The perils of using annual all-cause mortality data to estimate pandemic influenza burden

Viggo Andreasen\textsuperscript{a,b,*}, Lone Simonsen\textsuperscript{b,c}

\textsuperscript{a} Department of Science, Roskilde University, Denmark
\textsuperscript{b} Fogarty International Center, NIH, Bethesda, MA, USA
\textsuperscript{c} Department of Global Health, School of Public Health and Health Services, George Washington University, USA

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\textbf{A B S T R A C T}
Measuring the burden of historic pandemics is not straightforward and often must be based on suboptimal mortality data. For example, the critical 1918 pandemic global burden estimate was based on excess in annual all-cause mortality – calculated as the difference between deaths during 1918–1920 and the surrounding 3-year periods. One intriguing result was a ~40-fold between-country variation in pandemic mortality burden: ~0.2% of Danes died, compared to ~8% of populations in some Indian provinces (Murray et al., 2006 [16]).

Using the same methodology and data source we explore the robustness of this methodology for different age-groups. For infants the country estimates varied 100-fold, from 15 to 1500 excess deaths/10,000 population, while for adults ≥45 years estimates ranged from ~70 to 170/10,000 population. In contrast, estimates for children, 1–14 years, and adults aged 15–44 years, were far more stable.

We next used detailed mortality data from Copenhagen to compare such estimates to the more precise estimates obtained from monthly mortality time series data and respiratory deaths. We found that the all-cause annual method substantially underestimated due to an unexplained depression in all-cause mortality in Denmark in 1918 and deaths caused by other epidemic diseases during the baseline periods.

We conclude that country estimates for infants and older adults were highly variable by the Murray method due to substantial variability in annual all-cause mortality. A more precise 1918 pandemic burden estimate would be gotten from either focusing analysis on persons age 1–44 who suffered 95% of all pandemic deaths and had a substantial rise over their baseline mortality level, or if possible focus analysis on annual respiratory deaths. For less severe pandemics, including the ongoing 2009 H1N1 pandemic, the use of all-cause mortality data requires careful consideration of excess deaths in defined pandemic periods and a focus on age groups known to be at risk.

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1. Introduction

Because influenza is difficult to diagnose clinically, the seasonal burden of influenza is usually assessed indirectly, as excess deaths occurring during months of increased influenza activity above an expected baseline [1,2,17,19,20]. For contemporary epidemics where laboratory surveillance data are available, influenza-related mortality is also assessed using Poisson regression models [23,24]. Such methods tend to arrive at similar results and thus are considered a robust approach to measuring influenza mortality [24].

However, when it comes to estimating the mortality burden of the 1918 pandemic, oftentimes only annual mortality data without cause-of-death are available as an alternative to the heterogeneous data sources in earlier estimates [9]. Thus, the one study [16] that estimated the global burden of the 1918 pandemic using annual all-cause mortality data from multiple countries arrived at the much-cited global burden of ~60 million excess deaths for the 1918–1920 pandemic period, using the surrounding years as baseline. However, the necessary underlying assumption of a stable background mortality may lead to imprecise estimates, especially for young children and the elderly for whom the background level is high relative to the pandemic impact. Furthermore, studies using the annual “excess mortality” approach tend to report substantial negative “excess” mortality in the 1918 pandemic for senior age groups – suggesting a failure to adjust for the background mortality [3,11,13,16]. Finally, across-world countries [16] reported a 40-fold variability in excess deaths attributed to the 1918 pandemic, with Denmark scoring lowest impact at 0.2% and some provinces in India highest, at 8%.
To scrutinize in detail the findings of negative excess mortality in seniors and other unexpected observations seen in annual data, we focus on Copenhagen for which an age-detailed statistics on cause of death and month of occurrence is available. In Copenhagen, the 1918 pandemic consisted of a mild 1st wave during summer 1918, a severe 2nd wave during autumn 1918, a severe 3rd wave in early 1919, and finally a 4th wave in early 1920 [1,18]. Other studies have found similar multi-wave patterns in other locales, including NY City [17], and in multiple European countries [2]. As in other locales, the age specific impact in Copenhagen was highly heterogeneous, with young adults at extreme risk while infants and adults over 45 years of age experienced little increase in all-cause mortality during the pandemic [1,17,18].

We will here demonstrate that the apparently low pandemic mortality in Copenhagen in 1918 was explained by significant fluctuations in the background mortality in the extreme age-groups. Using age-specific mortality statistics for a set of European countries we will also demonstrate that the 1918 pandemic mortality estimates cannot be reliably obtained from annual AC-data without detail. We propose such global pandemic mortality estimates should focus on data from countries with at least 5 years of annual mortality data surrounding a pandemic, and at least one level of detail, such as age, month of death, and cause of death.

2. Materials and methods

2.1. Copenhagen data

2.1.1. Mortality data

Denmark did not publish national cause of death statistics until 1920 [8,10] but we obtained an age-detailed statistics for Copenhagen giving deaths by cause and by month for the period 1915–1923 [21]. The population and reporting system is described in [1,10,14]. We grouped deaths into 6 broad categories: Respiratory deaths, Tuberculosis, other Infectious diseases, Cancer, Circulatory deaths (defined as heart failure – morbus cordis – stroke – apoplexia cerebri –, and senility – marasmus senilis), and others causes.

2.1.2. Population census data

For all age-groups except infants, the Copenhagen population size was obtained by linear interpolation from the quinquennial censuses [22]. For the infants <12 months of age we used the annual birth data with a correction for migration.

2.1.3. Contemporaneous (1919) count of pandemic deaths

Finally we obtained contemporaneous counts of death due to influenza and pneumonia during the first year of the pandemic (July 1918 through June 1919) from the medical officer in Copenhagen [6]. The medical officer’s report was produced in late 1919 after the first three waves and does not include deaths during the 1920 wave. The report combines children under the age of 5 excluding a separate estimate of the impact on infants.

2.2. International mortality and census data

2.2.1. Country-wide annual mortality statistics and census data

Annual all cause (AC) deaths and population size by age were obtained for each year in the period 1913–1933 from the WHO mortality database for those 10 European countries where such information was available. In addition, for the United States (death registration states) we obtained age-specific AC deaths from [15] and population data from [12].

2.3. Statistical analysis

2.3.1. Age groups and gender: considerations

For each mortality dataset obtained for the study, we divided the population in 4 age groups that are known to differ in their risk of dying from pandemic influenza: Infants under 1 year of age, children (1–14 years), young adults (15–44 years) and old adults (45 years or more). Genders were combined (although women and men differed in their susceptibility to influenza, gender patterns in the back-ground fluctuations we are studying here were similar, cf. Fig. 1). Following [16], we considered only the female population in England, France and Finland as male-mortality in those countries was affected by WWI.

2.3.2. Calculating excess mortality by the “Annual Excess” method

Using the method of Murray et al. [16], we estimated the excess mortality during 1918–1920 over a baseline of average deaths during 3 years on each side of the pandemic (1915–1917 and 1921–1923). We denote by $D_{1915}$ the death rate in 1915 for the age-group in question. We then determined the excess mortality for each age-group due to all pandemic waves during the 3-year period by subtracting out the average 3-year mortality in surrounding years, as

\[
\text{Pandemic Excess Mortality}_{1918–1920} = \frac{(D_{1918} + D_{1919} + D_{1920}) - (D_{1915} + D_{1916} + D_{1917} + D_{1921} + D_{1922} + D_{1923})}{2}
\]

2.3.3. Estimating excess mortality using semi-annual data

We used monthly age-specific AC-deaths for Copenhagen to determine the total pandemic death rate during 1918–1920, now using only 6-month periods containing 2nd, 3rd and 4th pandemic wave: Fall 1918 ($F_{1918}$), Spring 1919 ($S_{1919}$) and Spring 1920 ($S_{1920}$). We have for this semi-annual method:

\[
\text{Pandemic Excess Mortality}_{1918–1920} = \frac{F_{1918} - (F_{1915} + F_{1916} + F_{1917} + F_{1921} + F_{1922} + F_{1923})}{6}
\]

\[+ \frac{(S_{1919} + S_{1920}) - (S_{1915} + S_{1916} + S_{1917} + S_{1921} + S_{1922} + S_{1923})}{3}\]
2.3.4. Estimating excess mortality using monthly data

This is the classical method for estimating influenza-related deaths, which uses a cyclical baseline and attributes to influenza all deaths above this baseline during influenza epidemic periods [19]. We used a Serfling-spline cyclical regression model applied to monthly AC mortality data [1,18] of the form:

\[ Y = a + bt + ct^2 + dt^3 + e \sin \left( \frac{2\pi t}{T_2} \right) + f \cos \left( \frac{2\pi t}{T_2} \right) \]

where \( Y \) is the observed number of deaths in that month, and \( t \) is the running year-month index. The model was fitted to the periods with no influenza activity (May–November of each year except 1918 where October was excluded from the non-influenza period). The model explained 57% of the variance in the baseline period for infants, 66% for the age-group 1–19 years, 60% for the young adults and 75% for those over the age of 45. The unexplained variance was used to determine the standard error on our Serfling estimate.

2.3.5. Confidence intervals on excess mortality estimates

To estimate the statistical error on our annual methods we considered deaths to be independent events and hence death counts to be Poisson distributed. We used a normal approximation to determine the 95% confidence interval. Accordingly, the 95% upper and lower limits for excess mortality by the annual method are found as:

\[ \pm 1.96 \times \sqrt{D_{1918} + D_{1919} + D_{1920} + (D_{1915} + D_{1916} + D_{1917} + D_{1921} + D_{1922} + D_{1923})/4}/\text{Population size} \]

This statistical method is quite common in the analysis of mortality data. However, the approach severely underestimates the true statistical error in the annual mortality data as we shall now demonstrate. We created the 95% CI limits for the semi-annual data using the same approach.

3. Results

3.1. Country all-cause all-age excess mortality estimates

Fig. 1 shows all-cause mortality per 10,000 for the period 1910–1930, for three Scandinavian countries, by gender (Fig. 1). Eye-balling these data it appears that Norway and Sweden had a ∼50% increase in all-cause mortality over the background in year 1918, while Denmark had no visible increase in deaths during 1918. Yet, the contemporaneous surveillance efforts by physicians in Copenhagen alone set the influenza death toll at 2364 deaths, or 45 per 10,000 population for the autumn and winter of 1918–1919 [6]. Clearly, some underlying variability in the annual Denmark data unrelated to the pandemic obscured the true pandemic burden, and would be missed using surrounding years as the baseline of mortality.

Applying the annual excess mortality method to all-cause all-age mortality data (both gender) led to estimates of 20 pandemic deaths per 10,000 in Denmark, compared with 59 and 67 per 10,000 in Norway and Sweden, similar to what was reported previously with this method [16]. For Copenhagen, the annual method yielded 33 pandemic deaths per 10,000 population.

3.2. Sensitivity analysis using Copenhagen mortality data with more detail

Using the Copenhagen mortality data by month, we next looked at semi-annual data instead of annual to strengthened the pandemic mortality “signal” by isolating the time periods of the three pandemic waves during fall 1918, spring 1919, and spring 1920 (Fig. 2). Using this strategy the pandemic mortality increase was more apparent, and we estimated 47 deaths per 10,000. Using monthly mortality data with a Serfling modeling approach, we estimated 53 deaths per 10,000 population in Copenhagen [1].

Taking advantage of the availability of cause-specific mortality data from Copenhagen, we next increased the specificity of the mortality signal by focusing on cause-specific deaths. Applying the annual method to respiratory deaths, we computed an excess mortality of 56 per 10,000 for the period 1918–1920.

Taken together, the detailed mortality data from Copenhagen demonstrated that the use of annual all-cause statistics led to substantial underestimation of the total pandemic mortality burden in Copenhagen, capturing only 60% of the true burden.

At the national level the annual method captures only about 1/3 of the true death toll as seen in Norway and Sweden and as obtained when increasing the specificity of the mortality signal using Copenhagen data. The semi-annual method applied to all-cause data produced higher excess mortality estimates than the annual method but did not capture the entire burden. However, using either mortality data by cause (annual respiratory deaths) or mortality data with more temporal detail (monthly all-cause deaths), the estimated mortality for Copenhagen was in better agreement with both the contemporaneously observed count of pandemic deaths in that city, and with data from Norway and Sweden.

3.2.1. Reasons for underestimation by annual method

We next investigated reasons why the Murray method underestimated the true pandemic burden in Denmark, and found that it can be explained by considerable variability in the background mortality levels in particular due to increasing background mortality in the 1915–1917 period from other epidemic diseases especially for infants and those over 45 years. Fig. 2 shows semi-annual data for Copenhagen demonstrating profound variability in mortality during the pre-pandemic period, where measles and pertussis epidemics during the springs of 1916 and 1917 dwarf the pandemic mortality increase seen during 1918–1920 for infants, children as well as those over the age of 45. We discuss implications for each age group below.

3.2.2. Excess mortality in young adults aged 15–44 years

For the young adults aged 15–44 years who were known to be at an extreme risk, our annual method generated a reasonably consistent level of excess mortality across countries, ranging from 52 to 169 deaths per 10,000 population (Table 1). For Scandinavia, the range was narrower, with 75, 97, 91 and 101 deaths per 10,000 population in Denmark, Copenhagen, Norway and Sweden, respectively.

Using the semi-annual excess mortality approach on Copenhagen data (Fig. 2), we found 99 pandemic deaths per 10,000 when applying to all-cause as well as to respiratory deaths. Using the Serfling approach with monthly AC data, we estimated a total of 102 excess pandemic deaths for the 1918–1920 period.

Taken together, regardless of the method used on Copenhagen data, we arrive at similar results for the young adult age group; furthermore, the estimate of ∼100 deaths in 10,000 young adults is in good agreement with estimates for Denmark as a whole and with other Scandinavian countries.
3.2.3. Excess mortality in adults aged 45 years and older

Applying the annual method to all-cause mortality data for this age group revealed considerable between-country variability in pandemic mortality, ranging from negative in Denmark, England, and the US (lowest at –80 in Denmark) to 134 and 156 deaths (Spain and Italy, respectively) per 10,000 population during 1918–1920 (Table 1).

For Copenhagen, using semi-annual data the fall of 1918 and the spring of 1919 periods were not associated with any increase in mortality – so in agreement with [1,17] we find no evidence of any pandemic impact on the senior age-group. The most striking feature in senior mortality, is that mortality in the spring of 1918 was unusually low. Whatever the source of the apparent negative excess mortality among the elderly in Copenhagen in 1918 it occurred in the spring and hence was not influenza-related. The performance of the annual, semi-annual and monthly data estimates varied. The annual method and semi-annual method applied to all-cause mortality both produced negative excess estimates (–80 and

Table 1

Country estimates of pandemic mortality burden 1918–1920 using the Annual Excess Mortality Method applied to annual AC mortality data, per 10,000 population, by age group. For Copenhagen, 1918–1920 excess mortality were also generated using more specific mortality data (respiratory deaths), using the semi-annual method, and the cyclical regression model applied to monthly mortality data.

<table>
<thead>
<tr>
<th>Setting (country or city)</th>
<th>Source</th>
<th>Type of data</th>
<th>Age &lt;1 years</th>
<th>Age 1–14 years</th>
<th>Age 15–44 years</th>
<th>Age 45+ years</th>
<th>All ages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual country wide data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Denmark</td>
<td>1 AC</td>
<td></td>
<td>15 ± 50</td>
<td>22 ± 3</td>
<td>75 ± 3</td>
<td>–70 ± 9</td>
<td>22 ± 3</td>
</tr>
<tr>
<td>Norway</td>
<td>1 AC</td>
<td></td>
<td>170 ± 40</td>
<td>44 ± 3</td>
<td>91 ± 4</td>
<td>4 ± 10</td>
<td>57 ± 3</td>
</tr>
<tr>
<td>Sweden</td>
<td>1 AC</td>
<td></td>
<td>200 ± 30</td>
<td>50 ± 2</td>
<td>101 ± 2</td>
<td>27 ± 6</td>
<td>66 ± 2</td>
</tr>
<tr>
<td>Finland (women)</td>
<td>1 AC</td>
<td></td>
<td>490 ± 20</td>
<td>36 ± 2</td>
<td>52 ± 1</td>
<td>–30 ± 3</td>
<td>28 ± 1</td>
</tr>
<tr>
<td>Finland (women)</td>
<td>1 AC</td>
<td></td>
<td>425 ± 75</td>
<td>134 ± 6</td>
<td>69 ± 5</td>
<td>47 ± 13</td>
<td>86 ± 5</td>
</tr>
<tr>
<td>France (women)</td>
<td>1 AC</td>
<td></td>
<td>1530 ± 40</td>
<td>31 ± 2</td>
<td>88 ± 1</td>
<td>18 ± 3</td>
<td>63 ± 1</td>
</tr>
<tr>
<td>Italy</td>
<td>1 AC</td>
<td></td>
<td>1510 ± 20</td>
<td>124 ± 2</td>
<td>169 ± 1</td>
<td>156 ± 3</td>
<td>141 ± 1</td>
</tr>
<tr>
<td>Netherlands</td>
<td>1 AC</td>
<td></td>
<td>350 ± 30</td>
<td>78 ± 2</td>
<td>74 ± 2</td>
<td>44 ± 6</td>
<td>70 ± 2</td>
</tr>
<tr>
<td>Spain</td>
<td>1 AC</td>
<td></td>
<td>560 ± 25</td>
<td>123 ± 2</td>
<td>157 ± 1</td>
<td>134 ± 4</td>
<td>149 ± 2</td>
</tr>
<tr>
<td>Sweden</td>
<td>1 AC</td>
<td></td>
<td>530 ± 50</td>
<td>40 ± 3</td>
<td>115 ± 3</td>
<td>90 ± 9</td>
<td>92 ± 3</td>
</tr>
<tr>
<td>USA</td>
<td>2 AC</td>
<td></td>
<td>180 ± 10</td>
<td>39 ± 1</td>
<td>92 ± 1</td>
<td>–22 ± 2</td>
<td>55 ± 1</td>
</tr>
<tr>
<td><strong>Annual, semi-annual and monthly Copenhagen (Cph) data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cph</td>
<td>3 AC</td>
<td>Annual Data</td>
<td>–70 ± 140</td>
<td>21 ± 8</td>
<td>97 ± 6</td>
<td>–80 ± 20</td>
<td>33 ± 7</td>
</tr>
<tr>
<td>Cph</td>
<td>3 AC</td>
<td>Half Year Data</td>
<td>100 ± 90</td>
<td>20 ± 6</td>
<td>99 ± 5</td>
<td>–40 ± 14</td>
<td>47 ± 5</td>
</tr>
<tr>
<td>Cph</td>
<td>3 AC</td>
<td>Resp deaths Annual data</td>
<td>85 ± 60</td>
<td>15 ± 4</td>
<td>99 ± 4</td>
<td>2 ± 8</td>
<td>56 ± 3</td>
</tr>
<tr>
<td>Cph</td>
<td>3 AC</td>
<td>Serfling monthly</td>
<td>180 ± 110</td>
<td>24 ± 5*</td>
<td>102 ± 5*</td>
<td>–16 ± 18</td>
<td>51 ± 8</td>
</tr>
<tr>
<td>Cph</td>
<td>4 AC</td>
<td>Reported 18–19</td>
<td>19 ± 20</td>
<td>69 ± 20</td>
<td>20 ± 45</td>
<td>45 ± 12</td>
<td>52 ± 10</td>
</tr>
</tbody>
</table>


* For the Serfling analysis the age-classes were 1–20 years and 20–45 years.
−40 per 10,000, respectively), while the annual method estimates based on respiratory death data produced an estimate of only 2 pandemic deaths per 10,000 population, in better agreement with previous findings [1]. Applying the Serfling regression model to monthly all-cause mortality data yielded an estimate of −16 per 10,000 population.

Taken together, the annual and semi-annual excess method applied to all-cause mortality data exhibited a wide range of excess mortality estimates, ranging from a negative death toll to one that was higher than for the young adult age group. Only the annual method applied to respiratory deaths or the Serfling method applied to monthly all-cause data yielded estimates in agreement with other studies.

3.2.4. Infants <1 year of age

Infant mortality was reduced almost by a factor of 2 during the period studied, 1909–1925, but the significant fluctuations in the spring seasons make it problematic to establish a clear baseline. However, there was no visual mortality elevation in the fall of 1918 or spring of 1919. For the spring of 1920 one can detect an elevation depending on the choice of back-ground, but the effect is minor as reflected in the impact estimate of 100 ± 90 excess deaths per 10,000 using semi-annual data. Instead, the unusually high mortality in the spring of 1916 stands out – and the relatively low mortality in the spring of 1918. Thus, based on annual or semi-annual mortality data, the pandemic did not appear to have increased the infant mortality in Copenhagen above the normal mortality in that age group at the time. Using the annual excess mortality method, the excess mortality varied widely, from no excess deaths in Denmark to 1500 deaths per 10,000 in France and Italy (Table 1).

3.2.5. Cause of death statistics

Fig. 3 shows the annual age-specific cause of death. The figure provides insight into the cause of the mortality fluctuations. For young adults the 1918–1920 pandemic period has as a dramatic increase in respiratory deaths as expected. For children respiratory deaths are also elevated, while the remarkable peak in 1916 is caused by other infectious diseases (in particular pertussis and morbilli). The concurrent epidemics of measles and whooping cough in 1916 certainly had a bigger impact on infant mortality than the 1918-pandemic. For persons over 45 years the low 1918 mortality is attributable to a substantial decline in deaths due to circulatory diseases and cancer throughout the year. There is no obvious explanation for this temporal decline in non-infectious deaths. One possibility may be a “harvesting effect” where frail adults died during the rough springs of 1916 and 1917. Perhaps a combination of seasonal influenza and pertussis elevated death rates among individuals suffering from cancer or circulatory disorders. Another possible explanation is that food (and in particular alcohol) rationing during WWI lead to an improved diet and hence to less deaths by life-style diseases [7]. We note that the number of registered deaths in Copenhagen due to alcoholism declined from an average of 60 deaths per year in 1912–1916 to 2 deaths in 1918.

4. Discussion

In a landmark study published in Lancet in 2006, Murray et al. [16] used annual mortality database maintained by the WHO to estimate and compare 1918–1920 pandemic mortality. They reported that the 1918–1920 pandemic mortality burden varied ~40-fold among world countries, ranging from ~0.2% in Denmark to ~8% in some provinces in India. One explanation may be that this is true – populations living in different areas with variable life expectancies, different prevalence of co-morbidities like TB, access to care and crowding etc. would experience pandemic impact very differently. Or, some countries in remote areas did not enjoy the “senior sparing” which was observed in more connected countries [4,5]. Alternatively, it is possible that much of this tremendous between-country variability can be explained by methodological difficulties measuring the pandemic mortality burden with accuracy.
Here we set out to look at the precision of the mortality estimates: we recreated the annual mortality estimates using data from the WHO database and the same approach to subtracting out the baseline. In addition, we conducted a detailed study of Copenhagen mortality, taking advantage of a detailed surveillance system. Thus, we could use mortality data with higher specificity for pandemic influenza – monthly data – to allow focusing the excess mortality estimates on the specific periods of pandemic influenza during autumn–winter of 1918–1919 and spring of 1920.

We have demonstrated that the annual excess mortality method may lead to over- or underestimation of the pandemic burden due to large uncertainties on excess mortality estimates in infants and seniors for whom influenza related mortality constitutes only a small fraction of the total mortality [1,17]. We used high-resolution mortality data from Copenhagen to demonstrate that the annual method greatly underestimated the pandemic mortality there (and by extension, probably in all of Denmark). Indeed, analyses using mortality with increasing specificity for influenza revealed that the annual all-cause all-age method had substantially underestimated the burden of the pandemic and that pandemic death rates in Copenhagen were in fact comparable to those of neighboring Scandinavian countries at ~0.6% of the population. These findings are in agreement with findings in the multi-country study [2]. The observed negative excess mortality in Copenhagen among the older adults corresponding to ~1000 missing deaths in that age group could be explained by the inability to adjust the mortality data for a 1918 period general decline in cancer and cardio-vascular deaths. The flu attributable deaths among children and the younger adults were ~2900 deaths, so the reduced senior mortality did in fact lower the annual method excess mortality estimate by ~30%, relative to the methods using more specific mortality data (Fig. 4).

The annual AC excess method did not allow a meaningful assessment of the impact of the pandemic in infants and older adults over 45 years of age, because the background annual mortality fluctuations in these age groups are far greater than the impact of the 1918 pandemic. For Denmark, the UK, and the USA these fluctuations in annual mortality in the years surrounding the pandemic explain the findings of an apparently “negative” pandemic mortality burden in persons aged 45 or older. The limited ability to estimate a low true pandemic impact in the extreme age groups that experienced high background mortality explains some of the large fluctuations in pandemic impact in these age-groups in various countries.

The large fluctuations in background mortality are particularly obvious in Fig. 2 and especially pronounced for the extreme age-groups. The inter-annual fluctuations by far exceed the 95%-confidence limit that we have indicated on figure. Our 95%-limits show the variation that could arise by chance based on the so-called Poisson assumption. This is the standard statistical assumption underlying our error estimate as well as that of others, so it is disturbing to observe how poorly our confidence limits reflect the true fluctuation in the Copenhagen mortality. This is a phenomenon that deserves further attention.

But because annual mortality data is the best that is available from most world countries at the time, we point out that better estimation may be achieved, either by using cause-specific annual mortality data or else by focusing exclusively on the age groups most affected by the pandemic in which the background mortality was far lower relative to the pandemic burden.

We were unable to access data from the Indian provinces where the estimated mortality burden was the highest in the world according to the annual mortality method [16]. It would be most interesting to further analyze the age specific data underlying this result as all our data come from European populations.

We conclude that country estimates for infants and older adults were highly variable by the Murray method and were affected greatly by substantial variability in annual all-cause mortality. A
more precise 1918 pandemic burden estimate would be gotten from either focusing analysis on persons age 1–44 who suffered 95% of all pandemic deaths and had a substantial rise over their baseline mortality level, or else – when possible – focus analysis on annual respiratory deaths rather than all-cause. For less severe pandemics, including the ongoing 2009 H1N1 pandemic, the use of all-cause mortality data should be attempted only with careful consideration of excess deaths in defined pandemic periods and in age groups known to be at risk, and with a better understanding of the magnitude of unrelated fluctuations in background mortality.

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