EDITORIAL COMMENTARY

How Low Is the Risk of Influenza A(H5N1) Infection?

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(See the major article by Gomaa et al on pages 1399–407.)

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For over a decade, we have heard predictions that avian influenza A(H5N1) may be nearing pandemicity and that the pandemic will be catastrophic when it arrives. These predictions derive from a belief that A(H5N1) may be only a few mutations away from full adaptation to transmissibility [1] and from its allegedly high propensity to infect and to kill people. The World Health Organization (WHO) has recorded a case-fatality ratio of 59% among the 650 human cases reported to date [2], which some interpret to mean that approximately 60% of everyone infected by A(H5N1) will die. In the current climate of alarm, routine and decades-old virologic research approaches, such as examining the effects of engineered mutations on phenotypic properties like experimental virulence and transmissibility, recently termed “gain of function” studies, have been called “absolutely crazy” and “exceedingly dangerous” (Robert May, as quoted in Ref. [3]). Calls for curtailing research on potential pandemic pathogens [4] have prompted governments to exert greater oversight of influenza virus experimentation [5], framing a fundamentally important question about whether influenza research is more likely to prevent, or cause, influenza pandemics [6, 7].

Curiously ignored, however, is evidence that calls into question A(H5N1) viral doomsday scenarios; for example, after countless people (certainly at least hundreds of thousands, if not millions) have been intimately exposed to A(H5N1) in poultry epizootics and live bird markets, almost none have been recognized as having mild infections, very few have A(H5N1) antibody at all, and, when detected, the antibody level is typically low and transient [8]. To understand human A(H5N1) pandemic risks, we need first to understand how a virus can expose enormous numbers of people over half the globe, for over 16 years, but infect as few as 650 of them, kill the majority of those infected, and yet leave even the very closest contacts of these cases, as well as their countless coexposed coworkers and neighbors, mysteriously free of disease or even immune evidence of exposure. Can a panzootically circulating virus be so poorly adapted that it has difficulty infecting anyone, yet so deadly that it kills most of the few people it does infect? Do these paradoxes tell us anything about A(H5N1) risks?

Gomaa et al address these questions in the current issue of The Journal of Infectious Diseases [9]. In a prospective study using stringent seroprevalence/seroinci-

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and dead birds. The disease risk for these A(H5N1)-exposed humans may, for each individual, be very low. However, when A (H5N1) exposes thousands or millions of people, rare spillover infections are inevitable without changes in infectious or epidemiologic properties of the otherwise poorly infective virus—again, analogous to many other animal viruses.

We have previously suggested that rare A(H5N1) and A(H7N9) disease outcomes may result from yet undetected and uncommon human genetic susceptibilities [13–15]. Evidence consistent with this possibility includes the recent identification of apparent host susceptibility genes for influenza virus disease severity [16]; evidence that household clusters of severe A(H5N1) disease disproportionately involve genetically related persons, rather than those most intensely coexposed or those who had the closest person-to-person contact; and the separation in time and place of severe cases in relatives [17–20]. Taken together, these data strongly indicate that many or most cases of severe H5N1 disease result from uncommon host susceptibilities. Such rare severe A(H5N1) diseases could also reflect unusual doses or routes of exposure or exposure to unidentified copathogenic factors. But the notion that the 650 reported severe cases indicate A(H5N1) adaptation and evolution toward human transmissibility and virulence is unsupported by any scientific fact. More plausibly, such cases reflect nothing more than rare and uncharacteristic outcomes of exposures to unadapted avian A(H5N1) viruses, a tip of the iceberg atop millions of silent infections and uninfec table exposed persons.

Consistent with the relative inability of A(H5N1) to productively infect humans are (1) the general inability of avian influenza viruses to cause highly productive infection upon human experimental inoculation [21]; (2) generally low human antibody prevalence to avian influenza viruses, even in poultry workers with intense exposures; (3) evidence in exposed seronegative persons of A(H5N1) T-cell immunity [22]; and (4) the complete absence over the past century of significant human outbreaks of avian influenza viruses (excluding occasional human case clusters during large poultry epizootics).

Regarding the ostensibly high A(H5N1) case-fatality rate, supposedly indicating partial human adaptation and potential pandemic deadliness, the evidence actually suggests the opposite conclusion. Published serologic studies from a variety of sampled A(H5N1) exposure groups, using antibody titers ranging from ≥40 to ≥160, have identified many asymptomatic human A(H5N1) cases (Supplementary Materials). Defining the A(H5N1) case-fatality rate as the ratio of all fatal cases to all severely ill cases meeting WHO criteria leads to a fundamental error in calculating the risk posed by a poorly adapted virus. Missing from the denomi nators used to calculate such case-fatality rates are at least 3 important categories of persons: (1) those who are silently infected and mount a very low-level subthreshold immune response (eg, those with a reciprocal neutralization titer of <40), (2) those who are infected and mount transient immune responses not detected in cross-sectional seroprevalence studies, and (3) those who are intimately exposed but do not become productively infected or do not mount an immune response [21].

The numbers of people in each of these 3 categories are unknown but probably in the millions; adding them back to the denominator greatly reduces the results of A (H5N1) lethality calculations. A very rough estimate of the true A(H5N1) case-fatality rate might be made by, for example, combining numerator and denominator data from the 5 published seroprevalence studies of low-exposure populations throughout China [23–27]. Such calculations suggest that there is only about 1 death for every 580 000 A(H5N1) infections, corresponding to a case-fatality ratio orders of magnitude lower than that of seasonal influenza or of any influenza pandemic in recorded history.

While it is important to be vigilant about the potential risks posed by all influenza viruses, including A(H5N1), and while we cannot conclude that the A(H5N1) risk is nonexistent, we see no compelling virologic or epidemiologic evidence to suggest that A(H5N1) or any other avian influenza virus is currently evolving toward human transmissibility, let alone pandemicity, or that such viruses are even capable of doing so. Clearly, there remain other much more obvious pandemic risks, including reassortment of a circulating human A(H1N1) or A(H3N2) virus with zoonotically derived influenza virus genes; the non-circulating 1957 A(H2N2) pandemic influenza virus, stored in laboratories around the world; a number of hyperevolving swine influenza viruses; some, like the progenitor of the 2009 pandemic A[H1N1] virus, containing genes from human influenza viruses; and A(H1N1) and A(H3N2) intrasubtypic reassortant influenza viruses, which have in the past caused significant influenza epidemics that, for reasons of tradition, are not referred to as pandemics, although they meet universally accepted pandemic criteria [28].

The study by Gomaa et al is valuable in helping us put pandemic risk considerations in context. There remains no scientific evidence that any particular avian influenza virus, including A(H5N1), is currently evolving to become capable of causing a pandemic or that it would be catastrophically fatal if it did. Countless humans are frequently exposed to a wide variety of avian influenza viruses through interaction with poultry, live bird markets, and wild birds. As human and poultry populations have grown, and as poultry practices and transport have become increasingly industrialized, such exposures are increasing, both in number and intensity. Despite producing more and better-recognized sporadic dead-end/ spillover human cases, some of them severe and fatal, there is no reason to think these accelerating exposures have any bearing on pandemic emergence. After all, the frequency with which influenza pandemics
emerge today is no different from what it was 500 years ago [29], when the global population was only 6% as large and poultry industries were nonexistent.

The study by Gomaa et al prompts the thought that the energy generated by alarmist predictions about A(H5N1) might be better directed to studying the larger question of how human- and mammalian-adapted influenza viruses emerge and evolve before they become pandemic/panzootic, including study of viral genetic mechanisms by which wild bird avian influenza viruses adapt to domestic poultry, mammals, and humans. At the same time, we must not lose sight of the pandemic risk posed by many other human- and mammalian-adapted viruses that are potentially capable of pandemic emergence via mechanisms that have already been documented.

Supplementary Data

Supplementary materials are available at The Journal of Infectious Diseases online (http://jid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyrighted. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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