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Original Article

Respiratory illnesses in Canadian health care workers: a pilot study of influenza vaccine and oseltamivir prophylaxis during the 2007/2008 influenza season

Brenda L. Coleman,[a,b,c] Andrea K. Boggild,[a,b,d] Steven J. Drews,[c,e] Yan Li,[f] Donald E. Low,[a,b,g] Allison J. McGeer[a,b]

[a]Mount Sinai Hospital, Toronto, ON, Canada. [b]University of Toronto, Toronto, ON, Canada. [c]University of Calgary, Calgary, AB, Canada. [d]Tropical Disease Unit, UHN-Toronto General Hospital, Toronto, ON, Canada. [e]ProvLab, Calgary, AB, Canada. [f]National Microbiology Laboratory, Winnipeg, MB, Canada. [g]Ontario Agency for Health Protection and Promotion, Toronto, ON, Canada.
Correspondence: Dr. Andrea K. Boggild, Tropical Disease Unit, Toronto General Hospital, 200 Elizabeth Street, North Wing, Room 1350, Toronto, ON M5G 1C4, Canada. E-mail: andrea.boggild@utoronto.ca

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Background Data regarding both rates of acute respiratory illness in health care workers and experience with long-term antiviral prophylaxis are sparse.

Objective To determine the efficacy and tolerability of oseltamivir prophylaxis versus seasonal influenza vaccine for the prevention of influenza among health care workers.

Methods We conducted a pilot, randomized control study during the 2007/2008 influenza season in a tertiary care setting. Adult health care workers 18–69 years of age were recruited and randomly assigned in a 4:1 ratio to receive either oseltamivir (Tamiflu®; Roche) 75 mg once daily prophylaxis or seasonal influenza (Fluviral®) vaccine.

Results Of 56 adults enrolled, 12 received vaccine and 44 received prophylaxis. Incidence of symptomatic laboratory-confirmed influenza was similar for participants in the vaccine and prophylaxis arms (17% and 24%, respectively; $P = 0{\cdot}71$). Participants who developed an acute respiratory illness during the study period reported working 85% of scheduled work days, and 29% stated that they worked despite feeling miserable because they were too busy to stay home. Of 42 participants who initiated oseltamivir prophylaxis, four discontinued it owing to side effects. Median duration of oseltamivir prophylaxis was 121 days, with 34 (81%) continuing ≥12 weeks.

Conclusions During an extended season of suboptimal vaccine match, 22% of health care workers receiving antiviral prophylaxis or seasonal influenza vaccine developed symptomatic laboratory-confirmed influenza. Long-term antiviral prophylaxis against influenza was generally well tolerated with good compliance.

Keywords Acute respiratory illness, health care worker, influenza, influenza vaccine, neuraminidase inhibitors, oseltamivir.

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Introduction

Influenza is a highly communicable disease with annual infection rates in unvaccinated healthy adults ranging from 2% to 23%.[1–3] Annual influenza vaccine offers the best available protection against influenza, but its effectiveness is limited by poor uptake among some populations (including health care workers),[4–7] by our limited ability to predict influenza evolution and match the vaccine to the infecting strain,[4,5] by limited efficacy of the vaccine in vulnerable populations[8,9] and by the time required to produce vaccine in the event of a pandemic.[10] Antivirals have also been shown to be efficacious in preventing influenza,[11,12] but experience with prolonged prophylactic use is limited.

This pilot study was intended to determine the rate of acute respiratory illness in working adults who received either influenza vaccine or antiviral prophylaxis and to assess the proportion of people who worked during acute respiratory illness. We also describe the tolerability, adherence and rate of influenza infection in participants receiving antiviral prophylaxis for a full influenza season.

Methods

Study participants

In October 2007, 56 adult employees or students aged 18–69 years responded to advertisements at our 472-bed hospital and agreed to participate in this study. We excluded

participants who: had a contraindication to influenza vaccine or oseltamivir; had received influenza vaccine or immunoglobulin within 6 months of study entry; expected to be unable to take oral oseltamivir for more than 72 hours or were planning to be >100 km from the study site for >2 consecutive weeks during the study period; were pregnant, breastfeeding or planning to become pregnant; had an immunosuppressive condition or a history of cardiovascular or pulmonary disease requiring prior hospitalization; or were participating in another trial requiring the administration of an investigational medication. This pilot study was approved by Health Canada and the research ethics board of Mount Sinai Hospital.

Allocation and concealment

Using proc ranuni in SAS (SAS Institute, Cary, NC, USA), participants were randomly assigned, at a ratio of 4:1, to receive either prophylaxis with oseltamivir during the influenza season or the 2007/2008 Fluviral® vaccine (GlaxoSmithKline Inc., Mississauga, Ontario, Canada). Participants and investigators were not blinded.

Study procedures

At enrolment, vaccine was administered to participants randomized to the vaccination arm. Participants randomized to the antiviral group were contacted at the onset of influenza season (definition: ≥2·5% of specimens submitted to the Ontario Provincial Public Health Laboratory for influenza testing positive for two consecutive weeks). They were prescribed oseltamivir, 75 mg once daily, until the end of the influenza season (protocol definition: <2·0% specimens positive for two consecutive weeks). The study proposal called for participants to receive prophylaxis for a maximum of 13 weeks. However, the 2007/2008 influenza season was longer than anticipated, and there was significant antigenic mismatch between the circulating strains of influenza and the vaccine. At 13 weeks, study participants randomized to oseltamivir were given the option of continuing prophylaxis, discontinuing oseltamivir and being vaccinated, or discontinuing prophylaxis without vaccination. Study participants randomized to vaccine were given the option of starting prophylaxis.

Data collection

Questionnaire-based personal, household and work-related data were collected at enrolment. Participants completed weekly diaries regarding symptoms of and contact with respiratory illness from enrolment until 2 weeks after the end of influenza season.

Illness diaries were started if the subject had either a fever or the acute onset of two or more respiratory symptoms (runny/stuffy nose, sneezing, sore/scratchy throat, hoarseness or cough) and were completed daily until illness resolved. Participants were given a thermometer and asked to take their temperature if they felt feverish and were asked to have a nasopharyngeal (NP) swab taken as soon as possible after the onset of respiratory symptoms. Acute respiratory illness was defined as an acute illness lasting >24 hours associated with either fever and one or more respiratory symptoms, or two respiratory symptoms.

Oseltamivir adherence was estimated by self-report, by pill counts at each visit and by data from electronic medicine vial caps which recorded the date and time each time the cap was replaced.

Laboratory procedures

Nasopharyngeal swabs were tested at the Ontario Public Health Laboratory using in-house polymerase chain reaction (PCR) for the detection of influenza,[13] viral culture and Seeplex® RV12 multiplex PCR.[14] Serum was collected at baseline, 14 days following vaccination (for vaccine group), the beginning of influenza season (antiviral group), midseason (February) and the end of influenza season. Hemagglutination inhibition (HI) assays were conducted at the National Microbiology Laboratory in Winnipeg, Manitoba, for the strains of influenza included in the 2007/2008 influenza vaccine (A/Solomon Islands/03/06, A/Wisconsin/67/05, and B/Malaysia/2506/04) and for the circulating strains A/Brisbane/10/07 and B/Florida/04/06. Influenza infection was defined as a fourfold increase in HI titre between samples other than pre- and post-vaccination. Each serum sample obtained from participants in the antiviral group had liver enzyme testing performed.

Data analysis

Descriptive statistics were performed, and differences were compared using Wilcoxon rank sum tests and Kruskal–Wallis one-way anova for continuous variables and chi-square or Fisher's exact test for categorical variables. Level of significance was set at $P < 0{\cdot}05$; all tests were two-tailed. Owing to small numbers, exact logistic regression was used to determine the association between laboratory-confirmed influenza and independent variables. All statistical calculations were performed using STATA v. 9·2 (StataCorp, College Station, TX, USA).

Results

We enrolled 38 women and 18 men with a median age of 42 years (range: 25–64); 52 (93%) were health care workers and 75% had been vaccinated in the previous year. Forty-four participants were randomized to prophylaxis and 12 to vaccine. Two participants, both in the prophylaxis group and in health care workers, dropped out before starting antiviral prophylaxis and are not included in the remaining analyses. Demographic characteristics of participants are

Table 1. Demographic characteristics of participants randomized to influenza vaccine or oseltamivir prophylaxis for the 2007–2008 influenza season in Toronto, Canada

Demographic variable	Vaccine group *N* = 12 (%*)	Oseltamivir group *N* = 42 (%*)	*P*-value
Median age (range)	41·3 years (25–63 years)	40·6 years (25–64 years)	0·80
Sex			
Female	9 (75)	28 (67)	0·73
Diagnosed with asthma	0	5 (12)	0·58
Current prescription medication	6 (50)	25 (60)	0·50
Influenza vaccine			
Not in past 3 years	0	7 (17)	
1 or 2 years	4 (33)	8 (19)	
All 3 years	8 (67)	25 (60)	0·30
Smoker (current)	1 (8)	9 (21)	0·29
Works in acute care	11 (92)	35 (83)	0·67
Direct patient care	6 (50)	19 (45)	0·77
Works in ED, ICU, or medical unit	7 (58)	16 (38)	0·32
Works with patients with ARI**	9 (75)	22 (52)	0·20
Works with children	1 (8)	1 (2)	0·35
Takes public transit for work or school commute	7 (58)	23 (55)	0·89
Household size			
1 person	2 (17)	6 (14)	
2 people	3 (25)	11 (26)	
3+ people	7 (58)	24 (57)	0·98
Child <2 years in home	2 (17)	1 (2)	0·12
Child in day care in home	3 (25)	5 (12)	0·36

ARI, acute respiratory illness; ED, emergency department; HCW, health care worker; ICU, intensive care unit.
*Of those responding to the question.
**Work that routinely brings the HCW into contact with patients who have ARI during winter cold or influenza season, including those with cough, influenza-like illness or pneumonia.

shown in Table 1. The 2007/2008 influenza season in Toronto was declared on 19 December 2007 and continued for 20 weeks until 10 May 2008.[15]

Of the 42 participants who started oseltamivir prophylaxis, 4 (10%) discontinued before 13 weeks owing to adverse effect, including: nausea (week 1), nausea and malaise (week 3), sleep disturbances (week 4) and headache (week 11). Thirty-nine of 42 participants (95%) reported taking six or seven capsules per week for the first 8 weeks; by week 12, 34 (81%) reported continuing to miss no more than one capsule per week.

At week 13, six (16%) of the 38 participants taking oseltamivir elected to discontinue prophylaxis; two requested vaccination. One of 12 people in the vaccine group elected to start oseltamivir. Thus, 33 participants were receiving prophylaxis as of week 14. By week 16, 26 (79%) of these participants reported taking six or seven capsules per week; by week 20, only 13 (33%) were continuing to report this level of adherence.

Study participants took oseltamivir prophylaxis for 5–155 days (median 121) and took a median of 87·5 capsules per 100 person-days (range 66–100). On average, adherence in those reporting taking any of the medication was higher within the first 10 weeks than in the latter 10 weeks of the study (86 versus 75 pills per 100 person-days of follow-up; $P = 0{\cdot}001$). At the exit interview, self-rated adherence to prophylaxis ranged from 70% to 100% (median 96·5%). There were no significant differences between self-reported adherence and adherence as measured by pill counts or e-cap records. No changes in serum hepatic transaminases were documented for participants taking oseltamivir.

Seventy respiratory illness episodes were reported by 36 of the 54 participants, with zero to seven illnesses reported per person (median 1). Fifty-two NP swabs were submitted by 32 participants, with seven yielding influenza and nine yielding other respiratory viruses (Table 2). Serologic testing confirmed influenza in all seven participants with positive NP swabs, and in an additional five participants. Of these five, four reported an episode of acute respiratory illness for which an NP swab was not submitted during the interval between the two blood samples with seroconversion. The acute respiratory illness rate was 6·4 per 1000 person-days, the influenza infection rate was 1·9 per 1000

Table 2. Serological and NP swab test results for respiratory viruses in study participants randomized to influenza vaccine (*N* = 10) or oseltamivir prophylaxis (*N* = 44) for the 2007–2008 influenza season in Toronto, Canada

		Oseltamivir group (*N*)	
Laboratory test source	Vaccine group (*N**)	Before start of prophylaxis	During time period of prophylaxis
NP swabs	Rhinovirus A (1) RSV A (1) PIV 3 & HCV OC43 (1) Influenza A (1)	RSV A (1) Influenza A (4)	RSV A (1) HCV 229E (3) PIV 2 (1) Influenza B (2)
Serology	Influenza A & B (1)	Influenza A (1)	Influenza A (1) Influenza B (2)

HCV, human coronavirus; NP, nasopharyngeal; PIV, parainfluenza virus; RSV, respiratory syncytial virus.
*Number of positive laboratory tests.

person-days, and the infection rate owing to other respiratory viruses was 0·6 illnesses per 1000 person-days.

Median symptom duration of acute respiratory illness was 6 days (range 1–35). Illness duration was 4 days (range 2–17) in cases of laboratory-confirmed influenza ($n = 7$), 8·5 days (range 1–15) in cases of laboratory-confirmed illness owing to other respiratory viruses and 2 days (range 1–13) in those who reported an illness but did not submit a NP swab ($P = 0·012$).

Participants reported working on 240 of 284 (85%) regularly scheduled work days during their acute respiratory illness, and, on average, each participant missed 0·6 days of work per illness episode. Cumulatively, a total of 4·0 working days per 1000 person-days were lost owing to acute respiratory illnesses. Of 240 days worked during acute respiratory illness, 70 (29%) were days for which employees reported feeling miserable but being too busy to stay home. There was no association between the likelihood of working while ill and the type of virus detected, gender, age, average hours worked per week or profession.

Ten of 42 (24%; 95% CI 12·8, 38·3) participants in the oseltamivir group and 2 of 12 (17%; 95% CI 2·4, 48·4) participants in the vaccine group ($P = 0·71$) were infected with influenza. Five of the ten influenza infections in participants in the oseltamivir group occurred before prophylaxis was initiated (Table 2). No demographic or clinical factors were found to be associated with infection with influenza in this pilot study.

Discussion

Our rate of acute respiratory illness during the 2007/2008 influenza season is similar to that reported by Belgian general practitioners, 53% of whom reported an upper respiratory illness over a 60-day period in each of two winter seasons,[16] and higher than those reported in two recent studies using post-season health care worker recall of infection, in which 35% and 36% of workers reported symptoms of an upper respiratory infection.[17,18] Health care worker recall may be an insensitive means of identifying acute respiratory infection. The relatively busy influenza season of 2007/2008, the vaccine/circulating strain mismatch[19] and the fact that study participants were health care workers may all have contributed to the relatively high influenza attack rate in this cohort.

The infection of several participants in the oseltamivir arm in the 10-day period before influenza season was declared emphasizes both the significance of the approximately 10-day delay in Canada in 2007 between influenza testing and seasonal activity reporting and the fact that a significant number of cases of influenza occur before the season is declared each year.

Rates of gastrointestinal upset owing to oseltamivir in this study were similar to those reported from other studies,[11,20] and in all cases were reported within days of starting oseltamivir. Our participants reported rates of adherence to prophylaxis over a prolonged period that were only slightly lower than those reported in studies of much shorter duration prophylaxis: 92% of people taking once daily doses for 6 weeks took 90% of their pills[20] and 88% of poultry workers took all doses of a 7-day course.[21]

As reported by other studies,[16,17] participants in our study reported working on the great majority of scheduled work days during their acute respiratory illness and almost a third worked despite feeling miserable. These findings support for the need to have hospital and workplace cultures that encourage staying home while ill with respiratory illness.[18,22,23]

This was a pilot study and was not powered to elucidate differences between study arms or to assess risk factors for illness or for adherence to prophylaxis. Participants were primarily healthy adult health care workers, who were willing to accept randomization to vaccine or antiviral prophylaxis, which limits generalizability. In addition, reliance on self-presentation for collection of NP swabs led to some underestimation of illness burden owing to non-influenza respiratory viruses.

Influenza vaccination is less expensive and more convenient than antiviral prophylaxis and does not select for antiviral resistance.[24,25] Nonetheless, our study demonstrates that when vaccination is not available (e.g. during the first wave of a pandemic) or contraindicated, prolonged oseltamivir prophylaxis may be a feasible alternative.

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Conflict of interest

The authors have no conflicts to declare.

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