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## Background

Influenza virus infections lead to a wide range of clinical manifestations, from severe pneumonia through to subclinical or even asymptomatic disease. There has been substantial controversy over the proportion of influenza virus infections that are asymptomatic, referred to as the asymptomatic fraction (AF). Knowledge on the AF, variation in the AF in certain groups, and the potential infectiousness of asymptomatic cases is extremely important in designing public health control strategies such as contact tracing and quarantine, and in estimating the burden of disease.

## Objectives

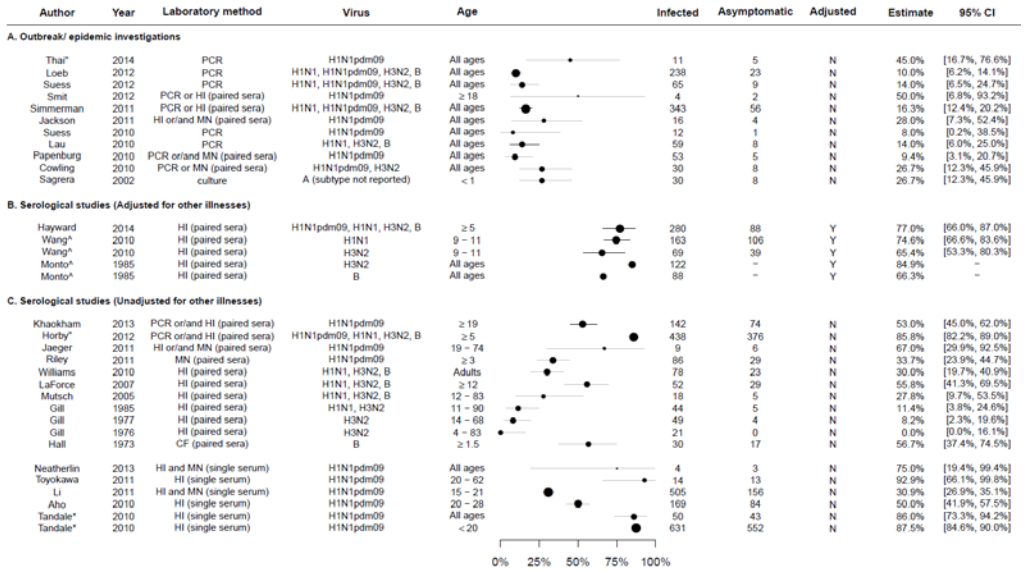
In this study, we aim to describe and summarize published estimates of the asymptomatic fraction (AF).

## Methods

We conducted a systematic review to assess and summarize the AF of influenza virus infections. Studies containing data on asymptomatic fraction of influenza virus were retrieved from the PubMed electronic databases on 11 April 2014. Laboratory-confirmed influenza infection was defined as an infection confirmed by RT-PCR or viral culture test result on a respiratory specimen; or serologic evidence of recent infection indicated by a  $\geq 4$ -fold rise in antibody titer in paired sera, or  $\geq 1:40$  titer in a single serum specimen. Asymptomatic illness was defined as specified by the respective studies. The AF in our study was defined as the proportion of influenza-infected individuals that reported no symptomatic illness, and was calculated for each study with a 95% confidence interval. Heterogeneity was estimated using the  $I^2$  statistic with a random-effects model.

## Results

Figure 1. Forest plot of estimates of the asymptomatic fraction, stratified by study design. A. Estimates from outbreak investigations. B and C. Estimates from trans-epidemic studies, with adjustment for rates of symptomatic illness in uninfected persons (B), or not (C).



463 titles were retrieved and screened, 110 abstracts and 68 full-length articles were then reviewed. 30 articles were identified and classified into two categories: outbreak investigations (11) and trans-epidemic studies (19).

Studies in the group of outbreak investigations included outbreak investigations in specific settings such as households. In these studies, respiratory secretions were usually collected and the acute infections were confirmed by RT-PCR or viral culture during intensive follow-up efforts with repeat collection of respiratory specimens from symptomatic and asymptomatic individuals. Point estimates of the AF from these studies fell within the range 8%–28% or had wide confidence intervals extending into this range (Figure 1A). Heterogeneity measured by the  $I^2$  statistic was medium (61%).

The other studies could be grouped together as serological studies where individuals were followed up across entire epidemics, and testing of single or paired sera was used to identify infections. Illness reports in the same individuals could then be used to infer how many influenza virus infections might have been symptomatic. Overall, point estimates of the AF from this group of studies spread across a wide range of 0%–93% with very high heterogeneity ( $I^2=97%$ ) (Figure 1B and 1C). Five estimates have been adjusted for rates of illness from other non-influenza causes with estimates in the range 65%–85% (Figure 1B), and were higher than most of the unadjusted estimates (Figure 1C). There was also less heterogeneity among the studies that reported adjusted estimates, with  $I^2$  statistics of 58% for adjusted versus 98% for unadjusted estimates.

## Conclusions

The true AF of influenza virus infections is likely to fall somewhere between the 8%–28% reported in outbreak studies and the 65%–85% reported in adjusted estimates from serologic studies. Variation in estimates could be partially explained by differences in study design and analysis, and inclusion of mild symptomatic illnesses as asymptomatic in some studies.

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