Response to Comment on "Seroevidence for H5N1 Influenza Infections in Humans: Meta-Analysis"

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Response to Comment on "Seroevidence for H5N1 Influenza Infections in Humans: Meta-Analysis"

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We address points made in the comment by Van Kerkhove *et al*. and explain why human H5N1 virus infections are much more common than was previously thought.

We would like to respond to several points made in the comment by Van Kerkhove *et al*. (*1*) regarding our recently published meta-analysis of seroevidence for H5N1 influenza virus infections in humans (*2*).

Taking into account only four of the countries with documented avian influenza H5N1 infections—Vietnam, Indonesia, Egypt, and China—there is a cumulative rural population currently of about 1 billion people. Each year, some fraction of those people is exposed to H5N1, and the cumulative seroevidence from a single time point of sampling shows that 1 to 3% of exposed people have been infected (*2*). Recent reports of human antibodies or of T cells specific for H5N1 viruses support the 1 to 3% rate of infection or provide evidence for infections without detectable antibodies (*3*, *4*). Over the many decades that H5N1 viruses have been circulating in poultry, millions of people have likely been infected.

The comment by Van Kerkhove *et al*. that "most of the studies considered by Wang *et al.* were conducted in high-risk populations, which limits the ability to extrapolate to the wider population" is inapplicable to our analysis because we made no attempt to extrapolate our findings to a wider population. The data are clearly relevant only for people with some exposure to H5N1 viruses.

We strongly disagree with the statement by Van Kerkhove *et al*. that existing studies likely overestimate the H5N1 antibody seroprevalence rates. In contrast to this assertion, Van Kerkhove *et al*. have previously discussed the many reasons that seroprevalence studies likely underestimate H5N1 infection rates (*5*). Indeed, the lack of sensitivity of H5N1 serology assays is well documented, as is the short period in which serum H5N1 antibodies can be detected in infected individuals. The high rate of false negative results from serum-based assays is exemplified by the rate of only ~70% seropositive findings from patients with polymerase chain reaction–confirmed H5N1 disease—and this is under the best of circumstances, when the time of infection is known.

There is no reason to "question the appropriateness of combining seroprevalence data from outbreaks in 1997 with data from outbreaks occurring from 2003 to the present because of H5N1 strain differences." Influenza viruses are continually changing, and we strongly believe that all data related to H5N1 virus infections in humans are equally informative.

Finally, the statement that "even if infections were being under-ascertained by a factor of 60 at the current time, natural H5N1 viruses would still be 100 times as lethal as the 2009 H1N1 pandemic virus" is arbitrary. The WHO criteria could result in under-documentation of H5N1 infections by several orders of magnitude; random calculations such as the one made by Van Kerkhove *et al*. (*1*) have little value in discussions related to H5N1 viruses in humans.

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