular disease. Thus, for each age group in each country, we estimated the cardiovascular mortality rate associated with the 2009 pandemic influenza A H1N1 virus as the base respiratory mortality rate multiplied by the ratio of cardiovascular to respiratory deaths and population.

	Minimum	Maximum	Median	Distribution
Symptomatic attack rate				
0–17 years	4%	33%	13%	Uniform
18–64 years	1%	12%	5%	Uniform
>64 years	1%	4%	2%	Uniform
Symptomatic case fatality ratio*				
0–17 years	0.0003%	0.033%	0.005%	Natural†
18–64 years	0.012%	0.327%	0.029%	Natural†
>64 years	0.009%	1.449%	0.124%	Natural†
Mortality multiplier for lower respiratory tract infection				
African region countries, all ages	3	7	5	Uniform
Non-African region countries with high child and adult mortality rates, all ages	1	4	3	Uniform
All other countries, all ages	1	1	1	Uniform

*Minimum and maximum values for each age group represent those of the sample of 10 000 points from which the final model was sampled. †Refers to the representative sample built from an equal number of samples selected from each of the six sources for the estimates; first, we built a triangular distribution setting the median of the triangular distribution as equal to the point estimate and the minimum and maximum set to the fifth and 95th percentiles, respectively; and second, we sampled each triangular distribution an equal number of times to produce a sample of 10 000 points from which the final model sampled.

Table 2: Parameters and probability distribution used in mortality model for 2009 pandemic influenza A H1N1

	Reported*	All ages n (range†)	Rate per 100 000	0–17 years (n [range†])	18–64 years (n [range†])	>64 years (n [range†])
Respiratory deaths						
Africa	168	58 800 (30 800–112 200)	7.0	18 500 (9400–32 400)	35 900 (19 100–68 000)	4500 (2300–11 800)
Americas	≥8533	17 500 (9400–34 500)	1.9	3000 (1500–5300)	11 400 (6200–20 900)	3000 (1700–8300)
Eastern Mediterranean	1019	17 900 (9200–35 400)	3.0	4500 (2200–8500)	11 700 (6100–22 700)	1700 (800–4300)
Europe	≥4879	16 400 (9000–33 400)	1.8	1800 (900–3100)	10 400 (5700–18 700)	4200 (2300–11 700)
Southeast Asia	1992	59 500 (30 400–119 200)	3.3	12 400 (6100–23 500)	40 500 (21 000–78 500)	6700 (3300–17 200)
Western Pacific	1858	31 100 (17 000–60 800)	1.7	4300 (2200–7400)	21 400 (11 800–38 700)	5300 (3000–14 800)
Global‡	≥18 449	201 200 (105 700–395 600)	2.9	44 500 (22 400–80 100)	131 300 (69 900–247 500)	25 400 (13 400–113 500)
Respiratory and cardiovascular deaths§						
Africa	168	65 600 (34 600–125 900)	7.8	18 500 (9400–32 400)	41 100 (22 000–77 300)	6100 (3200–16 200)
Americas	≥8533	29 700 (16 200–61 500)	3.2	3000 (1500–5300)	18 600 (10 200–34 000)	8100 (4500–22 300)
Eastern Mediterranean	1019	23 600 (12 300–47 100)	3.9	4500 (2200–8500)	16 000 (8500–30 400)	3100 (1600–8200)
Europe	≥4879	31 300 (17 200–67 600)	3.5	1800 (900–3100)	17 600 (9700–31 800)	11 900 (6600–32 700)
Southeast Asia	1992	78 600 (40 900–158 900)	4.4	12 400 (6100–23 500)	54 000 (28 400–103 000)	12 200 (6400–32 500)
Western Pacific	1858	55 700 (30 600–114 500)	3.1	4300 (2200–7400)	36 400 (20 100–65 800)	15 000 (8300–41 300)
Global‡	≥18 449	284 400 (151 700–575 400)	4.1	44 500 (22 400–80 100)	183 700 (98 800–342 200)	56 400 (30 500–233 700)

*Number of laboratory-confirmed deaths due to 2009 pandemic influenza A H1N1 reported to WHO during April, 2009, to August 1, 2010. †The range was calculated by summing the 25th and 75th percentiles of estimates in each age group per country. ‡The total of the regional estimates is not always equal to the global estimate because of rounding. §Cardiovascular deaths were only calculated for people aged 18 years and older.

Table 3: Reported and estimated respiratory and cardiovascular deaths associated with 2009 pandemic influenza A H1N1 by WHO region during the first 12 months of virus circulation in each country and by age

YLL

To further document the effect of the 2009 pandemic influenza A H1N1 that disproportionately affected young people compared with seasonal influenza epidemics, we estimated the YLL from respiratory and cardiovascular deaths associated with the virus as number of estimated deaths in each age group multiplied by the mean number of additional years of life expected for people in each age group in each country.

The average numbers of years of life expected for people in each age group were obtained from WHO's 2008 life tables.³² To show the differences in the mortality burden for age groups between the 2009 H1N1 pandemic and seasonal influenza epidemics, we estimated YLL that would have been lost if the age distribution of people who died with 2009 pandemic influenza A H1N1 had been similar to the age distribution due to seasonal influenza. We assumed that during typical seasonal influenza epidemics, 1% of deaths occurred in people younger than 18 years, 9% in those aged 18–64 years, and 90% in people older than 64 years.^{33,34} We then redistributed our pandemic deaths according to this seasonal age distribution and estimated the YLL using the same equation as above.

Role of the funding source

We received no external funding for the analysis. The corresponding author had full access to all the data used in the analysis and had final responsibility for the decision to submit for publication.

Results

The total of the median estimates of country-specific respiratory deaths associated with the 2009 pandemic influenza A H1N1 was 201 200 (range calculated by summing the 25th and 75th percentile estimates in each age group in each country), more than ten times the number of global deaths reported to WHO

for the period April, 2009, to August, 2010 (table 3). Summation of the fifth and 95th percentile estimates in each age group and country would have resulted in an estimated range of 39 000–1 315 800 respiratory deaths associated with 2009 pandemic influenza A H1N1. Results from the sensitivity analysis in which a uniform distribution was used instead of a triangular distribution to sample from each sCFR range were broadly similar (appendix p 5). To demonstrate the effect of adjusting for differences in respiratory mortality, the calculation was repeated without the RMM, which resulted in an estimate of 112 900 respiratory deaths (range 61 500–218 200) associated with 2009 pandemic influenza A H1N1.

29% of the 201 200 estimated respiratory deaths associated with the 2009 pandemic influenza A H1N1 occurred in the African region (table 3). The estimated mortality rate in the African region was about two to four times that in countries elsewhere (table 3). The estimated range of respiratory deaths by country are shown in appendix p 15.

65% of 2009 pandemic influenza A H1N1 deaths worldwide were in individuals aged 18–64 years (60% of global population), although the age distribution varied by region. Overall, 13% of respiratory deaths associated with 2009 pandemic influenza A H1N1 were in people older than 64 years (8% of global population).

An additional 83 300 cardiovascular deaths (range 46 000–179 900) associated with the 2009 pandemic influenza A H1N1 were estimated to have occurred in people older than 17 years, resulting in a total of 284 400 respiratory and cardiovascular deaths (table 3). 20% of these deaths occurred in people older than 64 years. With the inclusion of cardiovascular mortality, there was a reduction in the disparity in mortality associated with the pandemic by region, although the mortality rate in Africa remained about two to three times higher than elsewhere. Total numbers of respiratory and cardiovascular deaths by country are shown in appendix

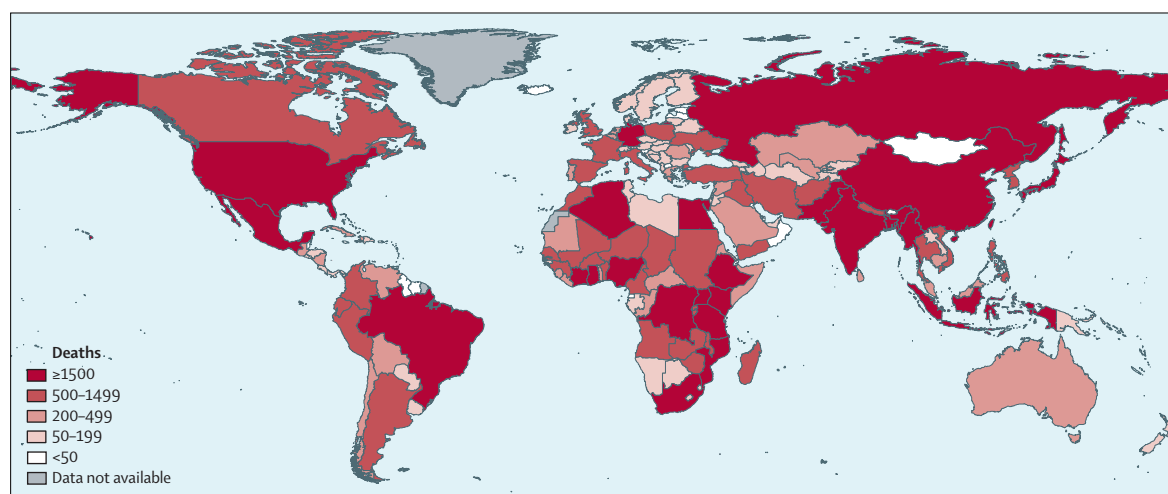


Figure 1: Global distribution of deaths associated with 2009 pandemic influenza A H1N1 during the first year of virus circulation by country

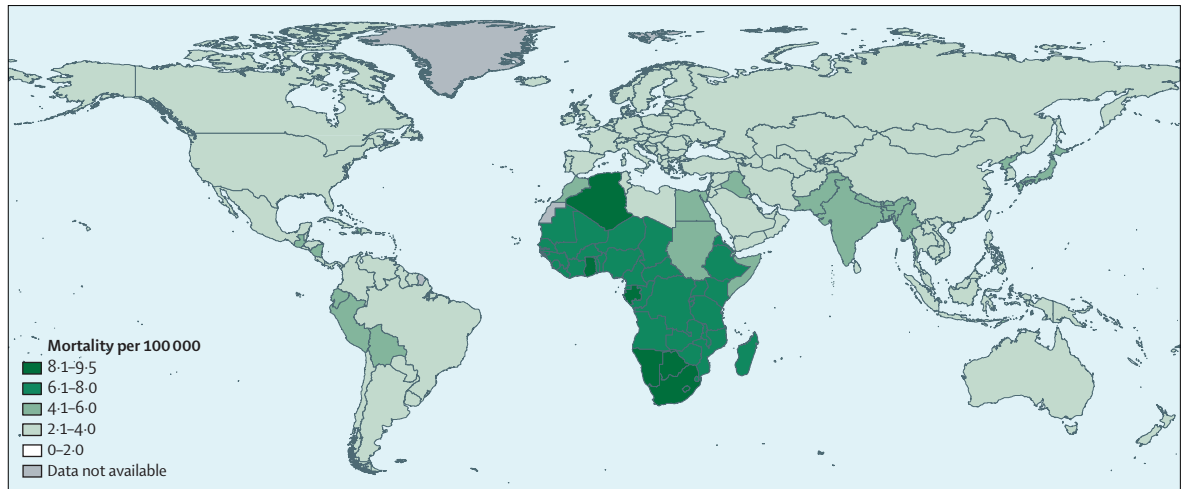


Figure 2: Estimated age-adjusted respiratory and cardiovascular mortality rate associated with 2009 pandemic influenza A H1N1 per 100 000 individuals by country

	Average life expectancy at birth (years) ³²	YLL due to pandemic influenza A H1N1 respiratory mortality	YLL if age distribution of deaths was similar to seasonal influenza*
Africa	53	2 278 800 (1 194 500–4 196 500)	556 100
Americas	76	1 050 600 (567 600–1 965 100)	361 800
Eastern Mediterranean	65	862 500 (446 100–1 645 900)	219 200
Europe	75	927 600 (506 800–1 756 400)	360 900
Southeast Asia	65	2 725 300 (1 407 900–5 243 400)	738 700
Western Pacific	75	1 862 200 (1 015 800–3 445 500)	605 000
Global	68	9 707 000 (5 138 700–18 252 800)	2 841 700

Data are total of medians (range), unless otherwise indicated. YLL=years of life lost. *Number of 2009 pandemic influenza A H1N1 deaths is redistributed across age groups to approximate the typical age distribution of seasonal influenza deaths in developed countries where estimates were available (90% for people aged >64 years, 9% for age 18–64 years, and 1% for age 0–17 years).

Table 4: YLL because of deaths associated with 2009 pandemic influenza A H1N1 during the first 12 months of virus circulation and YLL that would be lost with a seasonal influenza age distribution of deaths

p 19, and estimated H1N1-associated respiratory and cardiovascular deaths and mortality rates by country are shown in figures 1 and 2.

Estimated YLL were 9 707 000 during the first 12 months of the pandemic (table 4). Southeast Asia was the region with the greatest YLL (table 4). Total YLL attributable to deaths associated with 2009 pandemic influenza A H1N1 was 3–4 times higher than if the age distribution of deaths had been similar to that during seasonal epidemics in developed countries where age-specific estimates of seasonal influenza mortality are available (table 4). The increase in YLL associated with 2009 pandemic influenza A H1N1 was due to the increased rate of death in people aged 64 years and younger.

Discussion

During the first year of circulation of the 2009 pandemic influenza A H1N1 virus in each country, an estimated 105 700–395 600 people died of associated respiratory

illness. Addition of cardiovascular deaths associated with 2009 pandemic influenza A H1N1 among people older than 17 years increased the mortality burden to 151 700–575 400 deaths (table 3). Our global estimate was more than 15 times higher than the number of laboratory-confirmed deaths reported to WHO during the first 16 months of the pandemic. A disproportionate number of total deaths from cardiovascular and respiratory diseases (51%) was estimated to have occurred in the African and southeast Asian regions where 38% of the world's population live and where data for influenza incidence are scarce.³⁵ Additionally, most deaths were reported in people aged 18–64 years, consistent with previous reports.³⁶ These findings are in contrast to those for seasonal influenza deaths. Roughly 80–90% of these arise in people aged 65 years and older in Australia, Denmark, Singapore, and the USA, where age-stratified estimates are available.^{33,37–39} However, the age distribution of seasonal influenza-associated deaths might differ between settings because of differences in the prevalence of underlying illnesses (such as HIV/AIDS and tuberculosis) in younger adults in some low-income countries. The shift in the age distribution of deaths during the pandemic resulted in substantially more YLL than would have occurred if the age distribution of deaths had been similar to that of most seasonal influenza epidemics, consistent with observations from previous pandemics (panel).

Estimates from previous pandemics indicate that influenza mortality rates vary substantially between countries.^{9,47} Our accounting for differential risk of influenza-associated death between countries is supported by the findings of Cohen and colleagues⁶ that excess seasonal pneumonia and influenza mortality in people aged 65 years and older is at least three times higher in South Africa than in the USA. Further, data from the Americas and the western Pacific show that risk

of death associated with the 2009 pandemic was up to six times higher in indigenous than in non-indigenous populations.⁸ In both studies,^{6,8} the prevalence of underlying disorders (including malnutrition in South Africa) and access to health care were postulated to contribute to the increased risk of influenza-associated death. Nair and colleagues¹⁰ also estimated that mortality rates for influenza-associated acute lower respiratory tract infection in children younger than 5 years are three times higher in low-income countries than in high-income countries.

WHO has estimated that an average of 0.004–0.008% per year of the world's population (250 000–500 000 people) die as a result of seasonal influenza.⁴⁸ Estimates of pandemic influenza mortality ranged from 0.03% of the world's population during the 1968 pandemic to 1–3% of the world's population during the 1918 pandemic.^{7,9,47} We estimate that 0.001–0.007% of the world's population ($n=6891433594$) died of respiratory complications associated with 2009 pandemic influenza A H1N1 during the first year of virus circulation or 0.001–0.011% when cardiovascular deaths were included. However, our estimates are not directly comparable to those of mortality associated with seasonal and previous pandemic influenza for at least two reasons. First, the WHO estimate of global seasonal influenza mortality is an extrapolation of estimates from high-income countries⁴⁸ without accounting for regional variation in risk of death from outcomes that might be associated with influenza, though details of the methods have not been provided. Second, reported estimates of global pandemic mortality include data from several years of pandemic virus circulation, whereas our estimate includes data for only the first year of 2009 pandemic influenza A H1N1 virus circulation in each country.

We were unable to identify any factor or group of factors that allowed stratification of countries into transmission risk groups, and therefore we assumed the same range of 2009 pandemic influenza A H1N1 sARs for all countries. This approach results in point estimates that underestimate or overestimate deaths in countries that had very high or very low transmission, respectively, but should produce ranges for most country-specific estimates that are likely to capture the true number of deaths in each country. For this reason, we present only ranges for our country-specific estimates. The assumption of a range of 2009 pandemic influenza A H1N1 sARs for all countries is less likely to bias our regional and global estimates.

Our model was limited by the scarcity of globally representative estimates of sAR and sCFR. We relied on only 16 direct estimates of 1 year sARs for 2009 influenza A H1N1 that varied greatly, and were likely to be affected by an unidentified combination of factors such as differences in climate, population density, and population age structure. Data from serology studies of both symptomatic and asymptomatic infections support our

Panel: Research in context

Systematic review

We searched PubMed for reports of studies in any language from April, 2009, to March, 2012, with estimates of the number of deaths or mortality due to the 2009 pandemic influenza A H1N1. We identified 12 studies from eight countries in Europe, the Americas, western Pacific, and Asia.^{14,17,23,25,39–46} In two studies from Australia (New South Wales)⁴² and the UK,⁴¹ no deaths were estimated based on the excess all-cause mortality during periods of influenza virus circulation. Two other UK studies were reported—in the England-only study, the estimated number of deaths was 390–490²⁵ and in the study of only England and Wales the estimate was 1556.⁴⁴ In one of the two studies from Mexico, the estimated mortality was 35 per 100 000 people in San Luis Potosi,⁴⁰ whereas in the other study the estimate was 6200 deaths for Mexico based on excess pneumonia and influenza mortality or 26 500 deaths based on excess all-cause mortality.¹⁷ According to the estimates from two studies that included deaths in 2009 only, there were 6000 deaths in Bangladesh⁴⁵ and 0–256 deaths in Hong Kong, equal to an age-standardised mortality of 2.9–14.8 per 100 000 individuals. According to the estimates from the remaining studies, there were 8868–18 306 deaths in the USA,¹⁴ 121 or 151–473 in Denmark,^{23,39} and 266–958 in the Netherlands.⁴³

Interpretation

Our estimated ranges of deaths associated with 2009 pandemic influenza A H1N1 for each country overlap with reported estimates from Denmark (109–438 vs 151–473 or 121), the Netherlands (326–1289 vs 266–958), the USA (5834–22 697 vs 8868–18 306), China (Hong Kong only; 1.7–6.2 per 100 000 vs 2.9–14.8 per 100 000), and Bangladesh (3899–15 135 vs 6000). However, our estimated ranges are higher than most estimates from the UK (1237–4946 vs 0 for the UK or 390–490 for England or 1556 for England and Wales), and Australia (406–1589 vs mortality rate of 0 on the basis of excess all-cause deaths in the Hunter New England region) and lower than estimates from Mexico (1670–6105 vs 6200 excess pneumonia and influenza deaths or 26 000 excess all-cause deaths). Differences in study methods must be taken into account when estimates from these studies are compared. The results of our study add to the understanding of the global effect of the 2009 pandemic influenza A H1N1 because we have estimated the associated deaths in African and southeast Asian countries for which there is only one reported estimate from Bangladesh so far. We show that half of all global H1N1-associated respiratory and cardiovascular deaths could have occurred in Africa and southeast Asia and that mortality rates might have been two to three times higher in Africa than in other regions of the world.

findings that the 2009 pandemic influenza A H1N1 attack rates varied substantially both within⁴ and between countries.^{49–54} Second, we relied on only six estimates of sCFR from high-income countries because none were available from low-income or middle-income countries including China and India, which account for 37% of the world's population. Although the available estimates of sCFR were each calculated with different methods for ascertaining the numerator (number of deaths associated with 2009 pandemic influenza A H1N1) and denominator (number of symptomatic 2009 pandemic influenza A H1N1 virus infections), most of these estimates were fairly similar. However, each sCFR estimate had a substantial amount of inherent uncertainty, particularly for the older than 64 years age group in which the denominator for the sCFR was lower than in other age groups. The uncertainty of the individual sCFR estimates widened the confidence intervals of our final estimates.

The lack of influenza sCFR or mortality rate estimates for low-income and middle-income countries is an important knowledge gap in the understanding of the epidemiology of both seasonal and pandemic influenza. To overcome the lack of data to inform sCFR estimates for these settings, we developed an RMM from mortality rates for lower respiratory tract infection that are subject to several limitations. First, mortality rates consist of both disease incidence and case fatality rates. Thus, the RMM is affected by differences in the incidence of non-influenza respiratory infections, and the dearth of estimates of incidence of lower respiratory tract infection for most countries prevented us from adjusting for differences in incidence. Second, we used one RMM for all age groups because the age-stratified rate ratios in the 0–17 year group were up to 58 times higher than the all-age ratios, probably due to a larger difference in incidence of non-influenza respiratory infections in this age group. By contrast, the all-age rate ratios were similar to ratios in the older age groups that had the most number of deaths associated with the 2009 pandemic influenza A H1N1. Because the relative risk of influenza-associated respiratory death is likely to vary between age groups, use of one all-age RMM is likely to result in an underestimation of virus-associated mortality in children in low-income countries.

One additional potential methodological limitation of our analysis is that we summed the median and IQR estimates for each age group in each country to calculate a point estimate and range of the total number of deaths by country, region, and globally. The assumption with this approach is that symptomatic attack rates are positively correlated between age groups in each country (ie, it is unlikely for one age group to have an attack rate on the higher end of the global range of sARs and another age group to have an attack rate on the lower end of the global range). Had we summed the result of each Monte Carlo iteration for each age group in each country, then summed the results for each country, and taken the median and IQR of the distribution of the global estimates, our estimate would have been 25% higher. A final potential limitation is that we assumed that the life expectancy of people who died with 2009 pandemic influenza A H1N1 was equal to that of people of the same age in the general population, although people who die from influenza might be more likely to have underlying disorders that are associated with a reduced life expectancy.

We estimated that 151700–575400 respiratory and cardiovascular deaths associated with 2009 pandemic influenza A H1N1 occurred during the first year of virus circulation in every country in the world. Our findings emphasise the need to improve the global response to future influenza pandemics and expand production and improve delivery of influenza vaccines to Africa and southeast Asia because these countries might have borne a disproportionate burden of pandemic mortality during the first year of virus circulation. Additionally,

continued efforts to strengthen influenza surveillance worldwide, particularly for influenza-associated mortality, are needed both to guide seasonal influenza prevention strategies and to build influenza surveillance systems to provide better and more timely and globally representative data for influenza-associated mortality during future pandemics.

Contributors

FSD, ADI, M-AW, DKS, MIM, JB, and CR all actively contributed to the design of the analysis; CR, MIM, DKS, P-YC, DB, RFB, WAB, PB, DRF, KBF, AG, NTH, PH, QSH, MAK, AK, RL, JMM, KM, RP, AMP, HR, AS, YOT, JW, HY, and SV provided the data used in this analysis. FSD and ADI did the data analysis. FSD wrote the first draft of the report, and all authors contributed to the interpretation of the results of the analysis and to the revision and final preparation of the report for submission.

Conflicts of interest

We declare that we have no conflicts of interest.

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