Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Case fatality ratio of pandemic influenza

As pandemic influenza H1N1 spread around the world in 2009, disease severity was one of the main areas of interest. The case fatality ratio (CFR) is a representative measurement of severity of a disease that directly captures virulence (ie, the conditional risk of death for patients with a disease or infection), whereas mortality (ie, the risk of death in a population) depends not only on the disease severity but also the risk of infection in a population. Because there have been several conflicting estimates of the CFR for pandemic H1N1,[1–6] I offer an interpretation of these reports and identify key areas that need to be clarified.

In the early stages of the 2009 influenza pandemic, two approaches were taken when calculating the CFR. One approach focused on estimation of CFR during the course of the pandemic.[1–3] During outbreaks of severe acute respiratory syndrome from 2002 to 2003, use of a crude ratio of the cumulative number of deaths to the number of cases at a given point in time underestimated the CFR.[7] To avoid similar underestimations, accounting for the time delay from onset of disease to death, the confirmed CFR of pandemic H1N1, which took confirmed cases as the denominator, was estimated to be about 0·5%.[1–3,6] However, because the estimate depends on the proportion of symptomatic patients who have confirmatory diagnosis, it is not useful for prediction of the overall mortality.[6] In other words, the difficulty in case ascertainment remains a limitation of confirmed CFR. Motivated by this limitation, the second approach calculated the CFR by taking symptomatic cases as the denominator, although in this study the denominator was not clearly defined.[4] Despite several technical problems, this approach emphasised the importance of accounting for unconfirmed cases to yield an appropriate order of the CFR estimate (figure 1).[4]

Subsequent to these earlier efforts, Presanis and colleagues[5] have offered a way to predict the mortality in a population, by explicitly taking symptomatic cases as the denominator and thus calculating the symptomatic CFR. The symptomatic CFR among all medically attended cases was estimated to be 0·048%, one-tenth of the CFR estimate from confirmed cases. In other words, only one of ten symptomatic cases seems to have been confirmed. By use of self-reported influenza-like illness as the denominator, the estimate was even smaller. Presanis and colleagues[5] and a later study in the UK[8] have adeptly shown that 2009 pandemic H1N1 influenza can be subjectively perceived as mild.

Caution is needed when interpreting age-specific estimates (figure 2). The confirmed CFR in Mexico[9] and the USA[10] increases with age, most probably because underlying medical conditions that can increase the risk of influenza death are most common in elderly

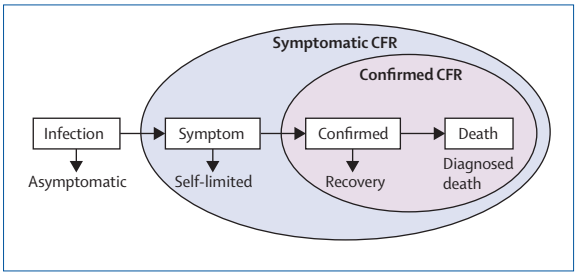

Figure 1: **Case fatality ratios and the natural history of infection**
The confirmed case fatality ratio (CFR) uses the confirmed cases as the denominator, whereas symptomatic CFR uses symptomatic cases. To predict mortality, symptomatic CFR (or ideally the CFR taking all infected individuals as the denominator) is required.

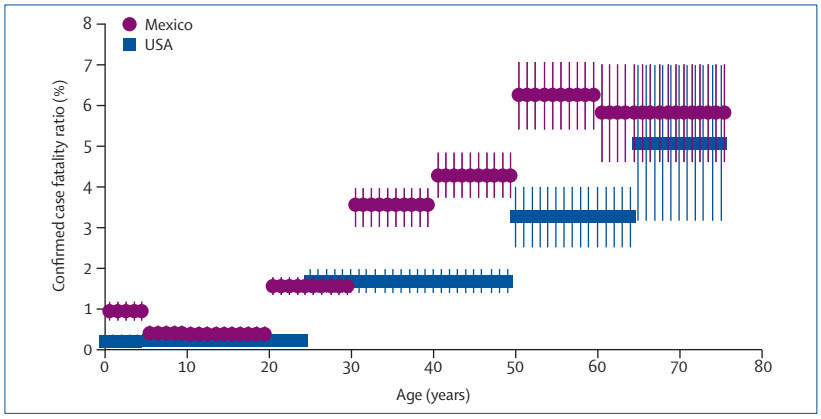

Figure 2: **Age-specific confirmed case fatality ratio in Mexico and USA**
In Mexico there were 72 529 cases and 1227 deaths (as of May 10, 2010) and in the USA there were 37 030 cases and 276 deaths (as of July 24, 2009).[9,10] Shaded area represents the 95% CI.

people.[10,11] The similar age-specific pattern is also seen in symptomatic CFR.[8] The differing CFR estimates between age-groups hamper precise estimation for entire populations during the early stages of the pandemic.[12] Furthermore, although there might be two countries with very different CFR estimates, comparisons will be futile unless the composition of the cases (ie, age-groups and risk-groups of fatal and non-fatal cases) is known.

The best way to describe the severity of pandemic influenza to non-experts is to compare its virulence with that of other influenza epidemics. However, because different methods have been used to predict the mortality impact associated with pandemic H1N1 and non-pandemic influenza, the strict comparison of virulence has been difficult. Estimations of mortality for non-pandemic influenza have been made mainly with Serfling cyclical regression,[13] which accounts for deaths that are both directly and indirectly associated with influenza. A recent study in the USA suggested that there were up to 44 100 excess deaths in May to December, 2009,[14] implying that the mortality effect of the influenza pandemic surpassed that of non-pandemic influenza seasons. However, because this estimate of excess mortality reflects both transmission potential and virulence, a comparative assessment of virulence alone has yet to be established.

In addition to the above-mentioned issues surrounding the estimation of CFR, pharmaceutical interventions such as antiretroviral treatment or immunisation programmes also bias the estimated risk of death. Thus, to provide an unbiased CFR for the 2009 influenza pandemic that can accurately represent the overall virulence and permit comparisons within and between populations, we are faced with a challenge to adjust for such potential treatment effects that may require substantial epidemiological and statistical efforts.

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