Reply to Kok and Dwyer

To the Editor—We appreciate the comments by Kok and Dwyer [1] that have stimulated further discussion about the design and interpretation of serologic surveillance studies. 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 blood samples obtained from donors [2]. However, we have continued testing specimens from a subset of donors who provided ≥2 specimens throughout our study period, and comparisons revealed that the seroprevalence for this subset was very similar to that for the overall analysis (unpublished updated data). In addition, we were involved in a separate study in Hong Kong that obtained paired serum samples from 770 individuals during the first wave of pH1N1 influenza [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 and after waves of infection, and they can provide important situational awareness on the progression of a pandemic [4]. Cross-sectional studies can be designed relatively easily on the basis of residual serum samples from various sources, such as blood donors or hospital inpatients, although it can be difficult to interpret postpandemic seroprevalence...
data without prepandemic baseline data for comparison [1]. In longitudinal studies in which specimens are available from the same individuals before and after a wave of pH1N1 influenza, IARs could be based on seroconversion (ie, the development of detectable antibody against pH1N1 influenza virus where none previously existed) [1]. However, if a substantial fraction of individuals have detectable pH1N1 influenza antibody before the first wave, even at low levels, it may be more appropriate to use such criteria as a ≥4-fold increase in antibody titers to indicate infection. In longitudinal studies, it is not necessary for the pre- and postwave serum samples to bracket the entire wave, and overall IAR estimates may be made even with nonbracketing serum samples if other surveillance data, such as on pH1N1 influenza-associated hospitalizations, are available [3]. For a given number of serum samples, longitudinal studies can provide more precise IAR estimates than do serial cross-sectional studies, although it may be more difficult to obtain large numbers of paired samples in a “passive” study based on residual serum specimens, whereas studies involving active recruitment and follow-up of participants can be resource intensive.

Regardless of whether data come from serial cross-sectional or longitudinal studies, IAR estimates should be corrected for the proportion of pH1N1 influenza infections that reach a specific titer (cross-sectional) or that lead to an increase 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 after 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 cases of H3N2 influenza rarely led to substantial cross-reactive increases in pH1N1 antibody [7]. Additional work is needed to clarify appropriate statistical methods for analysis and interpretation of serologic surveillance data, with adjustment for potential cross-reactions and the imperfect sensitivity of criteria used to indicate infection.

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