

**[LETTER]**

**Reply to Kok**

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Word count: 516

To the editor:

We appreciate Kok and Dwyer's comments that have stimulated further discussion about the design and interpretation of serologic surveillance studies [1]. Inclusion of serologic studies in revised pandemic plans could facilitate straightforward estimation of infection attack rates (IARs) during future pandemics.

We analyzed seroprevalence in serial cross-sectional samples from blood donors [2]. However, we have continued testing specimens from a subset of donors who provided two or more specimens through our study period, and comparisons of seroprevalence in this subset were very similar to the overall analysis (unpublished updated data). In addition we were involved in a separate study in Hong Kong that obtained paired sera from 770 individuals during the first pH1N1 wave [3]. We are therefore in a unique position to comment on the relative strengths and weaknesses of serial cross-sectional and longitudinal studies.

Serial cross-sectional studies have the advantage of permitting timely estimates of IARs during as well as after waves of infection, and can provide important situational awareness on the progression of a pandemic [4]. Cross-sectional studies can be set up relatively easily based on residual sera from various sources such as blood donors or hospital inpatients, although it can be difficult to interpret post-pandemic seroprevalence without a pre-pandemic baseline for comparison [1]. In longitudinal studies where specimens are available from the same individuals before and after a pH1N1 wave, IARs could be based on seroconversion, i.e. the development of detectable antibody against pH1N1 where none previously existed [1]. However if a substantial fraction of individuals have

detectable pH1N1 antibody before the first wave, even at low levels, it may be more appropriate to use criteria such as a 4-fold or greater rise in antibody titers to indicate infection. In longitudinal studies it is not necessary for the pre- and post-wave sera to bracket the entire wave, and overall IAR estimates may be made even with non-bracketing sera if other surveillance data such as on pH1N1-associated hospitalizations are available [3]. For a given number of sera, longitudinal studies can provide more precise IAR estimates than serial cross-sectional studies, although it may be more difficult to obtain large numbers of paired samples in a 'passive' study based on residual sera, while studies involving active recruitment and follow-up of participants can be resource intensive.

Whether analyzing data from serial cross-sectional or longitudinal studies, IAR estimates should be corrected for the proportion of pH1N1 infections that reach a specific titer (cross-sectional), or lead to a rise in antibody titer by a certain ratio (longitudinal) [5]. As noted by Kok and Dwyer [1], analyses may need to adjust for cross-reactive antibody responses following infections with other influenza strains. In 2009 in Hong Kong, a seasonal influenza A(H3N2) virus that circulated at the start of the first pandemic wave was quickly displaced by pH1N1 [6], and in a separate study we found that H3N2 infections rarely led to substantial cross-reactive increases in pH1N1 antibody [7]. Further work is needed to clarify appropriate statistical methods for analysis and interpretation of serologic surveillance data, adjusting for potential cross-reactions as well as imperfect sensitivity of criteria used to indicate infection.

## **ACKNOWLEDGMENTS**

This work was supported by the Area of Excellence Scheme of the Hong Kong University Grants Committee (AoE/M-12/06).

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