Population-based active surveillance cohort studies for influenza: lessons from Peru

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Introduction

Influenza has been a major threat to human health throughout history. Although safe and effective influenza vaccines are available, every year seasonal influenza affects from 5% to 15% of the world's population and causes an estimated 250 000 to 500 000 deaths worldwide.[1] Novel influenza A virus strains can cause sporadic pandemics, such as the 1918 "Spanish flu" that killed at least 3% of the world's population.[2] Although recent influenza pandemics, including the A(H1N1) pandemic in 2009, have been less severe, they nevertheless serve as vivid reminders of people's vulnerability to communicable respiratory viruses.[3]

Passive influenza surveillance

Disease surveillance, essential for guiding the public health response to influenza and other respiratory diseases, allows for early case detection and for the implementation of preventive measures. The World Health Organization (WHO) recommends passive health-provider based surveillance, or "sentinel surveillance", for influenza-like illness (ILI)[4] because it is simple and calls for standardized methods costing relatively little that can be implemented throughout the world. In many countries, the strategy can be easily integrated into the routine activities and existing infrastructure of health-care centres with minimal additional resource allocation. Combined with a proficient and reasonably well-equipped laboratory, passive ILI surveillance can provide information on seasonal trends, give early indication of increased disease incidence and lead to typing of circulating influenza viruses, including variant strains considered for inclusion in future vaccines against novel influenza A viruses with pandemic potential.

Passive sentinel influenza surveillance, however, only detects symptomatic cases severe enough to prompt the patient to seek health care and could easily miss mild cases in an incipient pandemic and delay the recognition of an outbreak.[5] Furthermore, although mild cases, by definition, do not contribute to mortality, they can enhance our understanding of the epidemiology and impact of influenza and help us design effective prevention and control measures. Another major limitation of passive surveillance is the lack of a precise population denominator from which to calculate attack rates and disease burden without resorting to additional studies, especially in developing countries, where accurate data on demographics and health service usage are rarely available.

Population-based active surveillance

Population-based active surveillance can complement routine passive sentinel surveillance systems by providing important public health data and insights into the complex epidemiology of influenza. Active surveillance of households can identify persons with ILI or with mild or even severe influenza-related illness who do not seek health care or who are kept from doing so by lack of time, financial constraints or cultural preferences. Community-based cohort studies can be particularly useful in pandemics because they can give early and unbiased estimates of household transmission parameters (e.g. the basic reproduction number, R_0) and the upper limit of case-fatality rates.[6]

The main advantage of population-based influenza surveillance is that it provides the data needed to determine the population at risk of infection and to calculate from it accurate attack rates and disease burden. In addition, it makes it possible to perform analyses of specific groups at high risk for influenza complications, such as young children, the elderly, pregnant women and people with specific comorbidities, including chronic lung disease, heart disease, diabetes and morbid obesity. Population-based approaches provide ideal platforms for the development of transmission models and for future testing of community control measures directed at influenza and other respiratory diseases, including both pharmaceutical (e.g. influenza vaccination) and non-pharmaceutical (e.g. hand washing) interventions.

Peru population-based cohort study

In 2009, the United States Naval Medical Research Unit 6 in Lima, Peru, with support from the Peruvian Ministry of Health, the Centers for Disease Control and Prevention in Atlanta, and the Armed Forces Health Surveillance Center in Silver Springs, implemented and has since maintained an active population-based household cohort study for ILI as a complement to the

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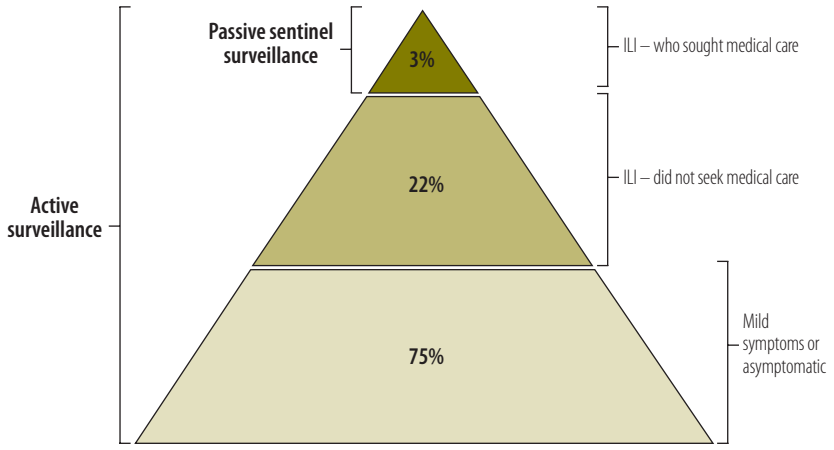
country's routine passive surveillance system.[6] The project is driven by the need to collect detailed epidemiological data to elucidate the complex transmission dynamics of influenza and other ILIs, which are major causes of morbidity and mortality in Peru. Five geographically distinct regions of Peru were selected to represent the country's diverse ecological niches (urban coastal desert, northern and southern tropical rainforest, dry tropical forest, and Andean highlands). Over 2500 households comprising more than 10 000 people were then selected randomly from a community geo-referenced census. The study protocol was approved by the Institutional Review Board of the United States Naval Medical Research Unit 6 in compliance with all applicable federal regulations of the United States and Peru governing the protection of human subjects. Each site is under the supervision of a physician or nurse with a small team of experienced field workers who visit each household as frequently as three times a week to screen household members using WHO's case definition of ILI.[4] Nasopharyngeal swabs are collected from identified cases and tested for influenza A and B virus by the rapid influenza test and real-time reverse transcriptase polymerase chain reaction (RT–PCR) with sequencing of amplification products. Detailed data on household characteristics and demographics – socioeconomic status, household crowding, ventilation systems, sanitation, contact with animals and comorbid health conditions, etc. – are collected. Clinical data are also recorded and participants are followed for 15 days to monitor and record the course of the illness. Project supervisors monitor the field team's work by conducting weekly confirmatory visits to randomly-chosen study households.

To the extent possible, cohort study activities are integrated into the regular functions of the staff of Peru's Ministry of Health to avoid duplication of effort. The incidences of ILI and confirmed influenza are reported weekly to the health ministry to help guide prevention and mitigation policies. Furthermore, the cohort study has the potential to actively promote healthy behaviours. For example, study team members readily counsel study participants in areas such as nutrition, vaccination and the proper use of antibiotics, and by doing so they encourage their adherence to the study. By performing these collateral duties, the team also improves overall health awareness and promotes good health practices in the study population and surrounding community.

Fig. 1. **Cases of A(H1N1)pdm09 infection detected through a population-based active household surveillance cohort study in Lima, Peru, April 2009–December 2010**



ILI, influenza-like illness.
Note: Data are shown on a subset of 325 participants on whom serologic testing was performed using a haemagglutination inhibition test specific for antibodies against A(H1N1)pdm09, in addition to the surveillance described in the text employing reverse-transcriptase polymerase chain reaction. Approximately 10% of the population was vaccinated for A(H1N1)pdm09 over the course of the surveillance period.

The Peru influenza cohort study was particularly informative during the 2009 A(H1N1) pandemic by providing key early data on the epidemic curve, clinical presentation and attack and incidence rates by age group and gender. The cohort study allowed us to demonstrate that A(H1N1)pdm09 was well established in the greater population of Lima at the time of the screening. We were also able to partially assess the efficacy of various mitigation measures and to demonstrate the likelihood that the seasonal influenza A(H1N1) virus would be replaced by A(H1N1)pdm09, as occurred later in many parts of the world.[6] By adding serologic testing to the cohort study we were able to detect a huge number of influenza virus infections not captured by routine passive surveillance (Fig. 1). We are presently using the cumulative attack rates from the Peru cohort studies to model global influenza pandemic mortality.

The benefit of the cohort study extends beyond the epidemiological data collected on influenza; the presence of influenza virus has been confirmed in only 32% of the 4400 respiratory specimens collected from people with ILI up to the writing of this paper, in October 2011. Testing of the negative samples has revealed a host of other pathogens, including coronaviruses, human metapneumoviruses, adenoviruses, respiratory syncytial viruses, human bocaviruses, rhinoviruses, enteroviruses and parainfluenza viruses, as well as numerous viral coinfections. We are presently exploring multiplex diagnostic platforms to simultaneously detect a broad array of respiratory pathogens, which is essential given the importance of possible recombination events and the historical evidence of viral–bacterial coinfection as a major factor in mortality associated with influenza.[7] As with the influenza virus data, incidence and attack rates, disease burden, seasonal trends and disaggregated risk factors can all be calculated. Finally, there is the potential to leverage the existing infrastructure of the influenza cohort study to monitor other syndromes. We are presently expanding our programme to include population-based surveillance of diarrhoeal illness as well as collateral studies on dengue fever.

Implementation of the Peru cohort project has taught us several important lessons:

i) To assess risk factors, risk factor data must be collected from all individuals in the cohort as frequently as possible.

ii) Having well-trained, proactive field workers is extremely important, since study participants count on a regular and positive interaction with field workers to continue to enrol.
iii) Data management is by far the most challenging issue because an intensive cohort study generates huge amounts of information requiring a detailed and intensive data management plan.

Conclusion

We recognize that the large amount of work and money required to mount population-based active surveillance cohort studies – this study in Peru, for example, cost approximately 100 000 United States dollars annually per site – may prevent them from being carried out. To our knowledge, influenza surveillance efforts similar to the one described in this paper have been undertaken only in a few developing countries, including Bangladesh, Guatemala, India, Kenya and Nicaragua.[7–11] However, cohort studies with active household surveillance and specimen collection generate data that are critical to understanding the epidemiologic distribution and behaviour of respiratory pathogens, including influenza viruses, and to detect disease of all degrees of severity in the early stages of a pandemic. Mustering the resources to include this valuable complement to passive surveillance systems should be a priority. Collaboration between developing countries and those with greater resources to dedicate to public health research, as exemplified by our project in Peru, is probably the most viable strategy for achieving this. ■

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