Comparison of clinical features and outcomes of medically attended influenza A and influenza B in a defined population over four seasons: 2004–2005 through 2007–2008

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Background There are few prospectively collected data comparing illnesses caused by different subtypes of influenza. We compared the clinical presentation and outcomes of subjects with primarily outpatient-attended influenza A and B infections during four consecutive influenza seasons (2004–2005 through 2007–2008).

Methods Patients were prospectively enrolled and tested for influenza following an encounter for acute respiratory illness. Influenza infections were confirmed by culture or reverse transcription polymerase chain reaction; subtype was determined for a sample of influenza A isolates each season. Clinical characteristics of influenza A and B infections were compared across and within individual seasons.

Results We identified 901 cases of influenza A and 284 cases of influenza B; 98% of cases were identified through an outpatient medical encounter. Thirty-six percent of patients with each strain

had received seasonal influenza vaccine prior to illness onset. There were no consistent differences in symptoms associated with influenza A and B. Influenza A infection was associated with earlier care seeking compared with influenza B during the 2005–2006 and 2007–2008 seasons, when H3N2 was the dominant type A virus, and in a combined analysis that included all seasons. Twenty-six (2·2%) of 1185 cases were diagnosed with radiographically confirmed pneumonia, and 59 (5%) of 1185 patients were hospitalized within 30 days of illness onset.

Conclusions Over four influenza seasons, aside from shorter intervals from illness onset to clinical encounter for infections with the A(H3N2) subtype, clinical symptoms and outcomes were similar for patients with predominantly outpatient-attended influenza A and B infections.

Keywords Influenza A, influenza B, comparison.

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Introduction

Influenza is a major cause of acute respiratory illness worldwide and is associated with tens of thousands of deaths in the United States in a typical season.^{1–3} Both influenza A and influenza B viruses circulate in human populations; seasonal epidemics of influenza A have been caused by subtypes H1N1 or H3N2 during the past four decades. Influenza A subtypes and influenza B viruses co-circulate each season, but only one or two variants are typically predominant in a single season. Studies suggest that A(H3N2) seasons are associated with higher pneumonia and influenza-associated mortality compared with A(H1N1) or B seasons.^{4,5}

Little is known regarding the differences in clinical features of influenza A relative to influenza B infection upon presentation for health care. In a small cohort study of seronegative infants and young children in a clinical trial, A(H3N2) infections caused typical febrile respiratory illness while A(H1N1) caused mainly subclinical infections.⁶ Clinical features of influenza A and B were not directly compared. Retrospective studies have suggested that children with influenza B are more likely to have myositis or myalgia, and there have been conflicting results regarding risk of pneumonia by influenza type.^{7,8} A cross-sectional study in which viral cultures were obtained in hospitalized and outpatient pediatric patients over 19 seasons demonstrated that influenza A infections

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than influenza B infections.⁹ Influenza A(H3N2) viruses were recovered significantly more often than influenza B among children with croup in that study.

Many earlier studies comparing clinical features of influenza A and B have focused on pediatric populations, and cases have been identified by physician ordered rapid antigen detection tests or viral culture. Very little is known regarding subtype differences in clinical presentation and severity in adults presenting for care with predominantly uncomplicated influenza infections, and molecular methods of influenza diagnosis provide an opportunity for more complete ascertainment of cases. We conducted a prospective, population-based study to compare the clinical presentation and risk of radiographic pneumonia and hospital admission among patients with medically attended influenza A and influenza B infections during four seasons.

Methods

Study population

This study involved participants in a population-based study to estimate influenza vaccine effectiveness during each of the four influenza seasons, 2004-2005 through 2007-2008.^{10,11} Our sampling cohort was restricted to community-dwelling individuals with at least 12 months continuous residency, or since birth if <1 year of age. Per U.S. Census Bureau and medical record data, this population is approximately 97% non-Hispanic white. Within this population, the electronic medical record captures 90% of outpatient visits, 95% of hospitalizations, and 99% of deaths. During each influenza season, individuals in the sampling cohort were eligible to be enrolled and tested for influenza during or shortly after a medical encounter for acute respiratory illness during the influenza season. For the 2004-2005 season, residents were eligible to be enrolled with acute respiratory illness if they were 6-23 months old or ≥65 years old on November 1, 2004, or if they were 2-64 years old and were diagnosed with a chronic medical condition conferring elevated risk for influenza complications.¹² The latter was determined by the presence of two or more encounters during the previous year with an ICD-9 CM diagnosis code for relevant chronic disease. These included diagnoses in the following chronic disease categories: diabetes mellitus, cardiac, circulatory system, immunosuppressive, liver, malignancies, metabolic, neurological/musculoskeletal, pulmonary, and renal.

Study eligibility evolved over the four seasons in response to changing recommendations for influenza vaccination in children and adults, as the primary purpose of this study was to estimate influenza vaccine effectiveness among those recommended to receive annual vaccinations. For the 2005– 2006 influenza season, eligibility for testing was expanded to include all adults ≥50 years based on new ACIP recommendations for that season.¹³ For the 2006–2007 season, eligibility was further expanded to include all children 6 through 59 months of age based on then-current ACIP recommendations.¹⁴ For the 2007–2008 season, we expanded recruitment to include all patients at least 6 months of age.

Ascertainment of influenza illness

Patients meeting eligibility criteria were recruited by a research coordinator during or after an inpatient or outpatient medical encounter for acute respiratory illness of <8 days duration in the 2007–2008 season or <10 days duration during earlier seasons. The duration of acute respiratory illness was shortened in the 2007–2008 season because potential participants with longer illness duration were unlikely to test positive for influenza.^{15,16} In each season, eligible illnesses included self-reported fever or fever-ishness, chills, or cough.

A nasopharyngeal swab (adults and children \geq 13 years old) or nasal swab (children 6 months to 12 years old) was obtained from all participants.^{17,18} Each participant (or parent) completed a short interview to assess illness symptoms and onset date.

Influenza virus detection and characterization

Viral cultures and real-time reverse transcription polymerase chain reaction (RT-PCR) were performed at the Marshfield Clinic Research Foundation as previously described.¹¹ Culture alone was performed on samples collected in 2004– 2005. A subset of influenza isolates was sent to CDC for subtyping and antigenic characterization each season.

Illness characterization

During the enrollment interview, patients or parents were asked to indicate the presence of the following symptoms at any point in their illness up to the enrollment interview: fever, headache, sore throat, ear pain, nasal congestion, muscle aches, cough, wheezing, fatigue, nausea, and vomiting. The interval from illness onset to the time of medical encounter was used as a measure of acuity. The median time interval from illness onset to the clinical encounter for all patients with influenza was 2 days in the 2004–2005 season and 3 days in the three subsequent seasons. We thus defined early care-seeking behavior as a clinical encounter occurring <3 days after illness onset.

Outcome measures included radiographically confirmed pneumonia and hospital admission occurring within 30 days after illness onset. The proportion of influenza cases with radiographically confirmed pneumonia and/or hospital admission was determined by medical record review. A case of radiographically confirmed pneumonia was defined as a clinically compatible illness in a patient with an infiltrate or opacity on chest X-ray that was not known to be chronic. All pneumonia episodes and hospital admissions were reviewed and validated by a physician (EAB).

Analysis of severity measures

The proportions of influenza A and influenza B cases exhibiting specific symptoms during their illnesses were compared using the exact Pearson chi-square test. The ttest was used to compare the mean interval from illness onset to medical encounter for patients with influenza A versus influenza B. Adjusted means were computed as least squares means derived from linear regression models with terms for age-group, gender, presence of a high-risk condition, and vaccination status. The coefficient weights for the least squares means were set to the observed marginal proportions of the variables listed above. Multivariable logistic regression was used to examine the association between early care-seeking behavior and influenza type with adjustment for the same covariates. Because there were very few partially immunized cases (children with only one vaccine dose when two were recommended), they were excluded from all analyses of the interval from illness onset to medical encounter (to avoid problems when adjusting for vaccination status). Odds ratios and 95% confidence intervals were computed for the occurrence of radiographically confirmed pneumonia and hospitalization in patients with influenza A versus influenza B.

Analyses were not stratified by influenza A subtype because this information was not available for all participants in every season. Additionally, power for analysis by subtype was low, because of low numbers of cases in the two seasons in which there was a mix of subtypes (2005–2006 and 2006–2007). However, the predominant subtype was known for each season, and within-season comparisons were made for influenza A and B infections. All analyses were conducted using SAS (SAS Institute Inc., Cary, NC, USA); *P*-values <0.05 were considered significant.

Results

We identified 901 cases of influenza A and 284 cases of influenza A, 704 cases (78%) were influenza A/H3N2, 70 cases (8%) were influenza A/H1N1, and 127 cases (14%) were untyped. Of the 284 cases of influenza B, 95 (33%) were B/Yamagata lineage, 28 (10%) were B/Victoria lineage, and 161 (57%) were not characterized. Fifty-seven percent of cases were enrolled and identified during an outpatient medical encounter; 38% of cases were enrolled after visits to urgent care, 3% after emergency room visits, and 2% following a hospital admission. The predominant influenza subtypes in the study population were influenza A(H3N2) in 2004–2005, B/Victoria lineage in 2005–2006, influenza A(H1N1) in 2006–2007, and influenza A(H3N2) in 2007–2008 (95%, 62%, 73%, and 72%

of subtyped samples, respectively). A mix of influenza A subtypes and a mix of influenza B lineages were only present in the 2006–2007 season. In every season but 2005–2006, the number of type A cases greatly exceeded the number of type B cases (Table 1).

The mean ages of patients with influenza A and influenza B infections were significantly different during the 2005-2006 and 2006-2007 seasons. Mean ages were 44 and 26 years (median ages 53 and 12 years), respectively, for patients with influenza A and B infections during the 2005-2006 season (P = 0.01). However, during the 2006–2007 season, mean ages were 18 and 40 years (median ages 4 and 52 years), respectively (P = 0.02). In an aggregate analysis that included cases from all seasons, age was not associated with influenza type (A versus B). No significant differences were observed in the distribution of gender between influenza A and B infections in any season, or when the seasons were combined. The proportion of influenza A and influenza B cases who received seasonal influenza vaccine was not statistically different for any season, or overall (36.0% and 35.6%, respectively; P = 0.48, chi-square).

When data from all four seasons were combined, adults infected with influenza A infection were more likely to have a high-risk medical condition compared to those with influenza B infection (35% and 17%, respectively; P < 0.0001). In contrast, pediatric patients with influenza B were more likely to have a high-risk medical condition relative to those with influenza A (21% and 13%, respectively; P = 0.04).

Patients with influenza A were more likely to receive a prescription for influenza antiviral therapy within 14 days after symptom onset than patients with influenza B in the 2007–2008 season (27% and 18%, respectively; P = 0.004). This association was also present when all years were combined (22% and 15%, respectively; P = 0.013). Ninety-five percent of the antiviral prescriptions were for oseltamivir; the remaining 5% of prescriptions were for amantadine.

Symptoms and early care-seeking behavior

Cough and wheezing were significantly associated with influenza A during the 2004–2005 season (predominant subtype H3N2), but not during the other seasons. In the 2004–2005 season, 95% of patients with influenza A and 79% of patients with influenza B reported cough (P = 0.05, exact Pearson chi-square); wheezing was reported by 51% of influenza A cases and 15% of patients with influenza B (P = 0.02). Sore throat and vomiting were associated with influenza A during the 2007–2008 season only (predominant subtype H3N2). Seventy-six percent of influenza A cases and 66% of influenza B cases reported sore throat (P = 0.006); vomiting was reported by 19% of influenza A cases and 13% of patients with influenza B (P = 0.05). There were no other significant differences in symptoms reported by patients with influenza A and B during

	2004–2005 Season	ason	2005–2006 Season	son	2006–2007 Season	ason	2007–2008 Season	Ison	All seasons	
	Influenza A (<i>n</i> = 153) [<i>n</i> (%)]	Influenza B (<i>n</i> = 14) [<i>n</i> (%)]	Influenza A (<i>n</i> = 21) [<i>n</i> (%)]	Influenza B (<i>n</i> = 30) [<i>n</i> (%)]	Influenza A (<i>n</i> = 95) [<i>n</i> (%)]	Influenza B (<i>n</i> = 7) [<i>n</i> (%)]	Influenza A (<i>n</i> = 632) [<i>n</i> (%)]	Influenza B (<i>n</i> = 233) [<i>n</i> (%)]	Influenza A (<i>n</i> = 901) [<i>n</i> (%)]	Influenza B (<i>n</i> = 284) [<i>n</i> (%)]
Aae										
6–23 month	29 (19)	5 (36)	3 (14)	5 (17)	19 (20)	(0) 0	31 (5)	12 (5)	82 (9)	22 (8)
24–59 month	8 (5)	1 (7)	(0) 0	3 (10)	38 (40)	2 (29)	64 (10)	21 (9)	110 (12)	27 (10)
5–49 years	29 (19)	0 (0)	5 (24)	13 (43)	15 (16)	(0) 0	415 (66)	152 (65)	464 (52)	165 (58)
50-64 years	21 (14)	3 (21)	11 (52)	7 (23)	21 (22)	5 (71)	77 (12)	31 (13)	130 (14)	46 (16)
65+ years	66 (43)	5 (36)	2 (10)	2 (7)	2 (2)	(0) 0	45 (7)	17 (7)	115 (13)	24 (8)
Male	73 (48)	6 (43)	7 (38)	15 (50)	44 (46)	4 (57)	288 (46)	107 (46)	413 (46)	132 (46)
High-risk medical condition*	110 (72)	6 (43)	12 (57)	17 (57)	24 (25)	1 (14)	87 (14)	29 (12)	233 (26)	53 (19)
Fully vaccinated	103 (67)	9 (64)	12 (57)	13 (43)	31 (33)	2 (29)	178 (28)	77 (33)	324 (36)	101 (36)
Partially vaccinated**	3 (2)	0 (0)	1 (5)	1 (3)	2 (2)	(0) 0	9 (1)	1 (0)	15 (2)	2 (1)
Influenza antiviral Rx***	10 (7)	(0) 0	2 (10)	2 (7)	15 (16)	(0) 0	171 (27)	41 (18)	198 (22)	43 (15)

individual seasons or in the combined group of patients from all seasons.

In an age-stratified analysis of all seasons combined, fatigue and wheezing were significantly associated with influenza B among adults (98 versus 93%, P = 0.01, and 59 versus 54%, P = 0.02, respectively). There were no significant differences in symptoms reported by children with influenza A or B. In both adults and children, the proportion reporting myalgia was similar for those infected with influenza A or B across all seasons combined and during each individual season.

The mean interval from illness onset to the clinical encounter for all patients with influenza was 3 days in each of the four seasons. In two of the four seasons (2005-2006 and 2007-2008), patients with influenza A sought medical care significantly earlier than those infected with influenza B (difference in mean interval from onset to encounter -1.7 and -0.5 days, respectively; P = 0.02 and P < 0.001, respectively). The 2007-2008 season was dominated by influenza A(H3N2) infections, whereas the 2005-2006 season was atypical, with similar numbers of influenza A(H3N2) and influenza B infections. The mean interval from onset to medical encounter was significantly shorter for those with influenza A relative to influenza B when all seasons were included in the analysis (difference in mean interval from onset to encounter -0.5 days, P < 0.001). Analyses adjusted for age, gender, presence of a high-risk medical condition, and vaccination status.

The interval from illness onset to clinical encounter was also analyzed as a categorical variable, where early care seeking was defined as an interval of <3 days from symptom onset to clinical encounter. In a multivariable logistic regression model, the odds ratio for early care seeking in patients with influenza A was significantly elevated in 2005-2006 and 2007-2008 (Table 2). The odds ratio was also elevated in 2004-2005, but the number of influenza B infections was low and the confidence interval included one. During both seasons with statistically significantly elevated odds ratios for early care seeking, the predominant influenza A virus was A(H3N2). Patients with influenza A were more likely to seek care earlier than those with influenza B when all years were analyzed together (odds ratio = 1.7, 95% CI = 1.3, 2.3).

Pneumonia and hospitalization

The incidence of radiographically confirmed pneumonia was similar in patients with influenza A and influenza B infections. Over the four seasons, 19 (2·1%) of 901 patients with influenza A and seven (2·5%) of 284 patients with influenza B had radiographically confirmed pneumonia within 30 days after symptom onset (odds ratio = 1·2, 95% CI = 0·5, 2·8). In addition, no significant association was found in the occurrence of radiographically confirmed pneumonia between influenza A and B cases in any one season.

Table 2. Early care-seeking behavior by influenza type and season

Season	Predominant influenza A subtype	Influenza A	Influenza B	Crude odds ratio (95% CI)	Adjusted* odds ratio (95% CI)
		No. received care <3 days	after illness onset/total cases (%)		
2004–2005	H3N2	79/150 (53%)	5/14 (36%)	2.0 (0.6, 6.3)	1.8 (0.6, 6.0)
2005–2006	H3N2	12/20 (60%)	10/29 (34%)	2.9 (0.9, 9.3)	5.3 (1.04, 26.
2006–2007	H1N1	42/93 (45%)	3/7 (43%)	1.1 (0.2, 5.2)	1.2 (0.2, 6.6)

Partially immunized children were excluded.

*Adjusted for age, gender, high-risk medical condition status, and vaccination status.

**Illness onset date unavailable for one patient.

No significant difference was found between influenza A and influenza B in the occurrence of hospital admissions when results were combined across all seasons. Forty-seven (5%) of 901 influenza A cases and 12 (4%) of 284 influenza B cases were hospitalized within 30 days of symptom onset during the 4-year period (odds ratio = 1.2, 95% CI = 0.7, 2.4). No significant association was found in the occurrence of hospitalization between influenza A and B cases in any one season.

Discussion

Results from this case series of patients seeking care for predominantly uncomplicated influenza illnesses resulting in a visit to a medical care provider suggest that influenza A and influenza B are virtually indistinguishable based on clinical features. In contrast to earlier studies, we did not find a higher rate of myalgia among patients with influenza B in any single season, or in the combined group from all four seasons.^{8,19} Myalgia occurrence was also similar for influenza A and B infections occurring specifically in children; findings of a higher rate of myalgia among pediatric influenza B cases in a previous study may have been associated with the older ages of the influenza B cases in that study population, which was not seen in our pediatric population.¹⁹ The risks of radiographically confirmed pneumonia and hospital admission were also similar among patients with influenza A and influenza B infections in combined analyses that included all seasons and in analyses of each individual season. These outcomes were rare among patients evaluated in a mostly outpatient setting, and power to detect differences by type was limited.

Individual-season analyses did not allow for stratification by influenza A subtype because this information was not available for all participants in every season, and the number of outcome events was too low to perform further stratified analyses in some seasons. Influenza A(H3N2) was the predominant influenza A strain in three of the four seasons, and thus, our combined data analyses were influenced largely by enrolled subjects testing positive for this strain.

Although clinical features and outcomes of influenza A and influenza B infection were similar in our population, patients with influenza A sought medical attention earlier than those infected with influenza B. This association was present in three of the four seasons, and the association was statistically significant in two seasons. The season when early care-seeking behavior was similar for influenza A and influenza B (2006-2007) was dominated by A(H1N1) viruses, which have been reported to cause milder clinical illness in pediatric populations.⁶ In contrast, the seasons where we observed earlier care seeking among patients with influenza A were dominated by A(H3N2) viruses. These findings suggest that influenza A(H3N2) may cause more acute illness than influenza A(H1N1) or influenza B. However, while statistically significant, the differences in onset to encounter intervals by strain were small, which may limit clinical significance.

The mean age of patients with influenza A infections was higher than the mean age of patients with influenza B infections in each of the three seasons when A(H3N2) was the dominant influenza A subtype, although the association was significant in only one season. The mean age of patients with influenza A was significantly lower than that of patients with influenza B in the one season when A(H1N1) was the dominant influenza A subtype. These results are consistent with a recent study by Kelly, *et al.*²⁰

The Tecumseh studies of the 1960s and 1970s found infection with influenza A to be more severe than infection with influenza B based on duration of illness, proportion of illnesses with physician consult, decrease in normal activity, and symptom location. Frequencies of individual symptoms by strain were not reported.^{21,22} The first study,

completed 1966–1971, reported on a total of 33 influenza A and 36 influenza B isolates, respectively; results by influenza A subtypes were not reported.²¹ The second study, from 1976 to 1981, identified a total of 46 influenza A(H3N2), 50 influenza A(H1N1), and 51 influenza B isolates, respectively; results were further stratified by age, limiting power. The strength of these studies was their ability to identify all influenza illness within the study cohorts, as opposed to only those which were medically attended. However, both studies were limited by low case numbers.

Previous studies looking at pneumonia and hospitalization by influenza strain have found mixed results. Foy et al.23 found that rates of pneumonia in adults doubled during six influenza A epidemics, while epidemics of influenza B had less effect; the impact on pneumonia rates among children was less evident. A standard case definition for pneumonia was not used in that study, and clinical pneumonia was not distinguished from radiographically confirmed pneumonia. The pneumonia diagnoses were not linked to influenza infections at the individual level, and misclassification of pneumonia was likely in the absence of a standard case definition or radiographic confirmation. A retrospective study of nearly 700 pediatric patients found no difference in rates of pneumonia by strain.8 A series of studies over 20 years (1957-1976) found a higher prevalence of influenza A(H3N2) infection compared with influenza A(H2N2) or influenza B in hospitalized children with respiratory disease. Influenza A(H1N1) was not circulating in the study population, thus not available for comparison.9 The impact of influenza A(H3N2) on hospital admission may have been affected by the immunogenically naïve nature of the study population, as the initial emergence of influenza A(H3N2) occurred during the study period (1968). Time series studies of hospitalization and influenza have found that infection with influenza A(H3N2) is more likely to result in hospitalization than infection with influenza B or other influenza A subtypes.24-26

Strengths of this study included the use of viral culture or RT-PCR to detect influenza and systematic screening and testing procedures during all seasons. RT-PCR was used in three of four seasons and is highly sensitive and specific.^{27,28} As a result, more complete ascertainment of cases was likely in this study compared with prior studies that utilized older technologies for influenza detection. The use of systematic screening procedures ensured that selection bias did not occur during any of the seasons. Physicians had no role in screening or testing patients for this study, and the physician diagnosis was not considered for the determination of eligibility.

This study had several limitations that may affect generalizability. The age distribution of our eligible study population expanded over the four seasons, as ACIP vaccine recommendations were modified to include older children, adolescents, and younger adults without chronic medical conditions. The eligible cohort was greatly expanded for the 2007-2008 season to facilitate estimation of vaccine effectiveness for all individuals ≥6 months of age. These age differences limited comparisons across seasons, and findings from across-season symptom comparisons should take potential age differences into account. However, the models used in our early care-seeking analyses did adjust for age. The evolving eligibility of the study population also influenced the proportion with a chronic medical condition across years. The presence of a highrisk condition could affect the clinical outcome of influenza. These differences could affect across-season comparisons, but would not impact within-season analyses. While the study had a participation rate of 81% across all four seasons, non-response bias could have affected study results if illness differed systematically in individuals who declined participation.

It is important to emphasize that this study was restricted to patients seeking medical care for acute respiratory illness, and most enrollments were carried out in the outpatient setting. As a result, we were unable to compare severity of influenza A and B in the community – specifically the effect of illnesses that did not trigger a health care visit. Our results should be interpreted to apply to medically attended influenza only, although severity differences in non-medically attended influenza may be less important from a public health perspective.

The number of cases available for analysis limited our power to detect differences by strain for rare, severe outcomes; our sample size should be considered when interfindings preting our regarding pneumonia and hospitalization. Influenza antiviral medications could have affected clinical outcomes (i.e. reduced likelihood of hospitalization). We found that influenza A cases were more likely than influenza B cases to receive an antiviral prescription in 2007-2008 and overall, which could have weakened any association between influenza A and pneumonia diagnosis or hospitalization that may have existed. In addition, we were unable to examine the relationship between influenza strain and mortality. Previous studies have found an increase in excess mortality in influenza A(H3N2) seasons, compared with seasons dominated by influenza B and other influenza A subtypes.^{5,29}

In summary, our findings suggest that the clinical features of patients seeking care for influenza A and B infections were very similar during four recent influenza seasons. While patients with influenza A(H3N2) infections sought care earlier than patients with other types of influenza, we found no individual symptom or group of symptoms that consistently distinguished influenza A and B infections in children or adults. Accurate identification of influenza A and B is becoming more important as antiviral resistance becomes more prevalent among different influenza subtypes. In settings with complex patterns of antiviral resistance, prompt identification of influenza A (including subtype) and influenza B will be important to guide appropriate use of antiviral agents.

Conflict of interest statement

The authors declare no conflicts of interest.

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