

## H5N1 influenza virus seroepidemiological studies: The facts revisited

The Perspective by Palese and Wang stated that they are providing the “facts, not fear” regarding H5N1 virus infection (1). Despite this claim, they did not provide an accurate picture of the facts as they relate to estimating the case-fatality rate for human H5N1 infection.

First, Palese and Wang cited 10 large seroepidemiological studies evaluating the rate of asymptomatic human infections with H5N1 virus. They stated that these studies demonstrate that the rates for previous H5N1 infection range “from 0.2% to 5.6%” (1). The World Health Organization (WHO) has established criteria for serologic detection of H5N1 in humans (2). Of the 10 studies cited, only seven reported results consistent with the WHO criteria. One is not relevant because it involves a survey conducted during the 1997 outbreak in Hong Kong, to which the current H5N1 viruses are not similar (3). One is a reanalysis of data from two studies already cited. This leaves five remaining studies that meet the WHO criteria. Of these five, only two reported any serologic evidence of H5N1 infection based on the WHO criteria. Combined results from these five studies demonstrate that only 0.675% of persons surveyed (25 of 3,703) had serologic evidence of previous H5N1 virus infection. Furthermore, approximately 4 wk after the initial online publication of the PNAS perspective (1), Wang et al. published a second analysis of H5N1 infection seroepidemiology in *Science* that includes a meta-analysis of 20 seroepidemiological studies addressing this issue (4). This later publication, which includes a number of additional studies, supports our assertion that the PNAS Perspective was an incomplete analysis and that no conclusions can be drawn from the data presented.

Although available evidence supports the fact that asymptomatic infections with H5N1 can occur in persons exposed to the virus, the evidence does not suggest that asymptomatic infections are common or that the case-fatality rate for H5N1

has been significantly overestimated (5). There is no evidence to support the statement by Palese and Wang that “the case-fatality rate that is offered by the WHO—and that is driving this controversy—is likely orders of magnitude too high” (1). One of us (M.T.O.) is a member of the National Science Advisory Board for Biosecurity; therefore, we can state that the primary reason for the Board’s initial recommendation regarding the redaction of the two originally submitted manuscripts to *Science* and *Nature* was related to the transmissibility of the viruses that were generated and not driven by their potential virulence, as stated by Palese and Wang (1).

We believe far too much attention has been placed on the H5N1 infection case-fatality rate, which is diverting attention away from the key issues at hand; these include how to (i) safely conduct and share influenza transmissibility research, (ii) ensure the use of biosafety procedures that prevent any accidental release of these viruses, and (iii) develop effective and timely countermeasures to respond to H5N1 as a potential pandemic threat.

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The authors declare no conflict of interest.

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