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Timely estimates of influenza A H7N9 infection severity

WHO guidance, released in May, 2013, established that estimates of disease severity are key for risk assessment of novel influenza viruses.[1] Unfortunately, epidemiological assessment of severity is difficult in the context of an emerging disease, when estimates are most needed to guide pandemic response. The case fatality risk is an estimate of the proportion of patients with a specific disease who have died; however, both the numerator and denominator of this estimator are elusive.[2–4] Case detection is typically skewed towards patients with severe disease; laboratory-based case ascertainment can vary geographically and temporally; and there are delays between onset, death, and reporting, potentially leading to overestimation or underestimation of fatality risk.[2,4]

Much work has been done to refine estimates of case fatality risk in the wake of the 2003 outbreak of severe acute respiratory syndrome and the 2009 influenza pandemic.[2] Different denominators have been considered, including patients who have been admitted to hospital,[5] symptomatic cases,[5] and all individuals with serological evidence of infection.[6] From a statistical point of view, survival analysis provides an appropriate framework to quantify case fatality with right-censored outcome data.[2,5]

In *The Lancet*, Hongjie Yu and colleagues assess the clinical severity of human infection with avian influenza A H7N9 virus on the basis of data from 123 patients with laboratory-confirmed infection who were admitted to hospital between March and May, 2013, in mainland China.[5] They estimate that the fatality risk for all ages was 36% (95% CI 26–45), and note that nearly all patients were admitted to an intensive care unit, received mechanical ventilation, or died (83%,

76–90). 71 (58%) of the patients were aged at least 60 years, and fatality risk was higher for these individuals (49%, 36–63) than for younger patients (18%, 6–29; p=0·0019), as is typical of influenza infection.[6]

To obtain an estimate of symptomatic case fatality risk, Yu and colleagues[5] extrapolated the total number of symptomatic individuals infected with avian influenza A H7N9 virus on the basis of the number of mild cases detected through routine influenza-like illness surveillance in Shanghai and Nanjing—the most affected cities. They estimate that the symptomatic case fatality risk could be between 160 (95% CI 63–460) and 2800 (1000–9400) per 100 000 symptomatic cases. This estimate is highly sensitive to assumptions about testing propensity, surveillance coverage, and health-care seeking behaviour.

Use of near-real-time estimates of case fatality risk to guide policy is typically limited by broad uncertainty (table). During early assessment of 2009 pandemic influenza disease severity,[4] information about the first 1100 laboratory-confirmed cases produced a severity estimate of 4%, which is even higher than Yu and colleague's new estimates.[5] However, the 2009 estimate was soon downgraded by more than two orders of magnitude as information accumulated during the summer of 2009 (table). Similarly, severity estimates for avian influenza A H7N9 virus will be refined as the fate of all patients admitted to hospital is resolved and as serological attack rates become available (attack rates could be generated from cross-sectional surveys because background population immunity is low[16]).

It is reassuring that head-to-head comparison of the fatality risk of admitted patients infected with avian

	Case fatality risk in patients admitted to hospital	Case fatality risk in symptomatic patients	Case fatality risk in individuals with serological evidence of infection
Influenza A H7N9, 2013			
Yu et al (China)[5]	36% (26–45)	0·16–2·8%* (0·06–9·4)	..
Influenza A H5N1, 2003–13			
Cowling et al (China)[7]	70% (56–83)	..	..
Fiebig et al (12 countries)[8]	56% (28–87†)	..	..
1957 and 1968 pandemics[9]	..	0·1%	..
1918 pandemic[9]	..	2–4%	..
2009 pandemic‡			
Earliest estimates: first 1100 laboratory-confirmed cases (Mexico)[4]	..	4%	..
Fraser et al (Mexico; June, 2009)[10]	..	0·4% (0·03–1·8)	..
Garske et al (15 countries; July, 2009)[2]	..	0·11–1·47%§	..
Baker et al (New Zealand; August, 2009)[11]	1·6%	0·005%	..
Presanis et al (USA; December, 2009)[3]	..	0·048% (0·026–0·096)	..
Echevarria-Zuno et al (Mexico; December, 2009)[12]	12%	0·9%	..
Wu et al (Hong Kong; November, 2010)[6]	0·6%¶	..	0·004% (0·003–0·017)
Yu et al (China; February, 2011)[13]	2·5%	..	..
Riley et al (Hong Kong, June, 2011)[14]	..	..	0·008% (0·006–0·010%)
Presanis et al (UK; summer wave; September, 2011)[15]	5·3%	0·015% (0·010–0·022)	0·005%
Presanis et al (UK, autumn wave; September, 2011)[15]	..	0·025% (0·013–0·040)	0·009%

Data in parentheses are 95% CIs, unless otherwise stated. Note the sharp reduction in estimates of case fatality risk in symptomatic patients for the 2009 pandemic as more information became available. By contrast, estimates of case fatality risk in infected individuals are more consistent, although these estimates were not available in the early stages of the 2009 pandemic or the influenza A H7N9 outbreak, and no comparable information for the historical pandemics of 1918, 1957, and 1968 is available. No estimate is available for seasonal influenza. *Range depends on assumptions about number of symptomatic cases of infection with avian influenza A H7N9 virus. †Range across 12 countries. ‡Estimates sorted by publication date. §Range across five regions surveyed. ¶Limited to individuals aged 5–59 years.

Table: Estimates of case fatality risk for the influenza A H7N9 outbreak in China, 2013, influenza A H5N1, and past pandemics

influenza A H7N9 or H5N1 suggests a substantially milder disease course for H7N9.[7] Use of these estimates of case fatality risk to extrapolate the potential severity of a full pandemic would be tempting; however, whether global dissemination of these zoonotic influenza viruses would result in a catastrophic pandemic like that in 1918, or worse, or would mirror the mild 2009 pandemic (table) is impossible to predict.

A remaining question relates to the age distribution of symptomatic infections should a zoonotic influenza virus acquire person-to-person transmissibility. So far, the age distribution of reported cases of infection with avian influenza A H7N9 virus has been skewed towards old ages, which is probably explained by behavioural age differences in exposure to the animal reservoir.[17] The age distribution of cases would probably shift towards younger ages in a full pandemic, resulting in a different and potentially decreased case fatality risk. Another issue would be to account for potential changes in disease severity as the virus rapidly evolves. Although conventional wisdom stipulates that virulence attenuates as a pathogen adapts to a new host, animal experiments suggest that influenza virulence could increase simultaneously with genetic drift.[18] Furthermore, evidence from the 1918 pandemic suggests that the situation can escalate: case fatality risk increased by six times from the summer to the autumn of 1918.[19]

The good news is that numbers of cases of avian influenza A H7N9 virus infection have stalled, probably in response to pre-emptive closures of live bird markets. However, the threat of this virus persists, and continued monitoring of infections, together with near-real-time estimation of case fatality risk and serological surveys, remains crucial. Investment in robust hospital surveillance of respiratory infections in a few globally sampled sites, combined with laboratory testing, would help to produce comparative severity estimates for novel and existing viral threats. Yu and colleagues[5] have provided the best severity estimates for avian influenza A H7N9 virus in view of the available information at this point in time; however, public health experts will have to make policy decisions on the basis of uncomfortably broad confidence limits.

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Education, audit, and outreach to prevent maternal mortality

Although progress has been made in reducing global maternal mortality, an estimated 287 000 women still died in 2010.[1] Maternal mortality disproportionately affects families living in low-income and middle-income countries, and most of these deaths are preventable. Effective and cheap interventions exist to prevent death from the major causes, including haemorrhage, hypertensive disease, sepsis, and septic abortion. What is lacking is evidence on implementation in view of local contexts, resource constraints, and cultural norms.[2] For many years, WHO has championed multidisciplinary maternal mortality audit as essential for reducing deaths.[3] For audit to achieve change, there must be willingness to identify problems, with leadership capable and motivated to institute changes. Audit involves far more than just counting deaths. Perhaps not surprisingly given the complexity of multidisciplinary audit, to date evidence from randomised trials that show a reduction in maternal deaths has been poor.[4]

In The Lancet, Alexandre Dumont and colleagues address this knowledge gap with findings from the QUARITE trial.[5] This cluster-randomised trial was done in 46 hospitals across Senegal and Mali. The authors assessed a complex intervention of maternal mortality audits, leadership development, training in emergency obstetric care, and outreach health practitioner education. Data for more than 190 000 women were collected over 4 years, giving the study power to detect a change in mortality. The intervention was based on the Society of Obstetricians and Gynaecologists of Canada ALARM (Advances in Labour And Risk Management) International Program. This programme uses adult learning techniques to teach essential evidence-based obstetric skills.[6] Hospitals allocated to the control group did not partake in the intervention and continued usual care.

The results showed a 15% greater reduction in maternal deaths in the intervention compared with the control hospitals over 4 years (odds ratio [OR] 0·85, 95% CI 0·73–0·98, p=0·0299).[5] This reduction was less