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Seroevidence for H5N1 Influenza Infections in Humans: Meta-Analysis

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Since 2003, there have been 573 World Health Organization (WHO) documented cases of avian H5N1 influenza infections in humans reported from 15 countries (*1*). Of the WHO confirmed cases, 58.6% have resulted in death (as of December 15th, 2011) (*1, 2*). These severe H5N1 infections were diagnosed using criteria developed by the WHO that are specific for H5N1 disease, but that lack the sensitivity to identify the total number of human infections (table *S*1) (*3*).

Given the fact that most H5N1 infections in poultry and in humans occur in resource-poor areas where access to health care is often arduous and expensive to obtain, we hypothesized that many people with H5N1 virus infection would not have been examined by a health provider to allow formal H5N1 disease confirmation. In addition, persons who are seropositive for H5N1 infection often report no history of influenza-like illness, and subclinical or mild H5N1 infections are not recognized under the WHO criteria for confirmed cases (*4–8*).

We conducted a meta-analysis of studies that evaluated the serological evidence of H5N1 infections in humans (table *S*2). The study participants, by and large, reported no recent respiratory and/or febrile illness. Variation between studies was taken into account using a random effects approach (*9*). We included in our primary analysis only studies that assessed serum samples based on modified WHO guidelines (*N*=19 study groups), or that presented data in such a way that modified WHO guidelines for H5N1 seropositivity could be applied [for modified WHO guidelines, see (*10*)]. In a secondary analysis, we compiled data from the remaining manuscripts based on the authors' criteria for positivity (*N*=10). Study participants with confirmed H5N1 infection were excluded to allow an analysis of seroprevalence in the persons without WHO-documented infection; exposure to poultry or humans with confirmed or suspected H5N1 infection was not a criterion for exclusion.

The primary analysis using WHO criteria was based on 7,304 study participants. All studies reported rates of seropositivity ranging from 0-5.3% with the exception of one study reporting 11.7% positivity among household contacts of infected individuals (*5*). Using WHO criteria, meta-analysis revealed an overall seropositivity rate of 1.2% with a 95% confidence interval of 0.6% - 2.1% (Fig. 1A). Analysis of studies, which could not be interpreted by WHO guidelines [(*10*), table S2, and references therein], included 6,774 participants and yielded a seropositivity rate of 1.9% with a 95% confidence interval of 0.5 - 3.4% (Fig. 1B). Using either criterion, the rate of human H5N1 infections within the study populations was approximately 1-2% (*10*).

Using WHO criteria, we performed sub-analyses of study participants who were specifically employed as poultry workers (*N*=2,729) (*4*) (table S2). This analysis revealed a seropositivity rate of approximately 1.4%. If reports from the 1997 outbreak in Hong Kong are considered separately, the rate of seropositivity is approximately 3.2% (*4, 5, 7*). Studies after 1997, and that use WHO criteria, show an overall seropositivity rate of approximately 0.5% (*8*) (table S2).

The data were compiled from 12,677 study participants in 20 studies. They show that avian H5N1 viruses can cause a rate of mild or subclinical infections in humans that is not currently accounted for and thus, the true fatality rate for H5N1 influenza viruses is likely to be less than the frequently reported rate of more than 50%. Although it is not possible to determine an accurate fatality rate for H5N1 infections based on the data presented here, if one assumes a 1-2% infection rate in exposed populations, this would likely translate into millions of people who have been infected, worldwide. It is possible that deaths caused by H5N1 infection, as documented by the WHO, are also underestimated. We suggest that further investigation, on a large scale and by a standardized approach, is warranted to better estimate the total number of H5N1 infections that have occurred in humans. This information is critical for calculation of a real fatality rate that is not solely based on hospitalized patients.

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Supporting Online Material
www.sciencemag.org/cgi/content/full/science.1218888/DC1
Materials and Methods
Tables S1 and S2
References and Notes (*11–40*)

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Figure 1. Forest plots of overall, and study-specific, seroprevalence estimates with 95% confidence limits. Analysis using WHO criteria (A) or other criteria (see SOM) (B) for seropositivity. Individual values for prevalence (seropositivity), lower and upper confidence limits are shown at the right of each plot.

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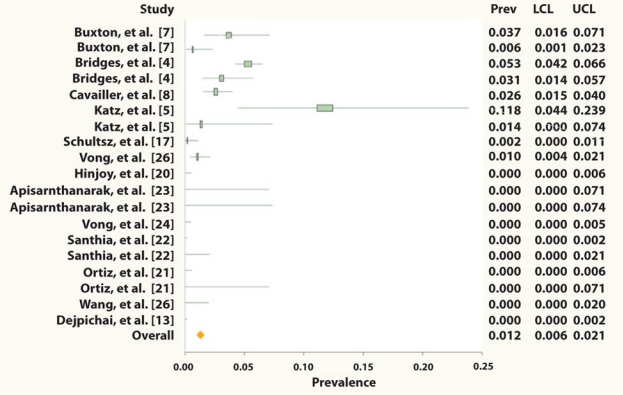
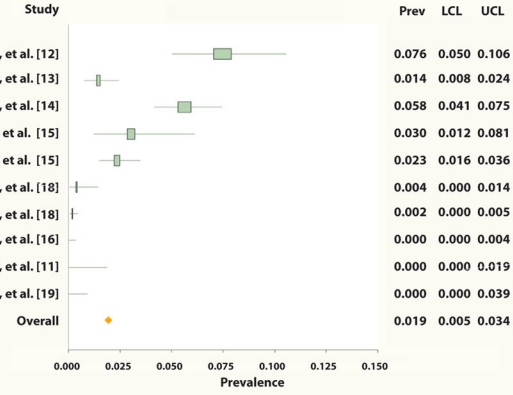

Estimates of Seropositivity (WHO Criteria)
Prevalence and 95% Confidence Limits
Study
Prev
LCL
UCL
Buxton, et al. [7] 0.037 0.016 0.071
Buxton, et al. [7] 0.006 0.001 0.023
Bridges, et al. [4] 0.053 0.042 0.066
Bridges, et al. [4] 0.031 0.014 0.057
Cavailler, et al. [8] 0.026 0.015 0.040
Katz, et al. [5] 0.118 0.044 0.239
Katz, et al. [5] 0.014 0.000 0.074
Schultsz, et al. [17] 0.002 0.000 0.011
Vong, et al. [26] 0.010 0.004 0.021
Hinjoy, et al. [20] 0.000 0.000 0.006
Apisarnthanarak, et al. [23] 0.000 0.000 0.071
Apisarnthanarak, et al. [23] 0.000 0.000 0.074
Vong, et al. [24] 0.000 0.000 0.005
Santhia, et al. [22] 0.000 0.000 0.002
Santhia, et al. [22] 0.000 0.000 0.021
Ortiz, et al. [21] 0.000 0.000 0.006
Ortiz, et al. [21] 0.000 0.000 0.071
Wang, et al. [26] 0.000 0.000 0.020
Dejpichai, et al. [13] 0.000 0.000 0.002
Overall 0.012 0.006 0.021
0.00
0.05
0.10
0.15
0.20
0.25
Prevalence


Estimates of Seropositivity (Other Criteria)
Prevalence and 95% Confidence Limits
Study
Prev
LCL
UCL
Ceyhan, et al. [12] 0.076 0.050 0.106
Dejpichai, et al. [13] 0.014 0.008 0.024
Khuntirat, et al. [14] 0.058 0.041 0.075
Lu, et al. [15] 0.030 0.012 0.081
Lu, et al. [15] 0.023 0.016 0.036
Schultsz, et al. [18] 0.004 0.000 0.014
Wang, et al. [18] 0.002 0.000 0.005
Robert, et al. [16] 0.000 0.000 0.004
Cai, et al. [11] 0.000 0.000 0.019
Zhang, et al. [19] 0.000 0.000 0.039
Overall 0.019 0.005 0.034
0.000
0.025
0.050
0.075
0.100
0.125
0.150
Prevalence

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