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Capturing the transmission dynamics of the 2009 Japanese pandemic influenza H1N1 in the presence of heterogeneous immunity

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ABSTRACT

Purpose: To explore the heterogeneous transmission dynamics for influenza and identify the optimal serum antibody titer cutoff values for estimating its cumulative incidence.
Methods: We constructed a mathematical model describing serologically dependent disease transmission. The diagnostic performances of two serum antibody titer tests (single serum test and paired sera test) were evaluated, and cumulative disease incidence estimators were formulated. The model simulated the 2009 Japanese influenza A/H1N1 epidemic and investigated the optimal cutoff values and cumulative incidence estimates for this epidemic.
Results: Our assumed model and parameters suggested that the optimal cutoffs for A/H1N1 influenza were 1:20 for the single serum test and a 2-fold increase for the paired sera test. Using these optimal cutoff values, the paired sera test was the most reliable. The cumulative incidence estimate for the pre- and post-epidemic serological data showed that the paired serological data were also more accurately predictive.
Conclusions: From a statistical perspective, the currently used cutoff values may be too strict for diagnosing influenza and estimating its incidence. The paired sera test, which was more accurate for diagnosis and cumulative incidence estimation, is the test recommended for seroepidemiological surveillance during an epidemic.

Introduction

Infectious disease surveillance usually relies on symptom-based data collection for clinically diagnosed cases or laboratory specimens. Although they play a major role in public health practice and epidemiological studies, the impact of asymptomatic infectious diseases is not captured by such frameworks. Nevertheless, the infection process involves an immunological reaction regardless of whether the case is symptomatic or not; thus, serological investigations provide better information on the extent of infection in a population. Seroepidemiological surveying is a practical option for estimating the cumulative disease incidence after an epidemic of, for example, influenza, where symptom-based surveillance or mortality data are known to be subject to ascertainment and reporting biases [1]. Serological tests such as the hemagglutination inhibition (HI) assay [2] and microneutralization (MN) assay [3] assess antibody titers in serum samples, and when the values meet the diagnostic criteria, the individuals concerned are considered immune. In clinical settings, two diagnostic tests are mainly used. The single serum test classifies cases as positive when their absolute titers are above a cutoff value, whereas the paired sera test focuses on increases in the relative titer before and after infection. Cutoff values for these tests are usually an antibody titer of four-fold the minimum detection level (1:40 for HI and 1:32 for MN) [4–7] and a four-fold rise for the before and after infection values [8–12]. Multiple studies have estimated the cumulative incidence from rises in the proportion of positive individuals using the single serum test [4,5,7,9] or the paired sera test [12]. These cutoff values are widely accepted, but they lack enough scientific evidence to be used in seroepidemiological surveys.

Misclassification in the serum test involves several factors: cross-immunity, individual variation, and measurement errors. Cross-protective immunity can mean that the pre-epidemic

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distribution of antibody titers is broad. This is especially so for influenza where partial immunity may be acquired from past infections with other strains (or even from vaccines targeting other strains) [4,5,13–15]. Serum titer rises after infection may vary according to individual variation in the immune response, as seen in infection-confirmed but seronegative cases in the English pH1N1 epidemic [5]. Also, the observed values may be subject to error [16] from variations in the technical procedures used or from biological fluctuations, making even paired serum samples from the same individual without infection subject to differing measurements. Diagnoses provided by a uniform cutoff value cannot avoid the possibility of misdiagnosis arising from such factors; however, the diagnoses should be carefully evaluated, and errors were minimized by choosing optimal cutoff values.

In the present study, we analyzed the optimal cutoff values for serum titer tests using a mathematical model that incorporates serologically dependent heterogeneous transmission dynamics. Diagnostic performance was quantified as a function of the cutoff values for the serum dilution level, and optimums were sought that enable the single serum test and paired sera test to most precisely capture the infected individuals. The diagnostic performance of the two tests was also studied to accurately estimate the cumulative disease incidence, another critical objective of serological testing. The model was applied to the 2009 pandemic influenza A/H1N1 epidemic in Japan, and optimal cutoff values and estimated cumulative incidence values were obtained.

Materials and methods

Mathematical model of heterogeneous immune transmission dynamics

Let x denote the pre-epidemic serum antibody titer of an individual against the target infectious disease on a logarithmic scale. Assuming that one's risk of infection is determined by the serum titer, heterogeneous immune transmission dynamics can be described using the classical SIR model [17]. The time evolution of the susceptible, infected, and recovered population (S, I, and R, respectively) is described as

$$\frac{\partial S(t,x)}{\partial t} = -\beta(x)S(t,x)\int_{-\infty}^{+\infty} I(t,y)dy,$$

$$\frac{\partial I(t,x)}{\partial t} = \beta(x)S(t,x)\int_{-\infty}^{\infty} I(t,y)dy - \gamma I(t,x), \quad (1)$$

$$\frac{\partial R(t,x)}{\partial t} = \gamma I(t,x),$$

where $\beta(x)$ is the immunity-dependent vulnerability and γ is the recovery rate ($1/\gamma$ corresponding to the mean infectious period). R_0 is defined as

$$R_0 = \frac{\int_{-\infty}^{\infty}\beta(x)S(0,x)dx}{\gamma}. \quad (2)$$

We do not differentiate the transmission dynamics between asymptomatic and symptomatic cases in the aforementioned formulation assuming that their epidemiological profiles are identical. However, our model is also applicable to the case where the transmissibility varies between asymptomatic and symptomatic cases (see Appendix A).

Population-level serological distribution

Infection-induced seroconversion means that the antibody titer distribution at a population level is altered after an epidemic (Fig. 1). Let us denote the distribution of serum titers in the uninfected population throughout the epidemic by $u(x)$, and that in the infected population during the epidemic by $v(x)$. The serum titers remain unchanged in the uninfected population, that is, $u_{pre}(x) = u_{pos}(x) = u(x)$, while the immune responses are boosted in the infected population. Suppose that $f(x,y)$ is the relative frequency of the postinfection titer given the preinfection titer y, while the post-epidemic serum titer distribution in the population who experienced infection $v_{pos}(x)$ is given as

$$v_{pos}(x) = \int_{-\infty}^{\infty} f(x,y)v_{pre}(y)dy, \quad (3)$$

where $v_{pre}(x)$ is pre-epidemic serological distribution in the same population (note that $u(x)$ and $v_{pre}(x)$ differ because the risk of infection depends on the serum titer level). In the present study, we assumed that f is determined by the difference between x and y,

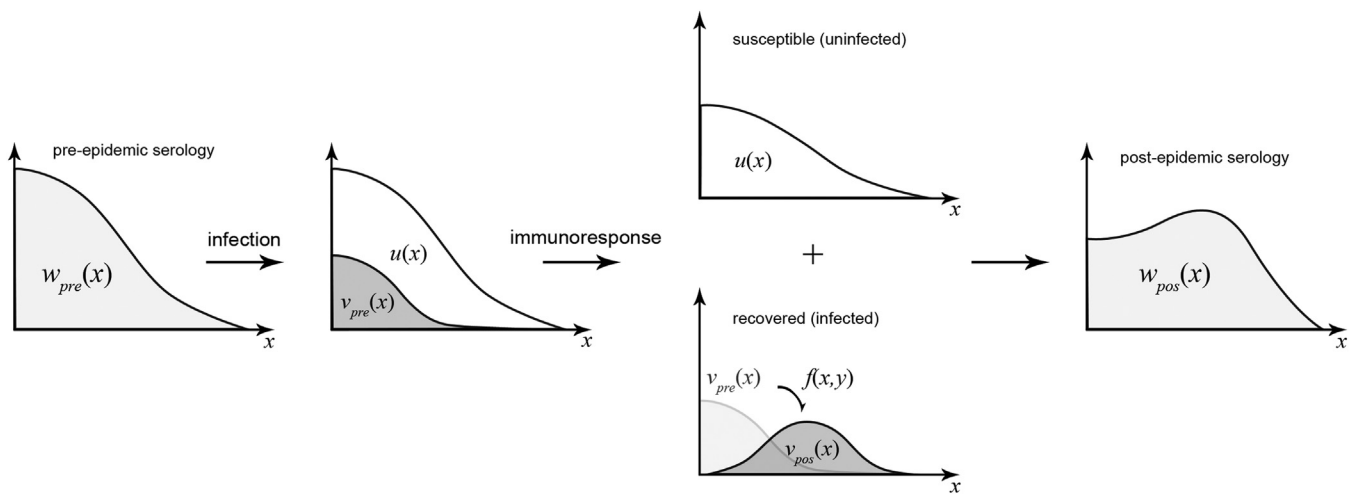

Fig. 1. Serological dynamics illustration before and after an epidemic. The graphs show the serum titer distributions in the population groups.

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