Estimation of potential global pandemic influenza mortality on the basis of vital registry data from the 1918–20 pandemic: a quantitative analysis

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Summary

Background **The threat of an avian influenza pandemic is causing widespread public concern and health policy response, especially in high-income countries. Our aim was to use high-quality vital registration data gathered during the 1918–20 pandemic to estimate global mortality should such a pandemic occur today.**

Methods **We identified all countries with high-quality vital registration data for the 1918–20 pandemic and used these data to calculate excess mortality. We developed ordinary least squares regression models that related excess mortality to per-head income and absolute latitude and used these models to estimate mortality had there been an influenza pandemic in 2004.**

Findings **Excess mortality data show that, even in 1918–20, population mortality varied over 30-fold across countries. Per-head income explained a large fraction of this variation in mortality. Extrapolation of 1918–20 mortality rates to the worldwide population of 2004 indicates that an estimated 62 million people (10th–90th percentile range 51 million–81 million) would be killed by a similar influenza pandemic; 96% (95% CI 95–98) of these deaths would occur in the developing world. If this mortality were concentrated in a single year, it would increase global mortality by 114%.**

Interpretation **This analysis of the empirical record of the 1918–20 pandemic provides a plausible upper bound on pandemic mortality. Most deaths will occur in poor countries—ie, in societies whose scarce health resources are already stretched by existing health priorities.**

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Introduction

The avian influenza epidemic in birds and the 258 cases recorded in human beings (as of Nov 29, 2006) in several continents[1] are generating tremendous media coverage, public concern, and policy debate.[2] Governments and donor agencies have joined together to pledge substantial funds to fight the spread of avian influenza;[3] for example, the US government has committed $3·8 billion for the USA[4] and Australia has set aside AUD$555 million.[5] This high degree of concern is in part due to estimates of potential mortality from a major influenza pandemic. Estimates from 2 million[6] to 360 million[7] and even up to 1 billion[8] deaths have been proposed. These numbers, combined with predictions of the inevitability of the next influenza pandemic, are driving continued attention and policy focus.[9]

Various models of the effect of influenza pandemics on mortality have been developed.[10–12] These models make strong assumptions about attack rates and case-fatality rates in influenza cases. Irrespective of the modelling assumptions, however, the three pandemics of the 20th century—in 1918–20, 1957–58, and 1968–70—are the main source of empirical evidence on the potential human toll of the next pandemic.[13–15] The 1918–20 Spanish flu pandemic caused the highest mortality by far and is often used to set the upper bound on the number of deaths caused by a future pandemic.[16] Medical historians have generated estimates of mortality in 1918–20 ranging from 20 million to 100 million.[17–19] These estimates are based on reviews of various historical documents, including national commissions, eye-witness accounts, and local government reports. With some exceptions,[20–22] these analyses have not distinguished quantitative analyses based on underlying high-quality vital registration data from qualitative accounts.

Systematic analysis of all available vital registration data would permit the calculation of pandemic mortality due to the major 20th century influenza pandemics in a comparable manner. Here, our aim is to assess vital registration data from the 1918–20 pandemic, since this pandemic was overwhelmingly larger than other 20th century pandemics and provides a clearly identifiable effect on mortality. We aim to develop statistical models that relate annual pandemic mortality to community attributes, and to use these models to estimate the effect on mortality of an influenza pandemic in 2004, the most recent year for which per-head gross domestic product in international dollars is available.

Methods

Data collection

We included all available vital registration data from 1915 to 1923—ie around the period of the 1918–20 influenza pandemic—from populations in which vital registration is believed to be 80% or more complete.[23,24] Data were mainly taken from the Berkeley Human Mortality Database[25] and

B R Mitchell's International Historical Statistics Series.[26] These sources were supplemented with subnational data for US states[27–35] and what were then described as provinces of pre-partition India.[36,37]

Epidemic and pandemic influenza mortality in previous studies were calculated in one of two ways: with seasonal and inter-year variations in mortality to calculate excess mortality in the influenza season[38,39] and with cause-specific mortality data. Comparisons of influenza-specific mortality, however, are confounded by changes in influenza coding across several revisions of the International Classification of Diseases[40] and variation in influenza certification and coding between and within countries.[41] We opted to use excess all-cause mortality because it avoids coding issues, captures the effect of influenza on other causes of death, and avoids inflating death figures when influenza merely hastens the deaths of already sick individuals, an occurrence known as harvesting.[42] Since mortality data by day or week are not available for the period from 1915 to 1923 for most countries, we are only able to calculate excess mortality with inter-year comparisons.

Statistical analysis

We used Stata version 9.2 for statistical modelling and analysis. For both influenza and all-cause mortality, we calculated excess mortality by comparison of annual death rates during the pandemic to the average of annual death rates before and after the pandemic. Because influenza pandemics might increase mortality not only in the year of peak incidence, but also in the following year or two, based on evidence on the time course of the pandemic, we compared death rates in a 3-year pandemic window with those in surrounding years. This approach also reduces short-term harvesting effects since deaths that would have taken place during the 3-year window in any case will not inflate the pandemic mortality rate.

For the 1918–20 pandemic, we calculated the average mortality rate in 1915–17 and 1921–23, and subtracted this from mortality in 1918–20. Formally,

$$PM_{1918-20}=\sum_{1918}^{1920}\left(M_t-\left[\frac{M_{1915}+M_{1916}+M_{1917}+M_{1921}+M_{1922}+M_{1923}}{6}\right]\right)$$

where PM is pandemic mortality. Observations where mortality is known to have been increased by World War 1 or civil war are presented in the tables, but were excluded from the statistical analysis. We calculated 95% CI for excess mortality by simulation.

To study the age-pattern of the pandemics, we calculated excess mortality for 1918–20 by use of the same approach but for every 5-year age-group and both sexes for countries for which such data were available. To increase our sample size to a maximum, we used all-age mortality for the regression analysis and to estimate mortality in 2004. We used ordinary least squares regression models to test the relation between the log of pandemic mortality and the log of per-head income and the absolute value of latitude. Absolute latitude was tested because of arguments in the 1920s that environmental factors such as diurnal temperature fluctuations were a key determinant of mortality.[43] Per-head income was measured in real international dollars (corrected for price changes).[44–47] The regression model generated a predicted all-age pandemic mortality rate. Age-specific estimates were generated with the relative age-pattern of pandemic mortality by age observed in 1918–20 for countries with age-specific data available. Confidence limits were estimated with 1000 draws from the multivariate normal approximation to the distribution of the parameters estimated in the model. The estimated number of deaths was calculated by country for every draw, and the quantities of interest (ie, predicted number of deaths by country, region, and age-group)

	Excess mortality
Argentina	0·54% (0·53–0·56)
Australia*	0·29% (0·28–0·31)
Austria	1·61% (1·59–1·64)
Belgium	0·83% (0·81–0·84)
Canada	0·63% (0·61–0·65)
Chile	0·52% (0·49–0·55)
Denmark*	0·20% (0·18–0·23)
England*†	0·34% (0·33–0·35)
Finland*†	0·85% (0·81–0·89)
France*†	0·75% (0·74–0·76)
Germany	0·76% (0·75–0·76)
India	4·39% (4·39–4·39)
Bengal/Sikkim	2·33% (2·32–2·34)
Bihar/Orissa	3·60% (3·59–3·61)
Bombay	6·18% (6·17–6·20)
Burma	2·12% (2·10–2·14)
Central/Berar	7·82% (7·79–7·84)
Coorg	3·44% (3·25–3·62)
Madras	2·59% (2·58–2·60)
Punjab/Delhi	4·57% (4·55–4·58)
United Provinces	7·09% (7·08–7·10)
Italy*	1·38% (1·37–1·39)
Japan	0·94% (0·94–0·95)
Netherlands*	0·70% (0·69–0·72)
New Zealand*	0·63% (0·59–0·67)
Norway*	0·57% (0·54–0·60)
Philippines	2·84% (2·83–2·86)
Portugal	2·64% (2·61–2·66)
Spain*	1·49% (1·47–1·50)
Sri Lanka	1·68% (1·65–1·71)
Sweden*	0·66% (0·64–0·69)
Switzerland*	0·92% (0·90–0·95)
Taiwan	1·44% (1·40–1·48)
Uruguay	0·29% (0·25–0·33)

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USA*	0·39% (0·39–0·39)
Colorado	1·00% (0·94–1·05)
Connecticut	0·66% (0·63–0·69)
Indiana	0·34% (0·31–0·36)
Kansas	0·35% (0·32–0·38)
Kentucky	0·50% (0·48–0·52)
Maine	0·40% (0·36–0·45)
Maryland	0·72% (0·69–0·75)
Massachusetts	0·64% (0·62–0·66)
Michigan	0·26% (0·24–0·28)
Minnesota	0·40% (0·37–0·43)
Missouri	0·39% (0·37–0·41)
Montana	0·75% (0·70–0·79)
New Hampshire	0·64% (0·59–0·68)
New Jersey	0·63% (0·61–0·65)
New York	0·44% (0·43–0·44)
North Carolina	0·76% (0·73–0·79)
Ohio	0·36% (0·35–0·37)
Pennsylvania	0·81% (0·80–0·82)
Rhode Island	0·66% (0·61–0·70)
Utah	0·48% (0·41–0·55)
Vermont	0·60% (0·53–0·67)
Virginia	0·47% (0·45–0·50)
Washington	0·53% (0·49–0·57)
Wisconsin	0·25% (0·23–0·27)
Venezuela	0·40% (0·37–0·43)

Data are estimate (95% CI). Percentages denote pandemic excess mortality per 100 people. *Age-specific mortality data available. †Male deaths not used due to excess mortality from World War 1.

Table 1: **Pandemic excess mortality calculations, based on vital registration data from 1918–20**

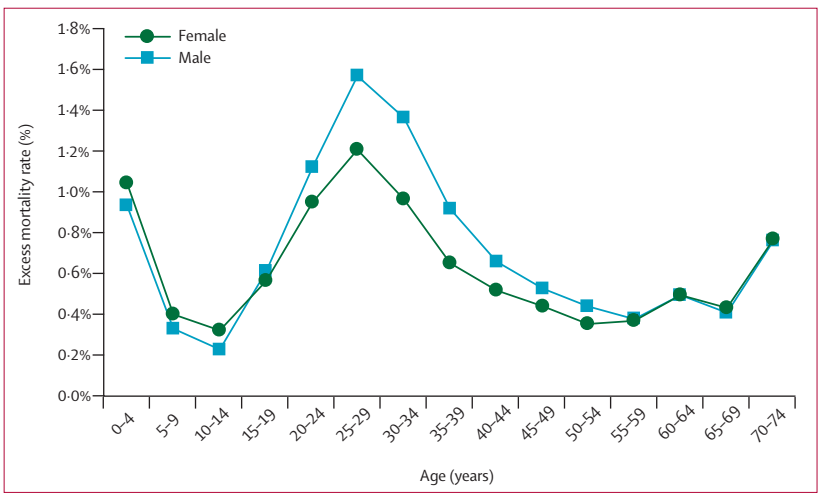

Figure 1: **Median excess mortality by age and sex for the 1918–20 pandemic, based on data from 13 countries with available complete age-specific mortality data**

derived from the distribution of simulated deaths for all countries. The simulation results capture both uncertainty in the model's parameter estimates (the result of having fewer than an infinite number of observations), and the variance in the excess mortality rate that is not explained by the independent variables, which is sometimes called the fundamental uncertainty.[48] 2004 population estimates were based on data from the 2006 World Health Report.[49]

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Table 1 shows pandemic mortality calculations for 27 countries for 1918–20, 24 US states with data available for the period, and nine Indian provinces. Pandemic mortality rates for the UK, France, and Finland for 1918–20 are based on females only, since male mortality is confounded by deaths due to war. In this sample of countries that are heavily weighted to higher income, median pandemic excess mortality was 0·75 deaths per 100 people (henceforth indicated as %) and average excess mortality was 1·06%. Excess mortality ranged from 0·2% in Denmark to 4·4% in India. Since there was some under-registration of mortality in India, total pandemic mortality could have been even higher.

Huge variation in the mortality rate from the 1918–20 pandemic is born out by subnational data. Table 1 shows that, for nine provinces in India, pandemic mortality ranged from 2·1% in Burma (covered by the Census of India at the time) to 7·8% in the Central Provinces and Berar. Commentators at the time attributed this huge variation to differences in nutritional status and diurnal fluctuations in temperature.[50] During the period 1915–23, vital registration systems were complete in 24 states in the USA.[51] Across these states, pandemic mortality ranged from 0·25% in Wisconsin to 1·0% in Colorado. Thus, from Wisconsin to the Central Provinces and Berar in India, the death rate from the 1918–20 pandemic varied 31-fold.

Figure 1 shows median excess mortality by age and sex for the 1918–20 pandemic. These data confirm the well-known observation that, unlike the 1957–58 and 1968–70 pandemics, mortality was concentrated in young adults, not elderly individuals.[17–19] In this set of countries, mortality was higher in males than in females, although sex-specific (but not age-specific) data in India showed excess female mortality in five of nine provinces (data not shown). The precise age-pattern varies considerably across the 13 countries, with some having almost no excess mortality in individuals aged over 60 years, and others having substantial mortality in the same age-group (data not shown).

Table 2 summarises the results of two regression models. For both, the dependent variable is the log of pandemic

	Dependent variable	R^2	Predictor variables	n	β	SE	p	t
Model one: per-head income only	Log (pandemic mortality)	0·473	Log (per-head income in 1918)	27	–0·885	0·187	0·000	–4·74
Model two: per-head income and latitude	Log (pandemic mortality)	0·482	Log (per-head income in 1918)	27	–0·967	0·229	0·000	–4·22
			Absolute value of latitude	27	0·005	0·008	0·531	0·64

Table 2: **Results from two ordinary least squares regression models on the log of the pandemic excess mortality rate 1918–20 for countries with complete vital registration data**

mortality. In the first model, the independent variable is the log of per-head income, and the second model adds the absolute value of latitude. Nearly 50% of the variance in pandemic mortality is explained by per-head income alone. Pandemic mortality is strongly negatively related to this variable. The coefficient for income ranges from –0·88 in the model with income alone to –0·97 in the model with absolute latitude. This means that a 10% increase in per-head income was associated with a 9–10% decrease in mortality. The coefficient for absolute latitude is not significant; this model was, therefore, not used to estimate mortality in 2004.

See Online for webtable

Table 3 shows estimates of global mortality in 2004 if a pandemic strain of influenza with similar severity as the 1918 strain were to emerge, taking into account population size, age composition of populations, and changes in per-head income for the world, regions, and major countries. The webtable shows estimates for all countries. The range of these estimates is based on both parameter uncertainty in the regression model and the variation in pandemic influenza recorded in 1918–20 that is not explained by per-head income. The median estimate of the number of deaths worldwide is 62 million (10th–90th percentile range 51 million–81 million). If these deaths were concentrated in a single year, global mortality would increase by 114% (10th–90th percentile range 93–147). Most deaths would occur in 15–29-year-old individuals, followed by those aged 0–14 years and 30–44-year-olds

	Mean number of deaths	Median number of deaths (10th–90th percentile range)	2004 population
Sub-Saharan Africa	17 865 920	17 243 647 (13 995 484–22 723 677)	721 955 000
Ethiopia	3 388 506	2 763 749 (1 259 189–5 953 963)	75 600 000
Nigeria	2 851 059	2 345 389 (1 135 347–5 038 748)	128 709 000
Middle East	6 065 429	5 835 025 (4 388 107–7 940 427)	534 197 000
Egypt	607 523	522 027 (253 014–1 103 690)	72 642 000
Iran	425 474	364 306 (180 699–743 360)	68 803 000
Pakistan	1 881 780	1 619 212 (762 053–3 213 478)	154 794 000
East Asia	12 926 570	11 348 696 (6 662 538–20 264 212)	1 539 787 000
China	10 605 101	8 996 794 (4 399 952–17 859 326)	1 315 409 000
Philippines	625 444	534 256 (257 651–1 089 602)	81 617 000
Vietnam	1 191 316	1 027 135 (506 579–1 985 188)	83 123 000
South Asia	20 143 199	17 356 790 (11 021 325–32 317 132)	1 632 096 000
Bangladesh	2 107 719	1 786 560 (873 494–3 704 316)	139 215 000
India	14 814 546	12 235 206 (5 983 008–26 939 656)	1 087 124 000
Indonesia	1 488 867	1 265 188 (607 771–2 662 276)	220 077 000
Thailand	260 184	217 241 (99 636–472 597)	63 694 000
Latin America and the Caribbean	2 490 895	2 391 218 (1 882 507–3 255 512)	442 571 000
Brazil	807 980	698 028 (319 843–1 461 797)	183 913 000
Eastern Europe and Central Asia	2 507 311	2 435 944 (1 863 056–3 255 659)	341,528,000
Russia	741 691	632 841 (302 700–1 288 132)	143 899 000
OECD	2 409 564	2 351 535 (1 805 461–3 072 218)	1 164 821 000
France	89 645	70 215 (29 248–166 402)	60 257 000
Germany	116 396	92 729 (37 534–222 210)	82 645 000
Italy	95 174	77 165 (30 278–182 033)	58 033 000
Japan	152 530	120 877 (43 789–308 715)	127 923 000
Mexico	422 558	352 397 (168 710–770 421)	105 699 000
Turkey	375 905	317 754 (143 624–689 077)	72 220 000
UK	93 004	71 781 (28 080–181 421)	59 479 000
USA	383 881	297 883 (114 483–744 226)	295 410 000
Total	64 408 888	62 118 132 (51 254 648–80 549 636)	6 376 955 000

Data broken down by region, with selected countries in these regions also shown. Uncertainty intervals are based on both regression equation parameter uncertainty and variation in pandemic influenza mortality in 1918–20 that is not explained by per-head income. OECD=Organisation for Economic Co-operation and Development.

Table 3: **Estimated number of deaths caused by the emergence of a pandemic influenza strain in 2004**

(figure 2). 96% (95% CI 95–98%) of the estimated number of deaths would take place in the developing world (figure 2 and table 3).

Discussion

Were a strain of influenza much the same as that which caused the 1918–20 pandemic to emerge in 2004, we estimate that it could kill 51–81 million individuals. This estimate is based strictly on recorded patterns of mortality in countries with nearly complete vital registration systems, rather than on theoretical models or assumptions about attack rates and case-fatality rates.

Our results indicate that deaths would be concentrated in the 0–14, 15–19, and 30–44 years age-groups. Various theories have been proposed for the unique pattern of mortality by age exhibited by the 1918–20 pandemic strain.[52,53] Our results suggest that deaths in the 15–19 and 30–40 years age-groups would probably be a result of high age-specific death rates, whereas those in individuals aged 0–14 years would most likely be due to the large population size and moderate mortality in this age-group.

Most of the strong relation that we observed between per-head income and pandemic mortality must be mediated through factors such as nutritional status, co-morbidity, community characteristics associated with poverty, and the effect of supportive care, since therapeutic interventions had little or no effect on mortality in 1918–20. This income effect is consistent with a contemporary observation of a relation in 1918–20 between household income and mortality.[50]

The 1918–20 mortality rates that we calculated from vital registration data are extremely high, reaching nearly 8% in one province of India. By comparison, global mortality from all causes of death was 0·92% in 2000. The more than 30-fold variation in mortality across communities within the 1918–20 pandemic can be explained by individual host and community factors. Variations in mortality could perhaps be due to the timing of the epidemic; countries with epidemics that began earlier might have had higher mortality than those that succumbed later. Pandemic mortality is a function of both the influenza attack rate and the influenza case-fatality rate. Available mortality data do not allow us to determine how much of the within-pandemic variation in outcome is due to transmission factors or case-fatality factors. Individual factors such as current immune function, nutritional status, acquired immunity through previous influenza infection, co-morbidity, and community and environment factors such as population density and mixing rates, access to health care, quality of care, and the physical environment could all have a role. Ultimately what matters is the effect on individuals that is captured by the overall pandemic mortality rate.

Our estimates of deaths by country exhibited wide confidence limits because, although per-head income explains half the variance in the pandemic mortality, half the variance remains unexplained. Furthermore, the method we used to calculate excess mortality rates in 1918–20 could exaggerate the effect of influenza because events such as wars, natural disasters, or other epidemics might also have increased mortality in pandemic years. However, observations where mortality is known to have been increased by World War 1 or civil war were excluded from the statistical analysis. Harvesting during the pandemic could also remove frail individuals from the population who would have died in the 3 years after the pandemic in any case. In other words, mortality after the pandemic window could be artificially lowered and thus increase the estimated excess mortality. However, because we used a 6-year average to establish the baseline mortality rate, we believe this effect will be small. Another potential source of bias is that global mean income is now much higher than it was in 1918, and most countries in the Organisation for Economic Co-operation and Development (OECD) have levels of per-

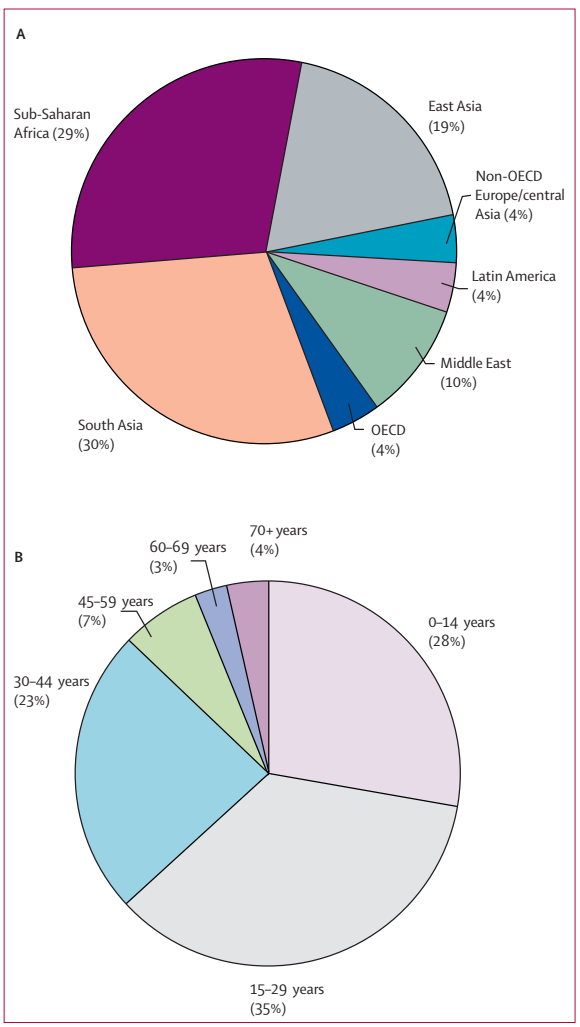

Figure 2: **Distribution of deaths due to the emergence of a pandemic influenza strain in 2004 by region and age-group**
OECD=Organisation for Economic Co-operation and Development.

head income beyond any recorded in 1918. Thus our extrapolations from data from 1918–20 must be viewed cautiously.

In most discussions of influenza, the 1918–20 pandemic sets the upper limit, in terms of mortality, on what might occur in future pandemics. However, there is no logical or biological reason why that pandemic—albeit very severe—should represent the maximum possible mortality in a future pandemic. Random genetic mutation could, in principle, produce a more lethal virus, although pathogens that are too lethal might not survive long enough in the host to effectively transmit to different populations.[54] In addition to this uncertainty about what is genetically possible, future mortality could be larger if the 1918–20 pattern of low older adult mortality were in fact due to some acquired immunity from the pandemics of the mid-19th century.[15] Concerns about increased travel and mixing, which lead to larger epidemics,[55] might not alter our extrapolations, since the historical record suggests that nearly all human populations were eventually exposed to the 1918–20 influenza virus.

Despite these fears, there are many cogent reasons to expect that the emergence today of a pandemic strain much the same as that which caused the 1918–20 pandemic strain would lead to much lower mortality than estimated here. First, symptomatic medical management is better now than in 1918–20. However, although individuals with access to health care in high-income and middle-income countries might benefit, health-care systems could become overwhelmed, which would attenuate this effect. Second, antivirals such as zanamivir and oseltamivir phosphate might have a positive effect on the reduction of transmission[56,57] and case-fatality rates.[58] Because we have not yet seen the next pandemic virus, the magnitude of this effect cannot be quantified. Third, vaccination with a lag of 4–6 months from the onset of a pandemic could reach a large fraction of the high-income populations.[59] The speed of the epidemic, perhaps affected by various efforts at quarantine, will determine the potential benefit of vaccination. Strict quarantine in American Samoa seems to have avoided the 1918–20 pandemic;[60] quarantine efforts in Australia are thought to have delayed but not avoided the pandemic,[61] but strict quarantine measures in other settings failed.[62] Mathematical models suggest that quarantine could be beneficial if highly effective and if administered in combination with prophylaxis under certain circumstances.[63–65] In view of the restricted vaccine production capacity and the reality of health system coverage, vaccination would have little or no effect on the poorest populations. Fourth, in 1918–20, a large proportion of deaths was due to secondary bacterial pneumonia after primary viral pneumonitis.[66] Antibiotics for pneumonia could have a substantial effect on case-fatality rates. In middle-income and low-income settings, prompt access to antibiotics could be the most affordable strategy that has the largest effect on mortality. One should note that all of these factors will lower mortality more in richer nations than in those with lower per-head income, which tends to strengthen the already observed inverse relation with per-head income.

Our results indicate that, irrespective of the lethality of the virus, the burden of the next influenza pandemic will be overwhelmingly focused in the developing world, as has been suggested for the 1918–20 pandemic.[67,68] Symptomatic treatment, antivirals, vaccination, and antibiotics for secondary bacterial pneumonia, combined with the underlying relation between per-head income and mortality, perhaps mediated through nutritional status, will reduce the effect of the pandemic in OECD countries. By contrast, the countries and regions that can least afford to prepare for a pandemic will be affected the most. The potential risk to populations of sub-Saharan Africa, south Asia, and other developing regions presents a policy dilemma. When resources to tackle the health problems already present in the community—including HIV, tuberculosis, malaria, cardiovascular diseases, and road traffic accidents—are already scarce, how much can these populations afford to spend on preparing for a potentially very harmful but also very uncertain threat?

This analysis of a worst-case scenario based on the 1918–20 pandemic provides no insight into the probability of an influenza pandemic in the next 1, 5, or 10 years. In the past century, only the 1918–20 pandemic qualifies as a dramatic change in human health. However, this does not mean that the threat of such a pandemic is 1% next year or any other year. There is also no way to revise estimates of the probability of a major pandemic because of the current H5N1 avian influenza outbreak. However, to prepare for such a possibility, especially focusing on practical and affordable strategies for low-income countries where the pandemic will have the biggest effect, is clearly prudent.

Contributors

C J L Murray conceived the idea and led the analysis. A D Lopez assisted with interpretation and drafting of the manuscript. K H Hill contributed to model development and data analysis. B Chin did the primary data analysis. D Feehan contributed to the primary data analysis and undertook the simulation and forecasting steps. All authors read and approved the final version of the manuscript.

Conflict of interest statement

We declare that we have no conflict of interest.

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