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Lessons learned from case fatality risk estimates of 2009 pandemic influenza

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Providing reliable indicators of the severity of emerging pathogens is key to public health decision-making. In particular, real-time estimates of the case fatality risk, defined as the risk of death among patients classified as cases, can help determine the type and strength of interventions required to mitigate an emerging outbreak.

Estimating case fatality risk has proved to be particularly challenging in recent emerging infectious disease outbreaks, including the 2003 SARS epidemic,¹ the 2009 A/H1N1 influenza pandemic,¹ and more recently the influenza A/H7N9² and MERS-coV outbreaks.³ In this issue of *EPIDEMIOLOGY*, Wong and colleagues present a systematic review of case fatality risk estimates of the 2009 A/H1N1 influenza pandemic based on 50 studies representing 33 countries or regions.⁴ This is a most welcome study assessing the lessons learned from a well-documented influenza pandemic, associated with an estimated 100,000-300,000 deaths globally -- a substantial number, although modest in comparison with earlier influenza pandemics.^{5,6}

The most salient finding of the review by Wong et al. is the high level of heterogeneity in published case fatality risk estimates of 2009 pandemic influenza. Such heterogeneity greatly undermines the use of these data for policy purposes. It is well known that case fatality risk values are highly sensitive to the choice of denominator (persons classified as cases).^{1,4} Three categories of cases are typically considered. One is laboratory-confirmed cases. These usually provide a gross underestimate of the total number of cases due to limitations in testing capacity and high propensity to diagnose severe cases. Nonetheless, lab-confirmed cases are often the only available denominator in the early stages of an outbreak.^{1,4} A second category is symptomatic cases. These can be limited to medically attended clinical infections, or can include cases who do not seek care. The third is serologically-confirmed infections. This category may produce more reliable case-fatality estimates, but it requires expensive and time-consuming biological measurements. In the great majority of case fatality risk studies, the standard numerator is based on laboratory-confirmed deaths (69 of 77 pandemic influenza estimates reviewed by Wong and colleagues), although some studies have used alternative metrics such as deaths from pneumonia and influenza, influenza-like-illness deaths, or model-derived excess deaths.⁴

Unsurprisingly, the review by Wong and colleagues⁴ found dramatic variation in case fatality risk estimates depending on the choice of denominator. These estimates ranged from 100 to 5,000 deaths per 100,000 laboratory-confirmed pandemic influenza A/H1N1 cases, 0

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to 1,200 deaths per 100,000 symptomatic cases, and 1 to 10 deaths per 100,000 serologic infections. What is perhaps more surprising is the high level of residual heterogeneity even after controlling for the choice of denominator and methodology. For instance, there was up to 10-fold difference in published symptomatic case fatality risk estimates based on data from the same country and influenza surveillance system.^{7,8}

Early estimates of case fatality can shape policy decisions in pandemic crises, but they can also evolve rapidly as more epidemiological information becomes available and treatment guidelines change. It is informative to consider the well-characterized Mexican 2009 pandemic experience.⁷⁻¹¹ The earliest documented case fatality risk estimate of 2009 pandemic influenza was an astounding 4%, based on the first 1,100 laboratory-confirmed cases reported by 5 May 2009 in Mexico.⁹ This estimate is higher than that of the catastrophic 1918 pandemic. Given the apparent severity of this new pandemic virus, the Mexican government closed the nation's schools for 18 days (24 April to 11 May 2009).⁸ By June, case fatality risk estimates had been quickly downgraded to 0.4% (0.03–1.8%), as more robust data on laboratory-confirmed cases and deaths accumulated.¹⁰

The review by Wong et al. suggests that laboratory-confirmed estimates of case-fatality risk are nearly meaningless in absolute terms. Although such estimates can be useful for monitoring time trends, it is difficult to grasp the meaning of the denominator.⁴ As an illustration, laboratory-confirmed case fatality risk estimates declined throughout the spring 2009 pandemic in Mexico, as the lag between disease onset and hospital admission shortened.¹¹ It is well-accepted that delayed hospital admission complicates influenza case management, limiting the effectiveness of antiviral treatment and, in turn, exacerbating disease severity. Then there followed a 3-fold rise in case fatality risk between the summer and fall 2009 in Mexico, coinciding with a drop in antiviral use from 50% to 9%.¹¹ The large impact of admission delay and antiviral use is further underscored by a large hospital study of more than 10,000 laboratory-confirmed pandemic influenza patients characterized by very short median admission delay and very high antiviral treatment rates – and reporting no pandemic-related death.¹²

The systematic review by Wong and colleagues⁴ includes case fatality risk information on case fatality risk from 33 countries. These data highlight interesting regional differences worthy of further investigation. Case fatality risk estimates were higher for Argentina, Mexico, and Colombia,^{4,13} consistent with a high excess mortality burden of the pandemic in this region as assessed by vital statistics data.⁶ This suggests that between-country differences in case fatality risk estimates are not purely methodological artifacts, and may reflect underlying geographic differences in influenza case management, access to antibiotics and antivirals,¹¹ uptake of seasonal influenza vaccines,^{7,14} prevalence of underlying comorbid conditions,¹⁵ co-infections with other respiratory agents, baseline health, and population demographics.⁴ Overall, a better understanding of the determinants of influenza severity globally would be important for improving pandemic preparedness plans.

A clear data gap identified by the accompanying review⁴ is the lack of case fatality risk estimates for seasonal influenza epidemics. Such estimates would have been highly informative for comparison purposes at the outset of the 2009 pandemic. We greatly need a population-level epidemiologic tool to compare influenza severity across pandemic and epidemic seasons.

A further issue is the paucity of robust influenza information from low-income regions, which undermines the validity of global predictions of pandemic influenza mortality burden.⁵ The relationship between influenza severity, income, and geography is not straightforward, as shown by the moderate case fatality risk estimates of 2009 pandemic

influenza in Mauritius, India and Nepal⁴ and the relatively mild excess mortality burden of the pandemic in Bangladesh and South Africa,⁶ relative to estimates in high-income countries. Clearly much more work needs to be done to understand these differences.

We wholeheartedly concur with Wong and colleagues⁴ that rigorous guidelines are needed to monitor influenza severity during seasonal and pandemic outbreaks and across geographic settings. The continued threat posed by novel influenza viruses (H5N1, 2009 H1N1, and most recently H7N9) underscores the urgency of establishing long-term surveillance systems that can assess severity in near real-time, and identify changes that might signal the emergence of atypical influenza viruses.¹⁶⁻¹⁸ Ideally, these surveillance systems would integrate measures informing the severity pyramid,¹⁹ including the risk of hospitalization among medically-attended infections and the risk of death among laboratory-confirmed hospitalized patients (see Yu et al²). A globally representative sample of such surveillance systems could shed light on the spectrum of factors that drive the risk of influenza-related death in inter-pandemic seasons, and provide an essential evidence base for decision-making when the next health crisis comes.

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