Two methodologies are used for describing and estimating influenza-related mortality: Individual-based methods, which use death certification and laboratory diagnosis and predominately determine patterns and risk factors for mortality, and population-based methods, which use statistical and modelling techniques to estimate numbers of premature deaths. The total numbers of deaths generated from the two methods cannot be compared. The former are prone to underestimation, especially when identifying influenza-related deaths in older people. The latter are cruder and have to allow for confounding factors, notably other seasonal infections and climate effects. There is no routine system estimating overall European influenza-related premature mortality, apart from a pilot system EuroMOMO. It is not possible at present to estimate the overall influenza mortality due to the 2009 influenza pandemic in Europe, and the totals based on individual deaths are a minimum estimate. However, the pattern of mortality differed considerably between the 2009 pandemic in Europe and the interpandemic period 1970 to 2008, with pandemic deaths in 2009 occurring in younger and healthier persons. Common methods should be agreed to estimate influenza-related mortality at national level in Europe, and individual surveillance should be instituted for influenza-related deaths in key groups such as pregnant women and children.

Introduction
The three influenza pandemics of the 20th century all resulted in substantial premature mortality (referred to as mortality in this review) which has been estimated by various parameters (Table 1) [1,2].

Mortality rates during past pandemics have differed considerably both between pandemics and within the same pandemic [1,3,4]. For example, estimates for the United States (US) varied from 30.5 premature deaths per 10^5 population (1968 pandemic) through 53.4/10^5 (1957 pandemic) to 450.9/10^5 (1918 pandemic) compared with an average of 16.9/10^5 for influenza A(H3N2)-dominated seasons from 1979 to 2001 [4]. The pattern of deaths (i.e. mortality rates by age, risk groups, pathogenesis and disease presentation) probably also differed between pandemics and seasonal epidemics, but this is less well documented [5-8]. Viboud et al.'s analysis in 2010 estimated the mean ages of premature deaths during the 1918, 1957 and 1968 pandemics as 27, 65 and, 62 years, respectively, and as 76 years for seasonal influenza A(H3N2) from 1979 to 2001 [4]. Finally the annual mortality has differed between seasonal epidemics [9-13]. All this variation is due to a complex mix of factors of which some are real effects on mortality, while others are related to the methodologies used to estimate mortality (Box 1). For example, substantial variations in the estimates of influenza-related premature mortality have been observed within the same epidemic or pandemic depending on the data sources, the analytic approach, and the geographical setting [14-21]. For these reasons, estimating the extent of influenza-related mortality is complex.

The published rates of deaths for the 2009 pandemic have varied nearly 70-fold from 0.02 to 1.46 per 10^5 population with a tendency to decline with the time passed between the start of the pandemic and the estimate, with more data being acquired and further analyses undertaken [4, 13,14, 22-26]. There is no evidence of changes in the virus that could be responsible for this decline in the estimates [27].

Citation style for this article:
For policy formulation, simply counting numbers of deaths attributable to influenza would be undesirable, even if it were possible. Robust comparable mortality analyses for seasonal and pandemic influenza are needed to determine risk groups, to guide and evaluate distribution of resources, to communicate and prepare the public and policy makers. These analyses have to accommodate some of the complexities mentioned above. The objectives of this review are to summarise the methods for estimating seasonal and pandemic influenza-related mortality, particularly describing the systems in place in Europe, to document and interpret the initial European mortality data for the 2009 pandemic, and to suggest how to develop better approaches to influenza mortality surveillance and estimates for Europe.

Methods for measuring influenza-associated mortality
The history of estimating influenza-associated mortality is as old as formal death monitoring. William Farr measured the impact of influenza in London in 1847 by subtracting the number of deaths recorded in a relatively influenza-free winter from the number recorded during an epidemic season [28]. In the 20th and 21st centuries, more sophisticated approaches to estimate mortality were developed and applied, including monitoring cause-specific mortality, statistical and modelling approaches and incorporating virological information into routine systems and special studies [21,29,30] (Table 2).

In the United States (US) it is customary to monitor and model trends in cause-coded death notifications due to pneumonia and influenza or all respiratory, cardiovascular and cerebrovascular conditions, while monitoring all-cause mortality is generally the approach in Europe. Since the 1957 pandemic, the US has had a specific system in place using pneumonia and influenza (P&I) death data from 122 US cities for estimating influenza mortality [21,37,38]. Simpler approaches to measure excess all-cause mortality have been applied in at least eight European countries (Table 3) and elsewhere [15,35,39-47]. In the following section we critically describe these various methods.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality impact</td>
<td>Absolute numbers of deaths due to influenza (seasonal or pandemic)</td>
<td>Needs to be converted to rates according to the population and period of time.</td>
</tr>
<tr>
<td>Case fatality rate (CFR)</td>
<td>Risk of death among those with clinical disease</td>
<td>Often expressed as a percentage.</td>
</tr>
<tr>
<td>Infection fatality rate (IFR)</td>
<td>Risk of death among those infected</td>
<td>A measure using serology to estimate the number of infections.</td>
</tr>
<tr>
<td>Population fatality rate (PFR)</td>
<td>Numbers of deaths due to influenza per unit population</td>
<td>Often expressed as per 100,000 resident population.</td>
</tr>
<tr>
<td>Years of potential life lost (YPLL)</td>
<td>An estimate of the cumulative number of years a person who died of influenza would have lived against standard life expectancy</td>
<td>This is often expressed as a total for a population. An alternative to death rates that gives more weight to deaths occurring among younger people. It can be used as a measure of the relative impact of various diseases and other lethal forces on a population. Special care has to be taken when applying this for influenza regarding deaths in people with chronic conditions, many of whom would have shorter than standard life expectancy.</td>
</tr>
<tr>
<td>Premature mortality</td>
<td>A death occurring earlier than it would have done without the intervention of influenza</td>
<td>Almost all influenza-related deaths are premature. However it is important to emphasise this point with seasonal influenza when many of the deaths are focused in older people and so are less premature than they would be in younger people.</td>
</tr>
<tr>
<td>Influenza infection and disease</td>
<td>Influenza is here defined as a laboratory-confirmed human infection with an influenza virus and influenza disease as the clinical consequence</td>
<td>This should not be confused with influenza-like illness (ILI) which has a European clinical case definition. A number of other organisms and conditions can cause ILI. Equally, influenza infection can be asymptomatic or cause symptoms that do not meet the case definition or entirely different symptoms.</td>
</tr>
<tr>
<td>Old and new seasonal influenza</td>
<td>Old: the seasonal influenza circulating between 1977 (when human influenza A(H1N1) viruses re-emerged) and 2008 New: influenza circulating from 2010 onwards</td>
<td>It should not be assumed that the new (from 2010 onwards) mix of seasonal viruses will have the same characteristics or mortality as its predecessor.</td>
</tr>
<tr>
<td>Method</td>
<td>Description</td>
<td>Limitations and biases</td>
</tr>
<tr>
<td>--------</td>
<td>-------------</td>
<td>------------------------</td>
</tr>
<tr>
<td><strong>1. Vital registration data</strong></td>
<td>Influenza mentioned on death certificate.</td>
<td>Especially weak in older people and people with chronic medical conditions; will underestimate total.</td>
</tr>
<tr>
<td><strong>2. Laboratory-confirmed deaths</strong></td>
<td>A death is only included if there is laboratory confirmation.</td>
<td>High specificity but can be very insensitive; will always underestimate totals, sometimes severely.</td>
</tr>
<tr>
<td><strong>3. Statistical and modelling techniques (see Table 4 for more detail)</strong></td>
<td>Estimates influenza-attributed mortality through comparing all-cause or selected-cause deaths during periods of intense and no influenza activity; applies a variety of models which may or may not be strengthened by surveillance data.</td>
<td>Without care can be confounded by rises in mortality due to other causes; the best approaches are further informed by virological surveillance and using data on competing causes (severe weather and other infections).</td>
</tr>
<tr>
<td><strong>4. Weighting deaths by years of potential life lost (YPLL)</strong></td>
<td>Estimating and totalling the numbers of years of life that deaths represent; can be combined with other methods such as 1-3.</td>
<td>Useful in comparing impact of deaths affecting different age-groups; limitations are difficulties in knowing the life expectancies for people with underlying illness; does not allow for disability and work productivity; can be especially difficult to apply to estimated numbers of deaths and deaths from multiple causes (influenza and an underlying condition).</td>
</tr>
<tr>
<td><strong>5. Emerging infection programme (US)</strong></td>
<td>Community-based surveys, notably the US emerging infection programme.</td>
<td>Especially helpful where surveys are enduring over years. May still miss some cardiac and cerebrovascular deaths due to influenza.</td>
</tr>
<tr>
<td><strong>6. Enhanced mortality analysis (US)</strong></td>
<td>Laboratory-confirmed deaths due to pneumonia and influenza from 122 US cities.</td>
<td>Also used to calculate YPLL and captures cardiac and cerebrovascular deaths.</td>
</tr>
</tbody>
</table>

US: United States.
* In the United States all age rapid mortality monitoring systems usually only includes diagnoses for influenza and pneumonia or all respiratory and circulatory diagnoses.
## Table 3

<table>
<thead>
<tr>
<th>Country</th>
<th>Period of study</th>
<th>Method</th>
<th>Results (mortality per 100,000 population in a year or season)</th>
<th>Investigated factors unrelated to influenza</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Average</td>
<td>Highest</td>
<td>Lowest</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>1982-2000</td>
<td>Statistical modelling for excess all-cause and cardiovascular mortality in association with surveillance of acute respiratory infections</td>
<td>26/105 all-cause deaths and 17/105 cardiovascular deaths</td>
<td>60.4/105 (1995/96)</td>
<td>No detectable deaths (negative values)</td>
</tr>
<tr>
<td>Germany</td>
<td>1985-2001</td>
<td>Time series analyses and cyclical regression applied to time series data looking for excess all-cause mortality in association with influenza epidemics (virological and syndromic data)</td>
<td>8.4 to 17/105 (depending on assumptions)</td>
<td>40.5/105 (1995/96)</td>
<td>4.5/105</td>
</tr>
<tr>
<td>Italy</td>
<td>1969-2001</td>
<td>Estimated excess deaths due to pneumonia and influenza and deaths from causes associated with influenza (cardio and cerebrovascular disease including during the pandemic winter of 1969/70</td>
<td>3/105 (range 0–3) for pneumonia and influenza and 18/105 for all causes (range 0–102)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The Netherlands</td>
<td>1967-89 1970-89</td>
<td>Poisson regression analysis</td>
<td>8.4/105</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norway</td>
<td>1975-2004</td>
<td>Poisson regression analysis applied to time series data looking for excess all-cause mortality in association with influenza epidemics (virological and syndromic data)</td>
<td>21.2/105</td>
<td>41.5/105 (1993/94)</td>
<td>5.3/105 (1976/77)</td>
</tr>
<tr>
<td>Portugal</td>
<td>2008-09</td>
<td>Cyclical regression model</td>
<td>18.5/105 (2008/09 only)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Switzerland</td>
<td>1969-85</td>
<td>Regression model applied to time series data looking for excess all-cause mortality in association with epidemics of influenza using Fourier and Autoregressive Integrated Moving Average (ARIMA) models modelling</td>
<td>271.6/105 excess mortality risk during influenza epidemics in the 70-89 year-olds was 1.7/105 1-59 year-olds</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK (England)</td>
<td>2004-09</td>
<td>Statistical model based on the Serfling method to establish a baseline of the expected weekly number of registered deaths; if the observed number is above the upper limit of a 90% confidence interval around this expected number for at least one week, an excess is said to have occurred.</td>
<td>8.8/105</td>
<td>21.1/105 (2008/09)</td>
<td>No detectable excess deaths</td>
</tr>
<tr>
<td>UK (England and Wales)</td>
<td>1975-79</td>
<td>Regression model applied to time series data looking for excess all-cause mortality in association with influenza epidemics</td>
<td>19.0/105</td>
<td>44.9/105 (1975/76)</td>
<td>8.19/105 (1976/77)</td>
</tr>
</tbody>
</table>


UK: United Kingdom.

amb: ambient temperature and other respiratory viruses such as respiratory syncytial virus (RSV).

a: Ambient temperature and other respiratory viruses such as respiratory syncytial virus (RSV)

Factors influencing observed influenza-related mortality

Box 1
Factors leading to real differences in influenza-associated mortality
• Characteristics of the virus: virulence and transmissibility;
• Characteristics of the populations affected: demographics, access to healthcare, health seeking behaviour, social and economic circumstances, prevalence of risk factors;
• Levels of pre-existing immunity in the population (due to e.g. innate immunity, previous exposure to influenza viruses, vaccination, genetic susceptibility);
• Prevalence of complicating co-infections and underlying medical conditions in the affected populations.

Factors related to diagnosis and reporting of individual cases
• Different case definitions and methods of ascertainment;
• Different mortality reporting systems;
• Different routine and enhanced surveillance systems established in pandemics;
• Changing awareness of clinicians and their testing practices;
• Availability and quality of testing, testing policies;
• Different disease presentations.

A policy of reporting laboratory-confirmed deaths was adopted early on in the 2009 pandemic in European countries [8]. This resulted in high specificity and quality, but low sensitivity, of data on risk factors. This approach tends to miss influenza deaths especially in older people and those in whom influenza is the trigger for a severe illness of a non-specific nature (cerebrovascular and cardiovascular deaths) [59]. This age effect may have been less important in the 2009 pandemic because older age groups had some pre-existing immunity and were less likely to be infected with the pandemic virus [63]. Also, since the criteria for using laboratory tests changed as the 2009 pandemic progressed, estimates relying on laboratory confirmation represent minimum totals, in particular for periods of intense transmission when a smaller proportion of clinical cases were being tested [60].

Some countries, for example the US and Australia, have special reporting systems developed for particular groups, notably children, to inform decisions on vaccination policies. Such routine systems are not found in Europe. Laboratory-confirmed influenza deaths in children have been notifiable in the US since the 2004/05 influenza season. This proved especially helpful in contrasting the impact of seasonal influenza epidemics with the 2009 pandemic [64]. Similarly, the Australian Paediatric Surveillance Unit resumed winter surveillance for any severe complication of influenza in children during the pandemic [65].

Statistical and modelling approaches
Statistical and modelling approaches (Table 4) analyse death data from vital registries, looking at multiple codes that are expected to capture influenza-related deaths, i.e. pneumonia and influenza or all conditions coded as respiratory or cardiovascular [66,67]. There are trends in clinicians’ preference for diagnosis and over time [13,52]. This is also true for seasonal influenza. In the Netherlands for example, it was estimated that for every death registered in the period 1967–89 as due to seasonal influenza there were another 2.6 unrecognised influenza deaths [41]. While in a study in Denmark during the 2009 pandemic that compared laboratory-confirmed deaths with those estimated from a regression model suggested a ratio of 10 deaths for every one confirmed death [61]. It is likely that there was less under-identification in death certification and laboratory diagnosis during the 2009 pandemic than for seasonal influenza in industrialised countries because awareness of influenza among clinicians was high, testing more readily available and more countries used or developed enhanced surveillance systems [13,60]. There are some indications that since the 2009 pandemic, influenza diagnostic tests have been more widely available and used in hospitals. This, in combination with pandemic patients typically being younger than those dying from seasonal influenza, will probably result in influenza appearing more frequently on death certificates [46,62].
death classification, with influenza diagnosis being more likely when epidemics are prominent while they would at other times be classified as due to pneumonia [13]. Authorities in the US look for surges in the combined number of deaths due to influenza or pneumonia as a percentage of all deaths, at the same time as laboratory reports of influenza rise. However there will still be misclassification when identifying absolute numbers of respiratory deaths since even in a pandemic not all pneumonias are due to influenza and obviously cardiac and vascular deaths will be missed. The latter was probably less important in the 2009 pandemic with the protective cross-immunity in older people among whom cardiac and vascular deaths are most important [59,63,68]. In Europe the preference has been to use trends in all-cause mortality. Often deaths are considered by age group. The trends are then examined using a range of statistical and modelling techniques to look for excess deaths in association with influenza epidemics and pandemics (Table 4) [9,32,33,37,69-74].

Various other modelling techniques have been used (Table 4), including the original Serfling method to develop a baseline and detect variations from that [37,71]. More sophisticated multivariate regression models have been employed to calculate the mortality during periods of influenza activity in a given population controlling for potential confounders (e.g. weather or other circulating respiratory viruses), and estimate the excess compared with the expected mortality in the same period based on historical data (Tables 2 and 4). These models have used different death end points ranging from all-cause, cardiac and respiratory to pneumonia and influenza. Each method has its advantages and disadvantages (see Table 2 and 4). Methods that include competing causes of deaths (confounders) are preferable as they avoid overestimation of the attributed mortality. Excess mortality is then calculated with confidence intervals for pneumonia and influenza or for respiratory and circulatory causes or for all causes [10]. Extrapolation from the US data to Europe was the basis for estimate from the European Centre for Disease Prevention and Control (ECDC) of influenza-attributable deaths in seasonal influenza (1977/78 to 2008/09) of up to 38,500 per year in the countries of the European Union and European Free Trade Association in recent years [10,75].

All-cause mortality attributable to influenza has been estimated in at least eight European countries (Table 3), sometimes with age-specific results [41]. However there are no routinely published outputs like those in the weekly influenza surveillance report FluView in the US [31,76] and therefore it is not possible to state a European normal seasonal influenza range. Estimating all cause mortality is also insensitive, as large numbers of influenza deaths need to take place before excess mortality is detectable across all age groups [13]. Hence paradoxically in a mild influenza season the best national estimate may appear as no excess of deaths due to influenza, when at the same time there are influenza related deaths that appear in death certificates [13,66]. There is, however, the danger of overestimating deaths attributable to influenza when important confounders are not considered such as other respiratory infections (notably respiratory syncytial virus) and ambient temperature.

### Table 4

<table>
<thead>
<tr>
<th>Method</th>
<th>Inclusion of virological surveillance data</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peri- and summer season rate difference models</td>
<td>No</td>
<td>Simple; can be undertaken with less than five years worth of data; Does not need virological data on type and subtype; cannot be used where seasonality of influenza is not clearly known (aequatorial areas).</td>
<td>Tend to produce inflated estimates when compared to other methods; Cannot be used to estimate differences in viral type and subtype; Other seasonal factors are hard to control for.</td>
<td>[67,68]</td>
</tr>
<tr>
<td>Serfling least squares cyclical regression model</td>
<td>No</td>
<td>Does not need virological data on type and subtype; cannot be used where seasonality of influenza is not clearly known (aequatorial areas).</td>
<td>Simple in comparison to other regression approaches. Cannot easily allow for other variables such as other infections (notably with respiratory syncytial virus (RSV), severe winters etc.</td>
<td>[8,37,69]</td>
</tr>
<tr>
<td>Serfling-Poisson regression model</td>
<td>Yes</td>
<td>Produces estimates on virus type and subtype; can allow for other variables such as other infections (notably RSV), severe winters etc.</td>
<td>Needs a number of years of data; Needs a number of years of virological data.</td>
<td>[33,70,71]</td>
</tr>
<tr>
<td>Autoregressive integrated moving average (ARIMA) models</td>
<td>No</td>
<td>Easy to update as more information is collected.</td>
<td>Complicated and can be difficult to use; Provide few advantages over the more simple linear models.</td>
<td>[32,65,72]</td>
</tr>
</tbody>
</table>
Methods of measuring mortality during a pandemic

Classical statistical approaches using historical influenza data may not readily be applied for pandemics because pandemic influenza activity often occurs outside of the traditional influenza seasons and baselines are hard to determine. More reliable data may only become available some time after the event and are subject to reanalysis even many years later [4,16,19]. Capturing mortality is particularly difficult in a pandemic, such as during the 2009 pandemic, which caused a relatively small number of deaths. A more sensitive approach is to look for age group-specific effects in younger people in whom background deaths are less frequent than in the elderly so that modest influenza-related signals may be detectable [77]. Another approach is age-specific regression modelling. Previously this has only been undertaken in individual European countries. Combining data from different EU countries and looking at age-specific excess mortality is more sensitive. This is the current approach used in the pilot European Mortality Monitoring Project (EuroMOMO). EuroMOMO found that overall all-cause mortality in the 2009 pandemic was within the expected range for seasonal influenza, but there was a short-term but significant increase in child mortality in the age-group of 5–14 year-olds [77]. A similar excess of deaths in children has been observed through regression modelling and enhanced surveillance and in the UK [78,79]. The latter indicated that many of the deaths were in children with underlying conditions. In addition, a disproportionate number of excess deaths was observed in certain ethnic minority groups [77]. The EuroMOMO and the UK approaches have an advantage over the US system in that they provide a measure of population impact almost in real time, and that sustained changes in mortality can be expressed as a proportion of the expected number of deaths. Individual case surveillance provides essential information on the epidemiological characteristics of the fatal cases which allows for the determination of risk factors and estimates of years of potential life lost (YPLL) [80]).

Another approach developed for pandemic planning is to use predictive modelling, producing projections or forecasts as ranges of deaths. This is useful for planning purposes, but is especially vulnerable to uncertainty since these projections are usually based on assumptions of the epidemiologic characteristics of the virus gathered early in the pandemic or based on the characteristics of past pandemic viruses. These estimates are usually based on reasonable worst case scenario assumptions (i.e. on a severe pandemic, but one that countries can with preparation still cope with), and as such tend to produce a range of estimates for cases and deaths that are high in their upper bounds [81]. This can easily confuse the general public as it may be seen as a prediction for a pandemic. Hence, mortality estimates generated using a worst case scenario must be presented very carefully to policy makers and the media who can seize on and misinterpret upper estimates [82]. Accuracy in case and death estimates greatly increases as more robust surveillance data become available and are incorporated into the models [34]. Such revised estimates of possible numbers of deaths, based on updated epidemiological and virological data, have been called ‘now-casting’ [34,83,84].

Potentially the most accurate method for estimating pandemic influenza-related mortality is using pre-existing population-based surveillance to estimate the absolute number of influenza-related deaths or to detect excess premature mortality associated with epidemics or pandemics. This has been done through the Emerging Infections Program of the US Centers for Disease Control and Prevention (CDC) which collects exhaustive hospital-based surveillance data in specific geographical areas [29,85]. This allowed the US CDC to estimate the number of influenza deaths by age group, deriving an all-age estimated range for the US in the first 12 months of the 2009 pandemic of between 8,870 and 18,300 deaths with a central estimate of 12,470, which is equivalent to a population rate of 4.14/10^5. These numbers compare with 2,125 reported confirmed deaths (population rate 0.69/10^5) [85]. From this it was possible to determine multipliers for the US that could be applied in that country to its all age or paediatric reported deaths to estimate true excess deaths [29,85]. However the US multipliers must not be applied in other countries.

A related US approach for estimating deaths caused by the pandemic applies the relationship seen between seasonal influenza and deaths coded as due to pneumonia and influenza and applying the observed age-group distribution seen in virologically confirmed deaths. This has been extended to calculate estimates of deaths and YPLL using pneumonia and influenza excess deaths as the lower bound and all-cause excess deaths as the upper [4]. The YPLL approach incorporates important qualitative aspects of deaths in young people in the 2009 pandemic and allows for more accurate comparisons with seasonal influenza. To date in Europe, only the Netherlands has published YPLL figures for confirmed 2009 pandemic deaths, estimating that the minimum YPLL were similar to those from seasonal influenza [36]. There are, however, difficulties with the YPLL approach since individuals with chronic conditions who die from influenza often have a shorter expected life span and attributing their years of life lost entirely to influenza will result in an overestimation [11,86]. It is also possible that for the very elderly and very ill, influenza infection only brings forward death by a few weeks or months.

Deaths due to the 2009 pandemic recorded on national websites versus deaths reported to ECDC

Aside from the EuroMOMO project, there was no routine European system for monitoring mortality during the 2009 pandemic using statistical or modelling
rate of 0.56/10^5 with national rates varying eight- to nine-fold from 0.18 to 1.51/10^5 [89]. National totals cited will have changed somewhat since April 2010 due to late reporting and data improvement. The official number of deaths reported to ECDC and WHO was lower. This was due to a few large countries hardly reporting any deaths (Figure). With the exception of age, comparing population rates of reported deaths yielded no obvious patterns [88]. It is likely that much of the differences in patterns are reflected by differences in diagnosis and reporting between countries. The age pattern of the cases reported was strikingly different from that observed with the previously circulating seasonal influenza (Table 5) [61,67]. Pandemic deaths were more often in children and young adults. Approximately 20% of deaths were in people over 65 years of age compared with the usual figure of around 90% for seasonal influenza deaths [33,90,91]. This likely reflects the underlying pre-existing immunity in the older sections of the population due to exposure to earlier similar influenza A(H1N1) viruses, which reduced their risk of infection and death [63,68]. However, elderly persons who were infected, had a significantly higher risk of dying than younger persons [88,92]. A number of national and international studies using individual data added important details, notably concerning the risk factors for deaths [79,91,93,94]. While these have confirmed that chronic underlying disease was a risk factor in adults and children, they found that between 18% and 30% of the deaths were in people without any

**Figure**

Cumulative confirmed fatalities due to influenza A(H1N1)pdm09, announced (n=2,900) versus reported (n=1,890), by countrya, 15 April 2009–10 May 2010

Each space on the x-axis represents an EU/EFTA Member State. The order has been randomised so as not to follow alphabetical order.
chronic health condition [24,79,90,93,94]. A UK study examined ethnic group effects and found that children of southern Asian origin were at higher risk of death than white children, a finding replicated for hospitalisations but not for perinatal mortality [79,95,96].

Interpretation of European 2009 pandemic mortality data
The 2,900 laboratory-confirmed deaths attributed to the 2009 A(H1N1) pandemic reported by EU Member States are a minimum number and a considerable underestimate of the true mortality [87,88]. Given the very different crude population death rates announced by different countries it is likely that the multipliers to estimate a more accurate figure of premature deaths differ from country to country and no single multiplier should be applied [89]. Differences in rates probably reflect national variation in diagnosis, testing, test availability, awareness in clinicians, and access to care. It would be interesting to investigate the reasons for different death rates within the EU, since the pandemic virus did not change. The modelling approach in Denmark has cautiously derived an estimate of 312 influenza deaths, whereas only 30 laboratory-confirmed deaths were observed. Hence Denmark has a multiplier of 10 and an estimated true death rate of up to 5.7 per 100,000 population [61]. While it is likely that many deaths were unreported, the magnitude of the underestimate almost certainly differs by country. There are likely to be unidentified pandemic deaths in older adults but they cannot be many or there would have been excesses in observed all-cause or older age mortality.

Table 5
Differences in the patterns of mortality during influenza seasons 2000/01 to 2008/09 and the 2009 influenza pandemic

<table>
<thead>
<tr>
<th>Intensity of diagnostic testing</th>
<th>Seasonal influenza 2000/01 to 2008/09</th>
<th>2009 pandemic influenza</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compared to the pandemic there was less testing for influenza</td>
<td>More intensive testing than during seasonal epidemics, although to varying extent between countries and over the period of the pandemic</td>
<td></td>
</tr>
</tbody>
</table>

| When deaths occurred | In season - mostly starting after Christmas in recent years, may have coincided with extreme weather | Started out of season with a spring/summer wave, then an early autumn/winter wave in Europe |

| Experiencing severe disease | Those in clinical risk groups and older people | Young children, pregnant women and those in clinical risk groups. About 30% with severe disease were outside risk groups. Many born before the mid-1950s were immune, but those not experienced severe disease. |

| Premature deaths | Around 90% are considered to occur in people 65 years or older | In laboratory-confirmed reported deaths around 80% were under 65 years-old. Increase in all-cause deaths in children detected across eight EU countries by EuroMOMO system |

| Mortality and years of potential life lost (YPLL) | Few confirmed deaths reported each year in official statistics. Estimated using statistical methods to be up to 38,500 on average in the EU | Substantial numbers of confirmed deaths announced by EU/EFTA Member States (n=2,900) but recognised to be an underestimate. Not estimated in any EU Member State but estimated in the US |

| Acute respiratory distress syndrome | Extremely rare | Uncommon but has been recorded in many countries, even in young fit adults. Partially explained by the tropism of the pandemic virus for epithelial receptors that predominate in the lung alveoli while the previous seasonal viruses bind best to receptors found predominately in the upper airways |

| Pathological findings | Viral pneumonia rare, but secondary bacterial infections more common in fatal cases | Fatal viral pneumonias relatively common with alveolar lining cells, including type I and type II pneumocytes the primary infected cells. More than 25% of fatalities also had bacterial infections |

There is more certainty in the characteristics of the fatalities. In contrast to seasonal influenza, global deaths from the 2009 pandemic occurred more often among children and young adults, and a substantial proportion of fatal cases did not have underlying chronic health conditions (Table 5). As in the 1918 and 1957 pandemics, the 2009 influenza A(H1N1) pandemic affected mainly younger members of society with many but not all older people (born before 1960) possessing some levels of cross-protective immunity [63,68,97,98]. Qualitatively and quantitatively, the deaths in Europe also reflected this pattern (Table 5). Cautious application of the YPLL approach shown by the Dutch investigators is a better way to proceed [36].

It is instructive to note how misleadingly high the early estimates of case fatality rates in Mexico were, although they were at the time based on the best available data [23,26]. The early broad clinical experience in New York City (US), Melbourne (Australia) and the UK were more instructive for judging the mortality and severity of this pandemic than the initial impressions and numerical analyses from Mexico [99]. Due to the mild symptoms of many of the cases the true case fatality rates were impossible to measure. Infection fatality rates are more reliable because they are less affected by differing definitions of mild cases. If accurate case fatality rates are to be derived in a timely manner in future pandemics and provide population-based fatality rates for comparisons between countries prior preparation for early rapid seroepidemiological studies will be needed [24,100-102].

Recommendations for practice, surveillance and study
Influenza epidemics and pandemics are important public health events with a significant impact at least on healthcare systems. What is needed are national routine systems for monitoring the annual numbers of influenza-associated deaths. Preferably methods should be consistent and corrected for confounding to avoid systematic overestimation. Monitoring international all-cause winter deaths during the influenza season through international surveillance building on the example of EuroMOMO is desirable. However, it is important to add data on cause. The EuroMOMO project has made an important start and includes more than ten EU countries. EuroMOMO now needs to grow and introduce analyses that can provide standard timely estimates of mortality attributable to influenza (both seasonal and pandemic), including cause-specific data. Regression modelling can provide a complementary approach to estimate the burden of influenza retrospectively and allows the opportunity to control for potential confounding factors. Participants of the annual meeting of the European Influenza Surveillance Network in 2011 (held jointly with WHO Regional Office for Europe) agreed there should be agreement on one or more preferred European methods for statistical national estimates of excess influenza deaths as well as preferred methods of formal individual death reporting in order to identify risk groups [102]. They further agreed that YPLL should be estimated as well as death totals, although such calculations need to allow for differing life expectancy in those with and without chronic conditions. In addition influenza infections should be suspected more readily as a potential diagnosis and more diagnostic tests should be used in hospitals. That will allow systematic investigation of the patterns of influenza-related premature deaths and their risk factors as these can indicate how these deaths and severe cases can best be prevented. This will require individual reporting of deaths particularly for key groups for whom vaccination and early treatment policy is uncertain, such as children, pregnant women and young healthy adults.

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