A very tricky business: the importance of accurately predicting the severity of swine flu

"In order to pick up any changes in severity in a timely manner so that the public health response can be adapted, it is … important to have estimates of the case–fatality ratio that are consistent over time."

Tini Garske
MRC Centre for Outbreak Analysis & Modelling, Department of Infectious Disease Epidemiology, Imperial College London, St Mary's Campus, Norfolk Place, London W2 1PG, UK
Tel.: +44 (0)20 7594 3427
Fax: +44 (0)20 7594 8321
t.garske@imperial.ac.uk

Each year, influenza viruses cause substantial morbidity and mortality worldwide. Occasionally, a new strain arises against which there is no immunity in the population, and that can therefore spread rapidly around the world, causing a pandemic. This strain usually replaces the previous seasonal strain and continues to circulate in the interpandemic periods, causing seasonal epidemics that are generally less severe than in pandemic years due to the build-up of immunity in the population. There is historical evidence of influenza pandemics since the Middle ages [1]; in the past century, there were three flu pandemics of very different severity. The 1918 pandemic caused an estimated 20–40 million deaths worldwide, whereas the 1957 and 1968 pandemics were less severe, responsible for around 1–4 million deaths each [1].

The case–fatality ratio, defined as the proportion of people exhibiting clinical symptoms who will die as the result of the disease, is an important indicator of the severity of a disease. Good estimates of the case–fatality ratio are particularly important very early on in the pandemic, in order to shape the appropriate public health response. If indeed the current pandemic had been caused by a strain similar to the avian strain H5N1 with an estimated case–fatality ratio of over 50% in humans [2], much more aggressive strategies for control would be needed than in the current H1N1 (2009) pandemic.

Flu viruses mutate rapidly, and selective pressure on a newly arisen strain would be expected to be even higher than the pressure on a seasonal strain as it still adapts to the human host. Indeed, in past pandemics different pandemic waves with different severity have been observed – for instance, a mild spring wave followed by a more severe autumn wave in the 1918 pandemic [3]. In order to pick up any changes in severity in a timely manner so that the public health response can be adapted, it is therefore important to have estimates of the case–fatality ratio that are consistent over time.

While the 1918 pandemic was very severe, with an estimated case–fatality ratio of around 2% [4], the other two pandemics in the last century were milder, with case–fatality ratios similar to those seen in seasonal flu. This also appears to be the case for the current influenza A H1N1 2009 pandemic strain. However, with a new pandemic flu strain, there is no pre-existing immunity in the population, and therefore the attack rates, that is the proportion of the population getting infected during the pandemic, are expected to be much higher than those seen in the interpandemic periods. Furthermore, the age groups that carry the largest burden of morbidity and mortality differ between pandemic and seasonal flu, with much of the mortality of seasonal flu restricted to the elderly, whereas in pandemics, and to a lesser extent also the first post-pandemic years, this tends to be shifted to younger age groups [5].

"Good estimates of the case–fatality ratio are particularly important very early on in the pandemic, in order to shape the appropriate public health response."

While the definition of the case–fatality ratio is straightforward, estimating it can be tricky, particularly in the early stages of an ongoing pandemic, when good estimates would be particularly useful. One issue with the real-time estimation of case–fatality ratios is caused by the delay between symptom onset and death. The problem is that if we simply divide the numbers of deaths by the number of cases observed so far, we include some cases with a recent onset of symptoms who will eventually die, but are not yet included in

part of future medicine fsg

the death count, therefore underestimating the case–fatality ratio. This bias is always there when the epidemic is ongoing, but it is particularly strong in the early exponentially growing phase of the epidemic. This can be accounted for as long as the typical delay from onset of symptoms to death is known [6]. Early on in the epidemic, when only few deaths have been observed, these data are scarce; however, typical characteristics of previous pandemic or seasonal flu strains can be used as an approximation.

> *"One issue with the real-time estimation of case–fatality ratios is caused by the delay between symptom onset and death … Another problem is that numbers of cases and deaths are highly uncertain."*

Another problem in the estimation of case–fatality ratios is that numbers of cases and deaths are highly uncertain. As the pandemic strain appears to cause mild, self-limiting disease in the majority of cases, many people may not seek medical attention, and therefore will not ever be recorded in the medical statistics. This then leads to an underestimate of true case numbers and, therefore, an overestimate of the case–fatality ratio. While these mild cases might not contribute much to the morbidity caused in the pandemic, they are still important from an epidemiological point of view, as they do contribute to transmission and population immunity to the strain. Once a sufficient proportion of the population has built up immunity, the epidemic saturates and case numbers will fall. Therefore, knowing the extent of mild infection is crucially important to predict when the epidemic might peak.

While it is difficult to determine the extent of mild infection through the standard syndromic surveillance systems, well-designed study protocols can address this problem, such as widespread testing and surveillance of household members of identified cases in well-defined communities, ideally combined with collection of serological data. Studies of this kind ideally need to be conducted in the early stages of local epidemics, when only a small part of the local population has yet developed immunity. If in parallel there is good case ascertainment of severe cases, for instance hospitalized cases, at the population level, the proportion of mild infection found in the local studies can be used to extrapolate to true case numbers, which will give a more accurate estimate of the case–fatality ratio [6].

Uncertainties about the level of ascertainment of deaths due to flu can also cause biases in the case–fatality ratio estimates. Although the ascertainment of deaths is probably better than that for cases, not all influenza deaths might be attributed correctly, as in many countries hospital surveillance systems are limited. Reasons for missing influenza as a cause of death may include atypical clinical presentation, or masking by other conditions (given that many of the recorded deaths have been in people with underlying chronic conditions).

Making consistent estimates of the case–fatality ratio over time is further complicated by the types of data that are available at the different stages of the pandemic. The WHO recommends testing of all suspect cases in the early stages of national epidemics [101], such that the confirmed case numbers at this stage should at least reflect those with clinical disease. Once the national epidemics are well established, this approach is no longer feasible due to the large case numbers and, at this point, testing is restricted to the most severe cases, so that the number of laboratory-confirmed cases from this time onwards cannot be compared with earlier data. When case numbers are large enough, standard influenza surveillance data becomes important. This typically records the number of people with influenza-like-illness (ILI) contacting a sentinel network of primary care facilities, and virological testing of a subset of these in order to establish the specificity of the symptoms. These data can then be used to calculate consultation rates.

> *"While … mild cases might not contribute much to the morbidity caused in the pandemic, they are still important from an epidemiological point of view, as they do contribute to transmission and population immunity to the strain."*

In the later stages of an epidemic, when the counts of individual deaths no longer give an accurate picture, mortality statistics can be used. However, the mortality data is much less sensitive than the surveillance data, particularly for low case–fatality ratios, as seen in the current pandemic. While in the mortality statistics the cause of death is recorded, the diagnosis of influenza is frequently missed, such that the excess mortality attributable to influenza classified as 'all-cause mortality' is, on average, about four-times that of the excess mortality for 'pneumonia and influenza' deaths [7]. This again indicates that the

ascertainment of deaths in the current pandemic is probably fairly low, as the reported deaths only include laboratory-confirmed cases, which form an even smaller subset of the total deaths attributable to this influenza strain than those classified as 'pneumonia and influenza' deaths in the mortality statistics. It is therefore clear that using the individual death counts of confirmed cases, together with the ILI consultation rates, would result in a severe underestimate of the case–fatality ratio due to the very different level in ascertainment of numerator and denominator.

> "*While it is important to employ the right methods in estimating the case–fatality ratios in order to avoid unnecessary biases, the real difficulty is that of the available data.*"

Good estimates of case–fatality ratios are important for public health planning, and differences between regions can highlight success or failure of the implemented control measures, whereas differences over time could indicate changes in virulence that might require an adaptation of the public health response. While it is important to employ the right methods in estimating the case–fatality ratios in order to avoid unnecessary biases, the real difficulty is that of the available data. Well-designed data collection protocols that guarantee surveillance of the full spectrum of disease from mild to severe (including deaths), and care in the analysis of the data in order to avoid using incompatible datasets, are needed in order to provide the best-possible guidance to public health planners.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Bibliography

1 Lazzari S, Stoehr K: Avian influenza and influenza pandemics. *Bull. World Health Organ.* 82(4), 242 (2004).

2 Li FC, Choi BC, Sly T, Pak AW: Finding the real case–fatality rate of H5N1 avian influenza. *J. Epidemiol. Community Health* 62(6), 555–559 (2008).

3 Reid AH, Taubenberger JK, Fanning TG: The 1918 Spanish influenza: integrating history and biology. *Microbes Infect.* 3(1), 81–87 (2001).

4 Brundage JF: Cases and deaths during influenza pandemics in the United States. *Am. J. Prev. Med.* 31(3), 252–256 (2006).

5 Simonsen L, Clarke MJ, Schonberger LB, Arden NH, Cox NJ, Fukuda K: Pandemic versus epidemic influenza mortality: a pattern of changing age distribution. *J. Infect. Dis.* 178(1), 53–60 (1998).

6 Garske T, Legrand J, Donnelly CA *et al.*: Assessing the severity of the novel influenza A/H1N1 pandemic. *BMJ* 339, B2840 (2009).

7 Lui KJ, Kendal AP: Impact of influenza epidemics on mortality in the United States from October 1972 to May 1985. *Am. J. Public Health* 77(6), 712–716 (1987).

Website

101 WHO: Human infection with pandemic (H1N1) 2009 virus: updated interim WHO guidance on global surveillance (2009) http://www.who.int/csr/disease/swineflu/WHO_case_definition_swine_flu_2009_04_29.pdf (Accessed 10 July, 2009)