Incidence, clinical features, and epidemiology of infection with influenza in health care workers and other healthy adults in Canada (Influenza Cohort Study)

Synopsis

(a) Research objectives

The objective of this study is to determine if health care workers (HCW) are at increased risk for illness due to influenza relative to other working adults, and to identify whether our current paradigm for exposure risk in acute care hospitals is accurate. Specifically, the primary hypotheses are: 1) hospital-based HCWs are more likely to develop influenza than other working healthy adults; and 2) within a cohort of hospital-based HCWs, those who care for patients with acute respiratory infections, those who work in high risk areas (emergency departments, intensive care units, and adult/paediatric medical inpatient units), and those who routinely perform procedures in which aerosols are generated are more likely to develop influenza than those working in other areas.

(b) Research methods

This will be a 3-year cohort study of adults aged 18-69 years employed full- or part-time either in an acute care hospital or a non healthcare related office workplace. Subjects will be followed for one to three influenza seasons, with the option to continue or withdraw made every September.

A total of 1650 subject-seasons will be recruited, with 1420 subject-seasons (400 in season 1, 495 in each of seasons 2 & 3) from acute care hospitals and 330 subject-seasons (100 in season 1 and 124 in each of seasons 2 & 3) from other employers of office-based workers. Office based workers are defined as non-industrial workers who work primarily indoors, who do not have regular contact with children during a work shift, and whose job does not require frequent, regular contact with the general public. Recruitment strategies will include the employers' intranet sites, information pamphlets using internal mail, postings in work areas, and attachments to pay stubs. The study will be approved by the Research Ethics Committees at participating hospitals and the human resources departments of participating non-hospital employers before initiation.

Eligible persons who provide informed consent will be asked to complete a baseline questionnaire detailing their influenza vaccination history, demographic data, potential work-related risk factors for respiratory virus infection (e.g. work environment, degree of direct contact with patients, infection control practices), and potential community risk factors (e.g. use of public transit, number of household contacts, exposure to children in day care). During each season, subjects will be asked to complete weekly diaries regarding acute respiratory or febrile illnesses, and documenting time-dependent risk factors such as contact with people (patients, coworkers, and family) who have symptoms of an acute respiratory illness (ARI). Weekly diaries will also be used to determine patterns of work attendance during ARI. Influenza incidence will be measured by asking subjects to provide a nasal swab (either self collected or collected by a study nurse) if they develop any symptoms suggestive of an ARI. Nasal swabs will be tested by polymerase chain reaction at the study laboratory.

Data will be analyzed following the second and third influenza seasons for the primary outcomes listed below. Incidence will be calculated using person-days of follow-up. Risk factor determination will be analyzed using generalized estimating equations to account for repeated measures.

(c) Intended research outcomes

Primary outcomes: 1) the incidence of symptomatic influenza in HCW and office-based working adults; and 2) workplace exposure risks (working with patients with respiratory symptoms/infections, working in high risk area, performing aerosol generating medical procedures) for influenza in HCW. Secondary outcomes: 1) patterns of work attendance during influenza and other ARI; 2) community risk factors for influenza; 3) factors associated with

attendance at work while ill with influenza or other ARI; 4) number of work days lost due to influenza, and 5) influenza vaccine effectiveness. An exploratory analysis of workplace risk factors other than exposure risk for acute care hospital workers will also be conducted.

(d) Relevance

The proposed study will be the first to compare rates of symptomatic influenza in acute care health care workers and other adults. Knowing whether working in an acute care hospital increases a person's risk of influenza infection is important to workers, employers, and health and safety experts, in that it informs recommendations about the particular importance of vaccination or other protective measures for healthcare workers. It will also support decisions about whether, in situations of vaccine shortage (e.g. pandemics), healthcare workers should have priority over other essential service providers for early vaccine or antiviral prophylaxis.

The proposed study will also benefit healthcare workers and their employers by improving our understanding of the relationship between exposure to influenza in the workplace and the incidence of influenza. We are primarily interested in environmental variables that experts believe are associated with increased risk of infection because of increased exposure to influenza. These include the department an employee works in (e.g. emergency department or intensive care unit), whether they provide direct care to patients with influenza, and the nature and frequency of potential high risk exposures (e.g. intubation). Whether these exposure factors are associated with influenza infection will be interpreted after adjusting for other potential infection risks including having children at home, using public transit, being vaccinated against influenza, smoking, having asthma, what types of patients are cared for, how many patients they see in a day, what their self-reported adherence to infection control practices is, and how they perceive their hospital's commitment to worker safety. In so doing, the study may be able to inform healthcare workers and employers about whether the risk(s) can be mitigated through education and training, the provision of personal protective equipment, or the institution of new or the enforcement of existing policies and practices.

The study will also investigate the attendance patterns of workers during episodes of influenza and other acute respiratory illnesses. This information will be valuable as it will provide an accurate estimate of the number of hours of work loss due to influenza and other acute respiratory illnesses. Documenting the degree of presenteeism associated with acute respiratory illnesses, and risk factors for presenteeism, may assist in estimating the risk of transmission of infections to patients and coworkers, and help staff and management understand the importance of legitimate absenteeism. Understanding rates of both absenteeism and presenteeism due to influenza should inform on-going discussions about best practice recommendations for work restriction of healthcare workers with ARI. Finally, the documentation of community risk factors for influenza may assist pandemic planners in understanding which population groups of adults will be at highest risk of infection during the next influenza pandemic, and may provide some guidance on how their risks may be mitigated.

(e) Research transfer

The results of this research will be of interest to a variety of practitioners and workplaces. Although infection control and occupational health practitioners may find them of particular interest, front line care providers, their managers, the administrative officers of facilities responsible for the health and well-being of workers and patients, and decision makers at provincial and federal levels will also be engaged.

The investigators involved in this project bring together the expertise as well as the linkages inherent in many specialties. The group comprises infection control practitioners, an emergency room physician, microbiologists, a director of nursing, an epidemiologist, a statistician, and occupational health practitioners. They are members of, or have strong links to the Public Health Agency of Canada, Ontario Provincial Infectious Diseases Advisory Committee (PIDAC), the Ontario Agency of Health Protection and Promotion (OAHPP), the Ontario Safety Association for Community & Healthcare (OSASH), the Community and Hospital Infection Control

Association of Canada (CHICA-Canada), and local, regional, provincial and national pandemic influenza planning committees. They teach medical and nursing students at Ryerson University and the University of Toronto and are active in continuing education for many types of healthcare workers.

A variety of dissemination strategies will be used to share the findings of this research. These include presentations at conferences such as those organized by CHICA-Canada, the Industrial Accident Prevention Association, the Ontario Hospital Association, and the Ontario Regional Infection Control Networks. We will submit manuscripts for publication in the Canadian Medical Association Journal, the Journal of Occupational Medicine, the Health Education Quarterly, and the Canadian Communicable Disease Report. Results will also be disseminated to all study participants and in workplace communications (e.g. Mount Sinai Hospital's "Sinai Scene"). We anticipate providing reports not only to the WSIB, but also to the OAHPP and PIDAC, to the Ontario Hospital Association/Ontario Medical Association working group which maintains the Ontario communicable disease surveillance protocols, and to the Ontario Professional Colleges' infection prevention working groups (the colleges of Nursing, Physicians & Surgeons and Respiratory Therapy all have such working groups) with information directed to how our findings might be incorporated into current provincial infection prevention guidelines. We expect to use this information in our education programs at Ryerson, the University of Toronto, and our teaching hospitals. If there is sufficient interest, we could produce a 20 minute web-based interactive learning module for health care workers about risks for and protection from, influenza.

Background

Influenza is an acute respiratory infection, caused by human influenza viruses of type A, B or C (1). Influenza C causes respiratory illness in young children (2). Influenza C does not evolve rapidly; thus, the majority of humans develop protective antibodies against influenza C early in life, and do not subsequently develop clinical disease (3). In contrast, influenza of types A and B evolve continuously. Thus, protective antibody developed during infection with a particular strain of type A or B influenza in one year does not protect against infection in subsequent years, and humans are re-infected repeatedly over their lifetimes (1,4,5).

Vaccination is our most important defence against human influenza (1,5-8). Because of the evolution of influenza, vaccines must be updated and administered annually to be effective (1,4-8). Although vaccination is a critically important defence against influenza, its benefits are restricted by limited uptake in the population (including healthcare workers) (6,7,9-11), by our limited ability to predict the evolution of influenza and "match" the vaccine to the infecting strain (5-7), and by limited efficacy of the vaccine in the high-risk populations (eg. immunocompromised adults and children) (12-15). Thus, despite the direct benefits of influenza vaccine (13-18), and the fact that influenza vaccine uptake is higher in Ontario than in most other jurisdictions (9-11), seasonal influenza remains the most common infectious disease cause of death in Ontario, estimated to be responsible for 1,500 deaths and more than 25,000 hospitalizations every year (19,20).

The majority of influenza deaths and hospitalizations occur in the elderly (1,19,21). However, deaths and serious illness also occur in children and in healthy young adults. Population-based surveillance for paediatric deaths due to influenza is not currently performed in Canada: in the United States, paediatric deaths due to influenza have been reportable since 2004, with 47, 46, 73 and 87 deaths reported in 2004 to 2007, respectively (22, 23). Although tests for influenza are rarely performed in adults with severe respiratory illness, population based studies suggest that there is a small but non-zero rate of death due to influenza in healthy adults, with an estimated rate of about 1 per million population (21). In keeping with this, in laboratory based surveillance for influenza in Toronto during four influenza seasons from 2004 to 2008, in a population of 2.5M healthy adults aged 16-65 years, influenza has been identified as causing the death of 3 previously healthy adults of working age (youngest 17 years of age) (24, unpublished information, TIBDN surveillance). It is important to note that this surveillance underestimates the true incidence of influenza-related mortality because of the relative lack of diagnostic testing. During the 2006/7 and 2007/8 influenza seasons, a subset of hospitals in this surveillance area performed active surveillance for influenza by systematically testing patients with admission illnesses compatible with influenza during the influenza season. The rate of influenza-associated hospitalization in these hospitals was 6 and 11 fold higher (for medical and ICU admissions, respectively) than the rate in hospitals where influenza testing was as ordered by individual clinicians (25). Healthcare workers are not spared: while we have not identified any deaths in healthcare workers in Toronto in the past four years, a physician working at a teaching hospital in Toronto had a 48 day hospital admission due to influenza in 2007 (and was discharged home on renal dialysis), and a nurse in an acute care hospital has recently died from apparently occupationally acquired MRSA pneumonia complicating influenza (personal communication, Dr. R. Wax and Dr. M Salvadori).

Influenza is a communicable disease, with transmission rates of 15-25% in studies of transmission in households (26-30), and outbreaks being described in many different settings (31-33). Infection in healthy adults is common, but the rate is highly variable from year to year, depending on the virulence of the predominant circulating influenza strains, and their similarity to strains circulating in previous years. Reported annual infection rates over the last forty years (see Appendix A and Figure 1) in unvaccinated healthy adults have ranged from 2.1% to 23%, with a median of 11.5% (34-43). Thirty to fifty percent of influenza infections are associated with influenza like illness (febrile upper respiratory illness of sufficient severity to affect activities of

daily living), another 30-50% are associated with milder upper respiratory illness (a "cold"), and the remainder (15-40%) are asymptomatic (39,42-44).

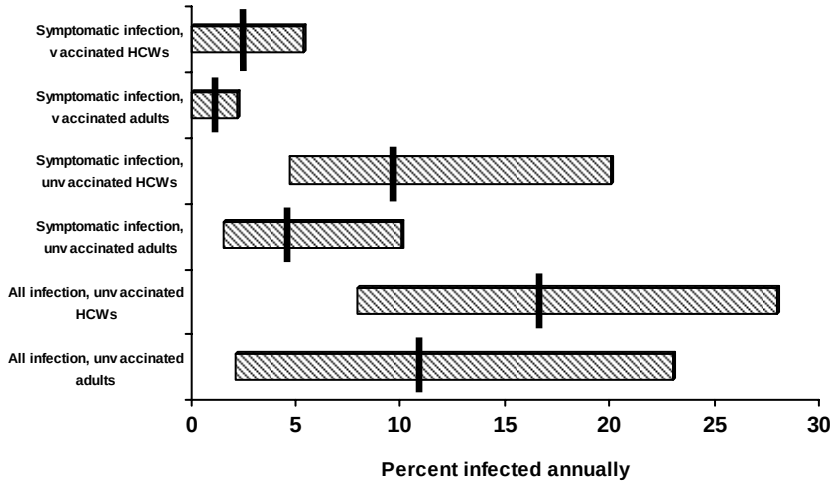
Very few data are available regarding risk factors for influenza infection. Influenza infection is consistently more common in children than in adults (34-37). The incidence of A(H1N1) infections tends to decrease through adulthood at least to some degree (37), but the rate of influenza B infection is similar in different age groups between 20 and 64 years of age (28); no data are available that compare the age-specific attack rate of influenza A(H3N2) in adults. High pre-season neutralizing antibody titres against the infecting strain are known to reduce the incidence of influenza (34-37). The prevalence of such high antibody titres in adults is higher for A(H1N1) than for A(H3N2) and B; it varies from year to year depending on the degree of drift in infecting strains; in most years for A(H3N2) and B, it is <10% (4). Recent previous infection with a similar or related strain also confers some degree of protection, although re-infection may occur (36). Smoking was identified as a risk factor in one study in an outbreak in an Israeli military barrack (38), and exposure to children was identified as a risk factor in a recent study in Germany (43). The only other recognized risk factor for infection in healthy adults is failure to receive influenza vaccine: in healthy adults, influenza vaccine is 55-90% effective in preventing influenza infection, depending on the virulence of the infecting strain, and the degree of match/mismatch between the vaccine and the infecting strain (16,39,40,45-48).

One frequently proposed risk factor for influenza infection is being a healthcare provider (49). Outbreaks in long term care facilities are very common, occurring in as many as 50% of facilities each year (33), and there are also reports of outbreaks of influenza in acute care hospitals (although these are reported much less commonly) (32). Since influenza is transmitted primarily by close contact, and many healthcare workers have close contact with persons ill due to influenza, it is logical to assume that transmission of influenza from patients to healthcare workers poses a significant risk. However, influenza is also very common in the community; children are most often affected, and household transmission is frequent. In addition, the relative contributions to transmission of close contact at home or work, brief close contact in other situations (eg. on the subway), indirect contact via the environment, or longer distance aerosol spread are unknown (50-52). Thus, without evidence, it is not possible to conclude that working in healthcare significantly increases an adult's exposure to influenza or their annual risk of disease.

Currently, evidence of risk of influenza infection associated with healthcare is sparse. Healthcare workers are often affected by influenza outbreaks occurring in hospitals. Apisarnthanarak *et al*. identified three outbreaks in intensive care units in a single hospital in a two year period, involving 18 healthcare workers who appeared to have developed illness after exposure to patients admitted with influenza, and in whom other obvious exposure had not occurred (53). However, infection rates in health care workers without known exposure were not reported. Further, since it is possible that asymptomatic persons can transmit influenza, it is not possible to be confident that disease is due to exposure to ill patients rather than to contacts with other asymptomatic persons. Buxton-Bridges et al., in a study of the 1997 H5N1 outbreak in Hong Kong (54), identified influenza infection in eight (3.7%) of 217 healthcare workers who provided care for infected patients, compared to 2 (0.7%) of 309 control workers (P=.01). During the first wave of the 2009 influenza pandemic, the US CDC reported on 26 infected healthcare providers, 50% of whom were deemed to have been infected in an occupational setting (12 from a patient, and 1 from another healthcare provider) (55). These three studies clearly demonstrate that transmission can occur, but do not prove that cumulative risk over a season is higher in healthcare workers than other adults.

Numerous studies of rates of infection in healthy adults and in healthcare workers have been published (35-50). The results of these studies are summarized in Appendix A and Figure 1.

Figure 1: Reported annual rates of influenza infection in healthcare workers and other healthy adults. Solid black lines represent the median infection rates in all studies; hatched bars illustrate the range of infection rates in different years and studies.



These data suggest that health care workers are at higher risk of influenza infection than other adults. However, there is clearly a great deal of overlap between the groups. Thus, because the rate of influenza infection is so variable year to year, and location to location within a year, it is not possible to be certain that these differences are due to healthcare worker status as opposed to other differences between studies.

A single recently published study has compared rates of influenza infection (by seroconversion) and ILI in healthcare workers and older adults (43). In this study, healthcare workers had higher rates of ILI, and a higher percentage of healthcare workers had antibody to the A(H3N2) influenza strain that had circulated in the previous year, but there was no difference in the proportion of healthcare workers and other workers who had influenza infection, as defined by seroconversion. In this study, the power to detect a 2 fold increase in infection in healthcare workers as compared to other adults was approximately 75%; in addition, 40% of their "healthcare workers" were student nurses; how much patient contact student nurses have was not described.

Another means to approach the question of what the contribution of healthcare provision is to influenza infection is to compare rates of influenza in hospital workers with different types of patient exposure. We identified a single study of this type. Kawana et al. (56) performed active surveillance for febrile respiratory illness in staff and patients of a general hospital in Tokyo over three influenza seasons (2003/4 to 2005/6). Influenza was defined as illness associated with fever (temperature >38°C), respiratory symptoms, and a positive enzyme immunoassay test for influenza. The annual rates of infection by occupational group are shown in Table 1.

Table 1: Rates of influenza infection in staff of the International Medical Centre of Japan, 2003/4 to 2005/6 influenza seasons (ref 56).

Occupational group	Number (%) influenza infections		
	2003-04	2004-05	2005-06
Nurses (N=585)	25 (4.3%)	68 (12%)	35 (6.0%)
Physicians (N=155)	14 (9.0%)	29 (19%)	8 (5.2%)
Laboratory technicians/pharmacists (N=100)	4 (4.0%)	8 (8%)	6 (6.0%)
Administrative personnel (N=80)	0	8 (10%)	0

While this paper also suggests that direct patient care is a risk factor for influenza, there are a number of reasons to question the generalizability of the findings. First, in most studies of adults, enzyme immunoassay tests for influenza have low sensitivity (20-50%), and only a fraction of influenza cases in healthy adults are associated with fever. These two factors suggest that influenza infection rates in this hospital were as high as 50 or 60% in the 2004/5 season, which would be unusual. The hospital is a 925 bed hospital, which, in North America, is a size that would require approximately 5000 staff, compared to the 920 described: it is not clear what the differences might be in patient population or care responsibilities. Finally, the active surveillance describes that a member of the infection control team visited each ward daily and reviewed possible infections with the head nurse; no active surveillance for administrative personnel is described. Thus, infections in administrative personnel may have been missed.

Identifying whether being a healthcare provider in acute care is a risk for influenza infection, and what types of care specifically increase the risk is important for both seasonal and pandemic influenza.. Understanding the quantitative increase in risk of influenza associated with healthcare provision will assist pandemic planners in assessing healthcare worker resource availability, in identifying whether antiviral stockpiles are needed for treatment and/or prophylaxis of healthcare workers, in appropriately prioritizing vaccine and personal protective equipment distribution, and in planning for the protection of the families of healthcare providers from infection from the providers themselves.

Identifying risk for influenza is also important for seasonal influenza. Healthcare workers are theoretically adequately protected by vaccine and routine and additional precautions; however, risk to them may persist for several reasons. Vaccine uptake is sub-optimal (50-60% in Toronto acute care hospital staff; personal communication, Dr. Irene Armstrong, Toronto Public Health), and adherence to routine and additional precautions imperfect (57-59). In addition, routine and additional precautions may be inadequate to prevent transmission. Currently, recommended precautions in most jurisdictions protect against transmission by direct contact (by recommending hand hygiene before and after patient contact, and wearing gloves when providing care), by indirect contact (by recommending hand hygiene before and after environment contact and recommending environmental cleaning/disinfection), and by large droplet (by recommending surgical masks and eye protection when providing care). Expert recommendations also differentiate between the personal protective attire needed to care for patients in usual circumstances and that needed to care for patients when “high risk procedures” (also called “aerosol generating medical procedures”) are performed. Aerosol generating medical procedures have been defined as those thought to be associated with a significantly increased risk of production of droplets and aerosols, and, in many jurisdictions, protection against small particle aerosols is recommended only when such procedures are being undertaken (60-64). There is, however, no empiric evidence that such procedures are associated with increased risk of influenza transmission, and studies of other respiratory infections have not uniformly identified them as important risk factors for disease transmission (65-68). In addition, if transmission of influenza occurs by small droplet inhalation when aerosol generating

procedures are not being performed, or over distances of more than 3-5 feet, or from patients not recognized as having influenza, currently recommended precautions may be inadequate.

This study is focused on identifying whether the current paradigm for risk of influenza exposure – that risk is focused in areas of the hospital the provide the most care for seriously ill patients with influenza, and that transmission risk is highest during aerosol-generating medical procedures – is valid.

Secondary, exploratory analyses may provide supporting evidence regarding modes of transmission of influenza and interventions effective in preventing such transmission. Possible exposure pathways for infection with influenza include hand and finger contact with contaminated surfaces with subsequent touching of the nose, mouth, or eyes; droplet spray directly from an infected person's exhalation (e.g. cough or sneeze) to another person's facial mucous membranes; and inhalation of airborne viruses in respirable or inspirable particles (1,5,6, 50-52, 69-73). The relative contribution of these different pathways is unknown, and expert opinion in this area is divided (69-73). Transmission of influenza during the provision of health care may be prevented by adherence to hand hygiene, environmental cleaning, and the use of different types of personal protective equipment: it is not possible at present to identify which of these is most likely to be associated with reductions in the risk of transmission.

Hand hygiene has been recognized for more than 150 years as an effective and cost-effective means of preventing hospital acquired infections and acute respiratory and diarrheal illness in the community (74-79). While it seems evident that increasing hand hygiene adherence would increase protection of healthcare workers from influenza, given that both soap and water and alcohol-based hand rub are effective in reducing the number of viruses on contaminated hands (80), this is not necessarily true. First, in contrast to transmission of other respiratory viruses, transmission of influenza could be predominantly by droplet deposition on the face or by inhalation; hand hygiene may be relatively unimportant. Second, hand hygiene is more important in some circumstances than others: we have previously shown that healthcare workers use their judgment effectively and are more likely to wash/disinfect their hands in circumstances of higher perceived risk (81). Thus currently available hand hygiene measures, even with 100% compliance, may not adequately protect against influenza, and increasing adherence to these measures may not reduce the risk of infection.

There is a paucity of evidence that the use of personal protective equipment such as gowns, gloves, masks, and face shields reduces the rate of influenza infection for HCW (50, 82,83). This may be because the area has not been studied, but may also be because exposure to unidentified cases (such that precautions are not recommended or taken) is as large, or larger than, the risk from recognized cases. Three recent studies suggest that, in community settings, both mask use and hand hygiene may provide some protection from influenza (84-86). However, their results are conflicting, and may not apply to the health care setting. Secondary analysis from this study may assist in a better understanding of the effect of hand hygiene and barrier protection in both the community and the hospital, although it is important to recognize that these analyses will be exploratory.

The ability to study risk factors for influenza in adults has been limited until recently by limitations in diagnostic testing. Identification of influenza during studies can either be done by testing nasopharyngeal swabs during episodes of acute illness, or by repeated serologic testing. The lack of sensitivity of rapid tests (enzyme immunoassays, or direct fluorescent antigen detection) and viral culture in adults (87-90), and the need to for a trained healthcare worker to obtain nasopharyngeal (NP) swabs or aspirates very early in illness are clear disadvantages of diagnosis by NP testing; in addition, this approach will miss asymptomatic or minimally symptomatic infection. The disadvantage of serology is the requirement for multiple blood tests, the limited availability and cost of serologic testing, and the lack of standardization and inter-laboratory reproducibility of serologic tests (90-93).

This study will take advantage of the recent availability of polymerase chain reaction testing, which dramatically improves the yield of testing adults for influenza, and the development by Copan Ltd, in collaboration with McMaster University, of flocked nasal swabs with yields on self-swabbing that approximate those of NP swabs. The yield from single nasal swabs is 84% of that from NP swabs, and the yield from two nasal swabs is equivalent to that from NP swabs (M. Smieja, personal communication). In our pilot studies, nasal swabs and NP swabs had equivalent yields. Participants in this study will be asked to submit two nasal swabs, taken sequentially, in the same vial of viral transport media. PCR testing in the presence of acute respiratory symptoms detects only symptomatic influenza infection; nonetheless, it is more valid to accept the misclassification of patients who are asymptomatically infected as not infected (anticipated misclassification rate 1-10%), than to accept potential misclassification of patients who have a measured rise in antibody titre that may not be reproducible (91,92; in our 2007/8 pilot study, testing of three patients with asymptomatic infection diagnosed in one national reference laboratory in a second national reference laboratory failed to confirm infection in 2/3 patients).

This study will also collect data on the burden of illness associated with influenza and acute respiratory illness, and on the rate of absenteeism due to influenza and acute respiratory illness in healthcare workers compared to other working adults. We will compare rates of presenteeism in the hospital workplace relative to their office-based counterparts, and examine risk factors for presenteeism in healthcare workers. Several studies have documented very high rates of presenteeism in health care (94-97), compatible with our pilot data that 86% of healthcare workers with influenza worked on the first and second days of their symptoms. However, few studies have examined the epidemiology of presenteeism. More information about presenteesim is particularly important in healthcare, because ill workers not only reduce productivity and pose a risk to other workers, they also pose a risk to the patients they care for.

In sum, this study will measure the incidence of symptomatic influenza infection in healthcare workers, and workers in office-based non-healthcare settings. Within the group of healthcare workers, we will ask whether currently accepted exposure risk factors for influenza are an effective way to differentiate healthcare workers at higher risk of exposure to and infection with influenza. Secondary analyses will explore community risk factors for influenza, and the epidemiology of presenteeism associated with acute respiratory illness.

Pilot studies/progress to date

During the 2007/8 and 2008/9 influenza seasons, 56 and 64 adults at Mount Sinai Hospital were recruited to pilot studies for this proposal; 765 healthcare workers were recruited to a study of pandemic influenza in 2009. Relevant elements of these pilot studies include:

(i) feasibility of recruitment: at a single hospital site, we recruited 49 and 64 HCWs in two consecutive years on very short timelines (study approvals/funding confirmed in mid-October in both years); between the first and second wave of the pandemic, we recruited 765 HCWs, from 5 hospital sites over a 16-week period for surveillance during the second wave of the 2009 pandemic (531 have agreed to be contacted for future studies).

(ii) the development of a web-based system for study forms and diaries, email reminders and real-time analysis that allows participants to easily and securely complete regular study diaries on the internet, and study staff to easily and in a timely manner check that diaries are complete; this year to date, diary completion has been >95% within 2 days of due dates;

(iii) establishing both the importance of obtaining lab specimens early in illness, and the processes that ensure that nasal swabs can be obtained within 48 hours of the onset of illness; in the year 2 pilot, 96% of episodes that required an nasal swab have had a nasal swab submitted, and 92% of nasal swabs were obtained within 48 hours of symptom onset;

(iv) assessment of the sensitivity and specificity of nasal swabs obtained early in illness compared to serologic testing for influenza infection. As expected, PCR is highly specific for

infection; pilot work is continuing (and data from other studies are pending – see below) to establish that, with nasal swabs obtained early and for all (including mild) illnesses, PCR will also be >85% sensitive for influenza.
(v) the establishment of reproducibility in HCW responses to questions about potential risk of influenza: within the pilot, agreement among HCW participants asked questions about weekly duration of exposure to high risk wards, exposure to patients with acute respiratory illness, and exposure to high risk procedures (those likely to produce aerosols) were good (Kappa>.8).
(vi) estimation of the proportion of healthcare workers developing influenza: 15% (7/47) HCWs were diagnosed with influenza in the first year (active year, with a substantial antigenic mismatch), and 5% (3/60) in year 2 (a much milder season). During the second wave of the pandemic, 15 of 765 (2.0%) of HCWs had symptomatic influenza infection. Serology testing is slated for August or September 2010.

Study Objectives

The primary objectives of this research are to determine whether health care workers (HCW) who work in acute care hospitals are at increased risk for illness due to influenza relative to other healthy adults and to identify whether our current paradigm for exposure risk in acute care hospitals is accurate.

The primary hypotheses are:

1) hospital-based healthcare workers are more likely to develop influenza than office-based workers, and

2) within a cohort of hospital-based healthcare workers, those who care for patients with acute respiratory symptoms and/or acute respiratory infections, those who work in high risk areas (emergency departments, intensive care units, and adult or paediatric medical inpatient units), and those who routinely perform aerosol-generating procedures are more likely to develop influenza.

METHODS

Study population

This project is a 3-year prospective study following a cohort of HCWs who work in an acute care setting and other adults working in non-healthcare-related settings. Each subject will be followed for one to three influenza (winter) seasons (2010-11 to 2012-13).

Healthcare workers will be recruited at the Mount Sinai Hospital (N=4392 employees/ physicians/ midwives), North York General Hospital (N=4092 employees/physicians/ midwives), St. Michael's Hospital (N=5725 employees/physicians/midwives), Sunnybrook Health Sciences Center (N~6200 employees/physicians/midwives), and the University Health Network (N~12000 employees/physicians /midwives). Non-healthcare workers will be recruited from several large Toronto employers. These include non-healthcare employees of the Ontario Agency for Health Protection and promotion (N~150 employees on-site at 500 University Avenue and at 81 Resources Road; see letter of collaboration: 45 workers enrolled in pandemic study), MaRS and its incubator companies (N~200 staff, at the corner of College and University Avenue; see letter of collaboration); the head offices of the Ontario Power Generation Corporation (18 workers enrolled in pandemic study) and Scotia Bank offices in Toronto (see letter of collaboration; 139 workers enrolled in pandemic study). In addition, employees and alumni/ae of the University of Toronto and Ryerson will be recruited through postings at these universities, advertisements in the University of Toronto bulletin, and the University of Toronto alumni magazine (165 workers at the U of T, and 27 at Ryerson have enrolled in the pandemic study).

Inclusion criteria:

1) 18 to 69 years old, inclusive, as of September 1st on the year of enrolment;
2) understand the study, agree to its provisions, and give written informed consent prior to entry;
3) available for follow-up during the study period;
4) have convenient access to a computer with internet access and basic skills for use of the internet;
5) if a healthcare worker: employed full- or part-time (>20 hours per week) by an acute care hospital, or, if a physician or midwife, working at least 20 hours per week OR
6) if not a healthcare worker: employed full or part time (>20 hrs per week) in an office environment in Toronto, without exposure to the general public or children when at work.

*Exclusion criteria***:**

1) planning to spend more than two consecutive weeks outside of Canada during the winter study period (November 15th to April 15th);
2) received immunoglobulin within six months of study entry;
3) planning to take leave from work for more than two consecutive weeks during the winter study period (e.g. maternity or medical leave);
4) participating in a trial that would result in the receipt of investigational medication during the study period;
5) attending school or university with a full-time course load (>3 courses or equivalent);
6) living in a communal setting (defined as a dormitory, or other living arrangement with more than five unrelated adults/children sharing eating or living quarters); and
7) for non-healthcare workers, regularly exposed to children and/or the general public at work.

Subjects will be enrolled whether or not they receive their influenza vaccine. The use of prescription, over-the-counter, and natural/herbal remedies, including antiviral medications for treatment or prophylaxis for influenza, is permitted.

Ethics review and approval

The study will be submitted for review by the Research Ethics Committees at all participating hospitals, Ryerson University, and the University of Toronto. It will also be approved by the human resource departments of all participating non-healthcare employers before initiation of the study. Informed consent will be obtained from each participant before each winter season. Participants may withdraw their consent to participate at any time without prejudice.

Study recruitment

Recruitment will occur from July to October of each year of the study. Strategies will include information posted on the employers' intranet sites, information pamphlets sent using internal mail, postings in work areas, notices in newsletters, and (if possible) attachments to pay stubs. Study nurses and assistants will also set up information booths and provide information sessions at participating workplaces.

Targeted recruitment of healthcare workers will be used to ensure that 30% of healthcare workers enrolled work directly with patients with acute respiratory symptoms and/or infections, 30% work high risk wards (e.g. ICU, emergency), and 20% perform or assist with procedures that generate droplets/aerosols (e.g. intubation). Short information sessions about the study will be provided at staff meetings in high risk units, pamphlets will be distributed to internal mailboxes in those areas, and notices will be posted in staff lounges and in communications books.

Study results will be posted, and emailed to all participants in the summer after each season, in order to support continued interest. In July or August, subjects who completed the study requirements for the previous season will be emailed, personally, to invite their participation in the following season.

Study procedures

At the initial study visit, subjects will have the study procedures described to them, have their questions answered, and will be asked for consent to participate. Of note, they will be informed that, since influenza is a reportable disease, their local Medical Officer of Health will be informed of each case of influenza identified. They will have their choice of permitting the study to provide information about their illness to the public health department or having the study pass on their contact information. Healthcare workers will also be informed that current recommendations suggest that they not work in the first few days of an influenza illness, and that the study will be recommending that they report their illness to their occupational health department if they are diagnosed with influenza and due to work. Potential participants may enrol at the first visit or return at a later date if they need time to think about participation.

Following consent and explanation of the study procedures, subjects will be asked to complete a baseline demographic questionnaire on-line, asking about personal, household, and work characteristics that may be associated with risk of influenza. They will be given a study package containing 1) a copy of the informed consent; 2) study contact information; 3) study definitions (e.g. what is an acute respiratory illness that requires reporting? what procedures are included in those generating aerosols); 4) instructions for completing diaries and other study forms, and 4) a nasal swab kit (including four swabs, two tubes of viral transport media, instructions for taking the swab, labelling the tube, and completing the requisition, and a pre-addressed, stamped padded envelope in case their nasal swab needs to dropped off for pickup). They will be shown how to do their own nasal swab and practice doing their own swab in the presence of the study nurse/research associate (pictorial instructions are also available on the study website).

An email will be sent to each participant within one week of their enrolment to welcome them to the study, provide an electronic record of the study's website address (for data entry) and the study email address and telephone number, and ask if they have any questions related to their participation..

Subjects will be asked to complete weekly diaries using web-based data entry. The first diary will be due to be completed on the first Monday after November 1st. Diaries will then be due weekly until the last Monday before April 15th. The weekly diary collects information regarding potential symptoms of respiratory illness. An email will be sent to each participant every Monday morning during the season, providing information about influenza, the influenza season, or the study, and reminding the participant to complete their weekly diary, and report and send in a nasal swab if they have any symptoms of an acute respiratory illness. Reminder emails will be sent 2 days later if the weekly form remains incomplete. Once every 4 weeks, a draw for a $25 gift certificate will be held for participants who completed all diaries within two days of the due date.

Once every three weeks (the particular week for each participant will be randomly assigned), participants who report no acute respiratory symptoms will have additional questions asked on the weekly survey regarding hours worked in the previous week, and household and workplace contacts with persons with acute respiratory illness.

A separate vaccination questionnaire will be posted on the website (simply asking date of vaccination). Participants will be reminded to complete this questionnaire once vaccine is available; those who have not completed it by February will receive additional reminders.

If a participant develops symptoms compatible with an acute viral respiratory illness (i.e. fever without another obvious source, or any new acute respiratory symptom: runny or stuffy nose, sneezing, sore or scratchy throat, hoarseness, or cough), they will be asked to:
(i) collect and submit a double nasal swab as soon as possible after the onset of symptoms. Participants may take their own swabs, or have swabs taken by study staff. Swabs will be either dropped off at the study office in each hospital/workplace, or other arrangements made with

study staff to have it picked up. All swabs will be sent, coded, to the Ontario Public Health Laboratory to be tested for influenza infection using polymerase chain reaction;
(ii) inform the study office by email of their illness;
(iii) register on the study website that they have a potential illness. This action will trigger them to complete the exposure questions from the q3weekly forms for the 7 days prior to their onset of symptoms, and to complete an illness diary, starting the day of symptom onset and ending on when all symptoms are either absent or mild, or for 2 days, whichever is longer.

Study staff will check that exposure and illness information forms are started for each nasal swab that is submitted, and that nasal swabs are received for each registered illness. If either nasal swab or information are missing, the participant will be reminded by email, and then by telephone, to complete the forms or submit the nasal swab.

The laboratory will fax or call test results to the study staff, with original forms following by post. All subjects will be informed of the results of their nasal swab on the day the results are received: those with a positive result will be contacted by telephone while those with a negative result will be contacted by email. Since influenza infection is a reportable disease in the province of Ontario, positive results will be reported to the local Medical Officer of Health. Treatment for influenza will be discussed with each infected participant by a physician investigator, with the AMMI and IDSA recommendations for treatment being followed.

Sample size

As noted previously, the rate of influenza infection varies substantially from year to year. It is not predictable prior to the season, so that it is not possible to run studies specifically in years in which infection rates are expected to be high. For this reason, this study will extend over three influenza seasons.

We assume, based on our pilot data, that 70% of HCW participants will be vaccinated (vaccination rates are approximately 45% in healthy adults in Ontario, and 50-60% in health care workers, but we believe it likely that people who accept vaccine may be more likely to enrol in this study than those who do not; in the 120 recruits to our randomized controlled trials of antiviral prophylaxis versus vaccine, 72% received vaccine in the previous year). Based on the data presented in Figure 1 and Appendix A of the study background, the annual rate of symptomatic infection in non-healthcare workers with a 40:60 ratio of vaccinated to unvaccinated would be expected to be 0.9-6.8%; and the rate in healthcare workers with a 70:30 ratio would be expected to be 2.5-10%.

We have selected a sample size of 1650 evaluable “person-seasons” of follow-up, at a ratio of 4 healthcare worker (1320 seasons): 1 non-healthcare worker (330 seasons). Including an expected 5% within season rate of loss to follow-up, we plan to recruit 400 healthcare and 100 non-healthcare workers in season one (due to the short period of recruitment available), and 495 healthcare workers and 124 non-HCWs In each of seasons 2 and 3, for a total of 1390 HCWs and 348 non-HCWs. The ratio of 4 HCWs to 1 office worker has been selected to maximize the sample size to detect workplace risk factors in healthcare while still permitting the primary comparison of infections in healthcare vs. non-healthcare workers.

The loss of power associated with repeated measures in workers enrolled in more than one season is difficult to predict, given that it depends on variation in predominant strains from year to year, the rate of evolution of viruses, and the degree of year to year retention in the study; we have increase the estimated required sample size by 15% to account for this.

Table 1 below illustrates the size of risk associated with healthcare that can be detected with a significance level of 0.05, and a power of 80%, using our selected sample size, at different baseline rates of non-HCW influenza infection. Given that

(i) the lowest estimated annual rate of ILI adults (given 40% vaccinated) from previous studies is 0.9%,

(ii) it is unusual to have two consecutive seasons of low influenza activity (low activity seasons occur once every 8-10 years)
(iii) we expect to detect a higher rate of infection than previous studies, because we are going to be testing not only ILI, but also milder forms of disease,

we believe that our sample size of 1650 seasons will allow us to detect and label as statistically significant a relative risk of infection associated with healthcare work of approximately 2.

Table 1: Risk associated with healthcare work that can detected and labelled as significant with defined sample size, given a 4:1 ratio of health care workers to others

Community-based influenza infection rate (3-year average)	Number of healthcare worker seasons (3-year total)	Number of non-healthcare worker seasons (3-year total)	Detectable relative risk associated with healthcare work
1.0%	1320	330	3.76
1.5%	1320	330	3.07
2.0%	1320	330	2.69
2.5%	1320	330	2.46
3.0%	1320	330	2.29
3.5%	1320	330	2.16
4.0%	1320	330	2.07
4.5%	1320	330	1.99
5.0%	1320	330	1.92

Given the selected sample size for the primary outcome, Table 2 demonstrates that we will be able, in the secondary analysis, to detect and label as statistically significant a relative risk between 2.0 and 3.0 for risk of infection for healthcare workers who are exposed high risk procedures (those that generate aerosols/droplets).

Table 2: Ability to detect risk of influenza associated with exposure to high risk procedures among HCWs, with 1320 HCW seasons of exposure.

% of HCWs exposed to high risk procedures	% of low risk HCWs with influenza per season	% of high risk HCWs with influenza per season	Relative risk of developing influenza in high risk HCWs	Number of HCW seasons required
30%	2%	5.2%	2.7	1307
30%	4%	8.1%	2.1	1327
20%	2%	5.7%	3.0	1325
20%	4%	8.8%	2.3	1300

Analysis

We will initially conduct descriptive analysis of the baseline characteristics of the study population, their episodes of acute respiratory illness, and their nasal swab test results. Tabular analysis will be used to ensure that data are internally consistent (eg. homes with children in daycare should record children <5 years as household contacts), to identify variables for which missing data exist and determine whether these data need to be collected or can be imputed, and to identify whether presumptively independent variables intended for use in the model are related to each other, and how to account for this in the analysis.

Using our outcome (lab-confirmed influenza infection), we will then perform univariable analysis for baseline and weekly diary risk factor information. These associations will be used to determine which variables should be included in the multivariable analyses. Multivariable GEE logistic regression modelling will then ask whether the proportion of participants developing symptomatic influenza is greater in HCWs than other adults, adjusted for potential covariates. The model structure, with proposed covariates, is shown in Figure 1.

For this primary analysis, the potential covariates and mediators will only be of interest insofar as they alter the relationship between the primary predictors and the outcome. Because influenza may occur in outbreaks (although this is rarely described in office workplaces or acute care hospitals), and this may skew the results, this analysis will be repeated, but with any cases due to workplace outbreaks removed. For this analysis, cases will be defined as outbreak-associated if the participant reports that they were part of an outbreak, and an outbreak was reported at their workplace as being on-going during at the time of onset of their infection. (Toronto Public Health outbreak locations are posted and available to infection control departments routinely).

The secondary analysis will have similar structure, and will compare subsets of HCWs to determine if HCWs providing direct care for patients with acute respiratory illness, those working in high risk areas and those who perform/assist with aerosol generating medical procedures on acutely ill patients have an increased risk of influenza. Initial analysis will be used to confirm the hypothesis that these exposure risk factors are ordered: all workers who regularly perform/assist with aerosol-generating medical procedures in patients with acute respiratory illness also work in high risk areas and (by definition) provide care to such patients, and all workers who work in high risk areas also provide care to patients with acute respiratory illness. The analytic approach will then ask if each of the potential predictors, in sequence, increases the risk of influenza, using univariable, then GEE multivariable, analysis. The model for the multivariable analysis is shown in Figure 2.

Figure 1: Theorized relationship between the risk of influenza and HCW status

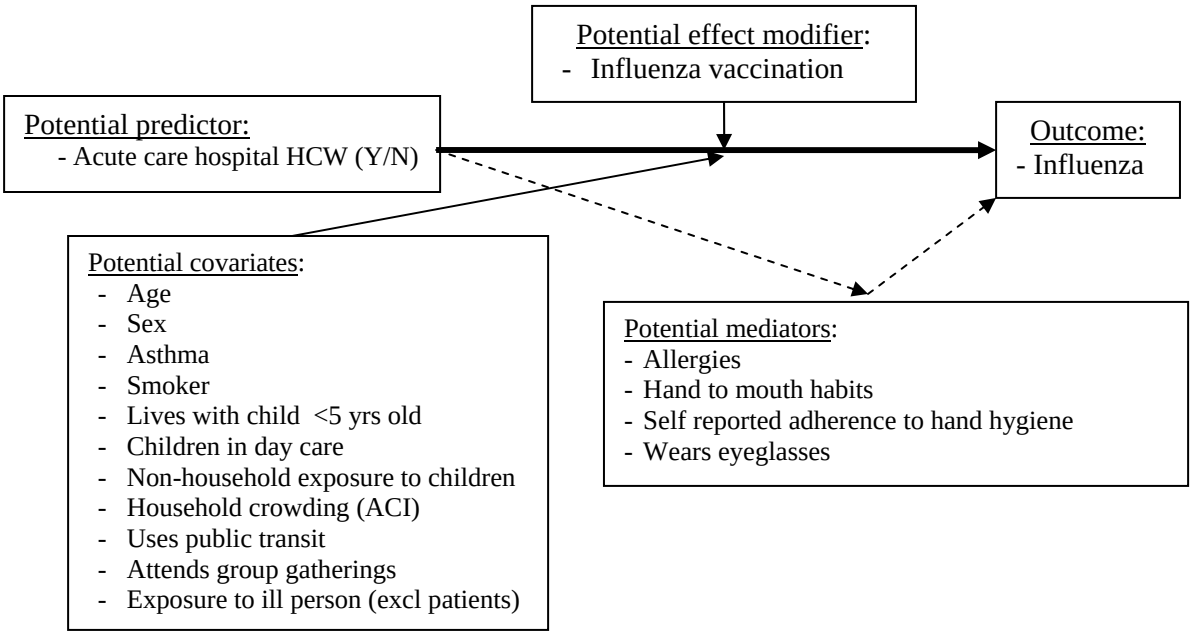
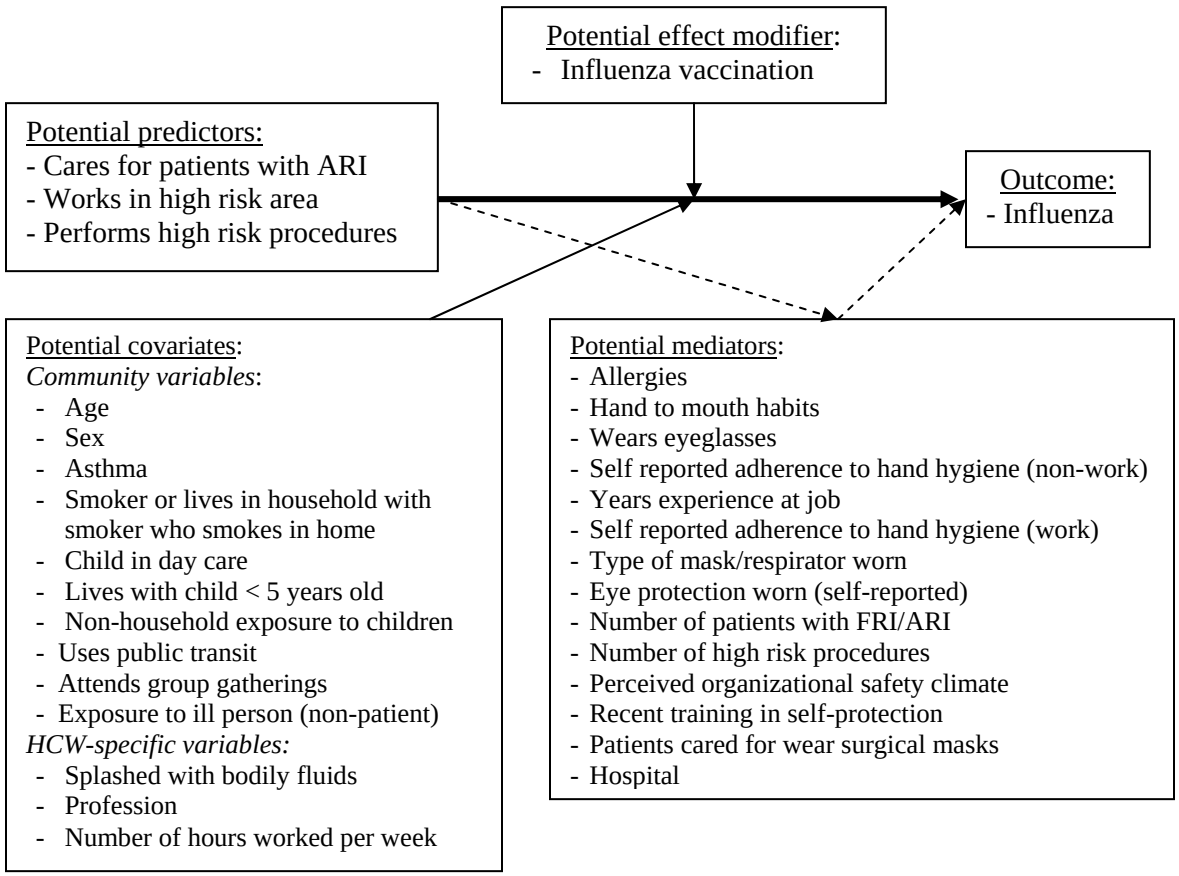


Figure 2: Theorized relationship between the risk of illness caused by influenza, HCW status, and other study variables.



These initial analyses are intended to ask if simple and easily applied criteria can be used to identify groups of adults and groups of health care workers at higher risk of influenza than others. However, risk factors for influenza have not previously been well-studied in either adults in general or healthcare workers, and much more detailed knowledge is needed to understand risks for influenza, and what interventions might best protect adults in the community and healthcare workers at work. Thus, the next secondary analysis will be an exploratory analysis to define these risk factors, using a broader range of variables from the questionnaires such that they can be validated in future studies.

Subequently, other exploratory analyses will include:

(i) The proportions of HCW and other adults who lost any days of work due to influenza, compared using a two sample test of proportions;

(ii) Pattern of work attendance (proportion of participants attending work by day of illness report), compared between HCW and non-HCW with two sample tests of proportions for each of the first four days of illness;

(iii) a descriptive analysis of workplace presenteeism due to acute respiratory illness in health care workers and other healthy adults.

(iv) If the sample size permits, logistic regression models will be used to identify predictors of attending work with moderate or severe symptoms of infection. Covariates of interest in this model will include age, sex, profession, years of work experience, and influenza vaccination in current season.

(v) If sample size permits, poisson regression models will be used to identify predictors of influenza infection in non-HCW adults. The dependent variable is infection with influenza (yes/no) with the potential effect modifier (vaccination in current season: yes/no), and potential community covariates (as listed in Figure 2 and defined in primary analysis).

(vi) assessment of Influenza vaccine effectiveness, calculated separately for each influenza season and as a summary for the three-season study period. Vaccine effectiveness is calculated as 1 minus the relative risk (attack rate in vaccinated divided by attack rate in unvaccinated). If the number of influenza cases is large enough, we will conduct a sensitivity analysis based on the published sensitivity and specificity of PCR and culture laboratory tests.

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Study Timeline