Characteristics of respiratory viral infections during influenza season in Canadian Hutterite Communities

Tae H. Kim,[a,b] Margaret L. Russell,[c] Kevin Fonseca,[d] Fred Aoki,[e] Gregory Horsman,[f] Paul Van Caeseele,[e,g] Khami Chokani,[h] Mark Voight,[I] Lorne Babiuk,[j] Lorraine Moss,[a] Richard Webby,[k] David J. D. Earn,[l,m,n] Pardeep Singh,[a] Cassandra Howse,[a] Mark Loeb[a,l,m,n,o]

[a]Department of Pathology and Molecular Medicine, McMaster University, Hamilton, ON, Canada. [b]Division of Infectious Diseases, Departments of Internal Medicine, Soon Chun Hyang University Seoul Hospital, Seoul, Korea. [c]Department of Community Health Sciences, University of Calgary, Calgary, AB, Canada. [d]Provincial Laboratory for Public Health and Department of Microbiology and Infectious Diseases, Calgary, AB, Canada. [e]Department of Medical Microbiology, University of Manitoba, Winnipeg, MB, Canada. [f]Department of Disease Control Laboratory, Saskatoon, SK, Canada. [g]Cadham Provincial Laboratory, Winnipeg, MB, Canada. [h]Cypress Health Region, Swift Current, SK, Canada. [i]Saskatchewan Health, Five Hills, Moose Jaw, SK, Canada. [j]University of Alberta, Edmonton, AB, Canada. [k]St. Judes Children's Research Hospital, Memphis, TN, USA. [l]Department of Mathematics and Statistics, McMaster University, Hamilton, ON, Canada. [m]Michael G. DeGroote Institute for Infectious Disease Research, McMaster University, Hamilton, ON, Canada. [n]Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, ON, Cananda. [o]Departments of Medicine, McMaster University, Hamilton, ON, Canada.
Correspondence: Dr Mark Loeb, McMaster University, 1280 Main Street West, Hamilton, ON, Canada L8S 4Z1. E-mail: loebm@mcmaster.ca

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Objectives: To determined the pathogen-specific incidence of respiratory virus infection in Hutterite communities occurring over the 2008–2009 influenza season and assess temporal characteristics of respiratory illness related to infection.

Methods: 3273 participants community members enrolled in a cluster randomized trial of influenza vaccine were studied.

Results: One hundred forty-nine participants had laboratory-confirmed influenza, and 595 had at least one episode of

laboratory-confirmed respiratory viral infection other than influenza. Entero/rhinovirus had the highest incidence among children <5 years.

Conclusions: A decline in the incidence of infections with age was observed for influenza as well as for most other respiratory viruses.

Keywords Cohort study, entero/rhinovirus, respiratory viruses.

Introduction

Viral respiratory infections, particularly in young children and the elderly[1], can lead to substantial morbidity, such as increased rates of lower respiratory tract infections and hospitalization.[2,3] Relatively few prospective, community-based studies to define etiologic agents for respiratory infection have been reported.[1–3] Moreover, existing studies are limited in that most are not prospective community-based studies[1,4] and did not use highly sensitive diagnostic testing such as RT-PCR.[2] Data are particularly sparse on the epidemiology of respiratory viruses other than influenza, Respiratory Syncytial Virus (RSV), and parainfluenza,[5,6] and most of these studies are based on culture, antigen testing or serology that are less sensitive and specific relative to molecular assays.

With the exception of influenza, specific vaccines or anti-viral medications are either not widely available or

have not proved effective for respiratory viral infections.[7] Nevertheless, as vaccine development evolves and new therapeutic agents are produced, characterizing the epidemiology of viral respiratory infections will delineate the appropriate populations in whom these agents should be targeted.[3] Furthermore, this could lead to better insights concerning those at highest risk for bacterial superinfection following viral infection.[7]

Hutterites live in British Columbia, Alberta, Saskatchewan, and Manitoba, as well as several north-central American states where they practice communal farming on small colonies of typically 80–120 people, relatively isolated from towns and cities. However, outbreaks of respiratory infection in Hutterite colonies occur regularly, as viruses are introduced from exposure to people outside the community. As the colonies are not very large, it is possible to obtain detailed demographic, health, and immunization information from all members.[8] The implementation of a

cluster randomized trial aimed at reducing influenza in the Canadian Hutterite community allowed us to prospectively collect data on other respiratory viruses. In this report, we sought to determine age-specific incidence of laboratory-confirmed respiratory virus infection occurring in the Hutterite community and to document the temporal relationship of virus-specific attack rates.

Methods

Study participants
Participants were 3273 community members of 46 Hutterite colonies from Alberta, Saskatchewan, and Manitoba who were enrolled in a cluster randomized trial (September 22 to December 23, 2008).[8] By randomizing children in the Hutterite colonies to either trivalent inactivated influenza vaccine or hepatitis A vaccine, as a control, the trial was designed to determine the indirect effectiveness of influenza vaccine on unimmunized residents. The present data are based on the first year of the trial where children in colonies allocated to influenza vaccine received the vaccine recommended for the 2008–2009 influenza season (A/Brisbane/59/2007 [H1N1]–like virus, A/Brisbane/10/2007 [H3N2]–like virus, B/Florida/4/2006-like virus; Vaxigrip, Sanofi Pasteur, Lyon, France). There were no exclusion criteria for participant. All gave informed consent to participate in the study.

Follow-up
As previously described, participants were assessed for signs and symptoms of respiratory illness over the follow-up period, defined by the start date (>1 laboratory-confirmed influenza case in two consecutive weeks from sentinel sites) and stop date (no laboratory-confirmed influenza cases for two consecutive weeks in the sentinel sites).[8] This period extended from December 28, 2008, until June 23, 2009. Research nurses assessed all study participants twice weekly using a standardized checklist of self-reported symptoms or signs from study participants or parents. One representative from each household (e.g., the mother) was designated to complete the checklist for all family members and provide this when the research nurse made a site visit. The nurse would review the checklist. If anyone reported new symptoms, the nurse interviewed the study participant to confirm their symptoms and date of onset. A nasopharyngeal specimen was obtained if two or more of the following symptoms were present: fever (≥38°C), cough, nasal congestion, sore throat, headache, sinus problems, muscle aches, fatigue, ear ache or infection, or chills. Research nurses would also contact the household representative if the self-reported checklists were incomplete, to follow-up on missing data. We purchased identical thermometers for all study participants and provided instruction on thermometer use.

Influenza was detected using the Centers for Disease Control and Prevention's Human Influenza Virus Real-time RT-PCR Detection and Characterization Panel, which targets the matrix gene for influenza A and non-structural gene for influenza B. Respiratory viruses were detected using a RT-PCR method (xTAG RVP assay; Luminex, TX, USA). This assay detects coronavirus 229E, NL63, OC43, parainfluenza virus type 1, 2, 3, 4, entero/rhinovirus, respiratory syncytial virus A and B, human metapneumovirus, and adenovirus.

All 3273 participants were kept in the analyses for non-influenza viruses. However, to reduce the potential for biased estimates, 1945 participants who either individually received influenza vaccine or were in study colonies assigned to the intervention arm (influenza vaccine) were excluded from the analysis for seasonal influenza virus infection, leaving 1328 participants for the analysis. To calculate incidence, we counted only the first viral infection for a specific virus, as the numerators (age-specific), while the denominators were age-specific person-days, which included the entire period of surveillance for participants who were not infected with the specific virus along with the person-days up to the point of infection for those who were infected. If a participant was swabbed more than once within 14 days, and if the same virus was detected on ≥1 occasion in this time frame, then only the first episode detected was used in the analysis. To quantify the temporal relationship between the respiratory viruses, we defined an epidemic midpoint as the date when 50% of the cumulative cases of virus detected were reached over the period of surveillance.[9] This was calculated for both influenza and non-influenza viruses. We calculated incidence using events per 1000 person-days and estimated differences in rates assuming a Poisson distribution.[10]

Results

There were 3273 participants, of whom 1858 (57%) were female. Approximately, 40% of participants were 15 years of age or younger and co-morbidity was infrequent. 362 (11%) were aged 0–4 years, 366 (11%) aged from 5 to 8 years, 574 (18%) aged from 9 to 14 years, 310 (10%) aged from 15 to 19 years, 410 (13%) aged from 20 to 29 years, 380 (12%) from 30 to 39 years, 409 (13%) from 40 to 49 years, and 462 (14%) aged ≥50 years. There were 149 (11·2% of 1328) with laboratory-confirmed influenza and 595 (18·2% of 3273) with at least 1 episode of laboratory-confirmed respiratory viral infection other than influenza. Of the 149 with laboratory-confirmed influenza, 32 were also infected with another respiratory virus.

Influenza (including A (H1N1), A (H3N2), and B) had the highest incidence (0·80/1000 person-days CI: 0·74–0·87), followed by entero/rhinovirus (0·69/1000 person-days, CI:

0·65–0·73), RSV (0·28/1000 person-days, CI: 0·25–0·30), coronaviruses (0·26/1000 person-days), and parainfluenza (0·23/1000 person-days). The age group–specific incidence of respiratory virus infection is shown in Figure 1. Among children of age <5, entero/rhinovirus had the highest incidence (1·36/1000 person-days; CI: 1·20–1·53), but this was not significantly higher than RSV (1·29/1000 person-days, CI: 1·12–1·45), $P = 0.809$). Influenza A was not detected in those aged ≥50. Influenza B was not detected among those aged ≥30 and among those 40–49 years of age and older, a decline in incidence was observed for entero/rhinovirus, coronaviruses, RSV, and influenza A. The incidence of parainfluenza increased among those aged 40–49 years and older; in contrast, h-MPV (human metapneumovirus) was not detected in those 20–29 years of age or older (Figure 1). In addition, the highest incidence of parainfluenza was in children aged 0–4 years (1·11/1000 person-days, CI: 0·95–1·26).

Entero/rhinovirus had the highest age-specific incidence among participants with age ≥50 (0·33/1000 person-days, CI: 0·26–0·40), which was higher than for seasonal influenza (0·25/1000 person-days, CI: 0·14–0·36), although statistically not significant, $P = 0.744$) (Figure 1). The incidence of entero/rhinovirus in this age group was significantly higher than coronavirus (0·27/1000 person-days, CI: 0·21–0·33, $P = 0.01$) and to RSV (0·06/1000 person-days, CI: 0·03–0·09, $P = 0.005$).

The weekly occurrence of influenza and non-influenza viruses was plotted in bar graphs (Figure 2). The epidemic midpoint for seasonal influenza was March 23, 2009, whereas individual date values for influenza A (H1N1), A (H3N2), and B were March 9, April 7, and April 18, respectively. For coronaviruses, parainfluenza viruses, entero/rhinovirus, RSV, and h-MPV these values were March 2, March 2, April 30, March 9, and March 27, respectively.

Discussion

There are few prospective community-based surveillance data on the circulation of non-influenza viruses during the influenza season. In the Hutterite communities we studied, a high attack rate of influenza was followed by entero/rhinovirus and then by RSV, coronavirus and parainfluenza. Most respiratory viruses had their highest incidence in children aged 0–8, except coronaviruses and H1N1 seasonal influenza, which had the highest incidence in ages 40–49 and 15–19, respectively (Figure 1). Coronaviruses occurred among persons in all age groups.

Typically, RSV is the most common respiratory virus identified in hospitalized children under the age of 5 years.[3,4,7,11] The fact that the virus with the highest attack rate in children under the age of five was entero/rhinovirus and not RSV was unanticipated even though the difference in incidence between the two was not statistically significant. It may be explained by the fact that entero/rhinovirus has a wide spectrum of disease and milder cases in our community-based study were detected.[12] Previous studies have reported hospitalized children with lower respiratory tract disease or severe pneumonia,[3,4] emphasizing the predilection of RSV to lead to hospitalization, but not reflecting a dominant circulating virus in the community.

Our findings also suggest that the incidence of entero/rhinovirus infection in the community has been underestimated. The high incidence of entero/rhinovirus we detected might also be related to our use of RT-PCR, which yields a substantially higher sensitivity compared to conventional culture.[12] The co-dominance of entero/rhinovirus with influenza in this study is consistent with a recent study reporting a high incidence of entero/rhinoviruses during the influenza season.[1] Our data suggest that entero/rhinovirus may be more common in the elderly than previously recognized, because entero/rhinovirus had the highest age-specific incidence among participants with age ≥50. The relatively high incidence of entero/rhinovirus and coronavirus compared to RSV in this age group is in keeping with a previous report that included an elderly population[2].

Parainfluenza is generally reported as the second most common virus after RSV to cause lower respiratory tract diseases in young children.[7] In contrast, parainfluenza was less common in our study than influenza, entero/rhinovirus, coronaviruses, and RSV. The highest incidence was, however, in children aged 0–4.

From a clinical perspective, the high degree of co-circulation of other respiratory viruses along with influenza as shown in Figure 2 raises the question of the degree to
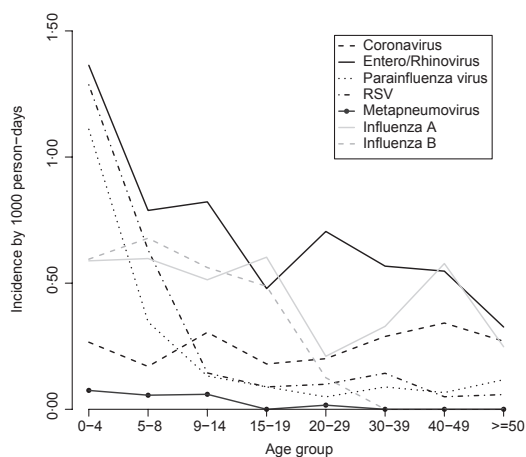

Figure 1. Age group–specific incidences of respiratory viruses, including seasonal influenza, during the influenza season per 1000 person-days.
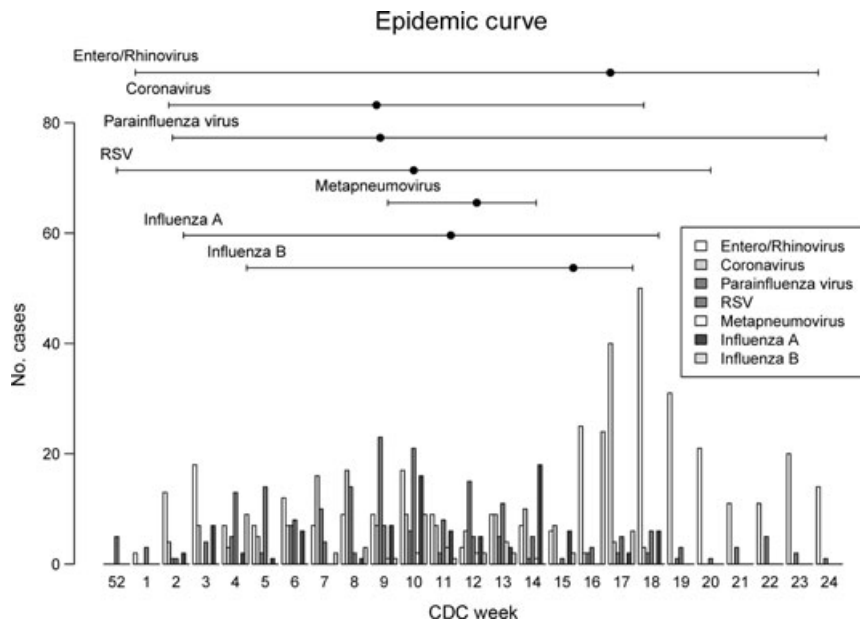
Figure 2. Periods of occurrence and numbers of cases of respiratory viruses by CDC weeks during the influenza season 2008–2009. The periods of occurrence for each virus are indicated by a horizontal line with the corresponding epidemic midpoint identified by a black circle.

which signs and symptoms of respiratory infection are falsely attributed to influenza, which has implications for the empiric use of anti-virals.

A consistent finding across all respiratory viruses was that the highest incidence was in children aged 0–4 years or from 5 to 8 years. The incidence generally decreases in teenaged participants and in young adults and then either reaches a plateau or increases slightly with advanced age. This could be explained by the higher incidence of viral respiratory infection in age <5 compared to older individuals, but also by the lower detection rate of respiratory virus in the elderly due to reduced viral shedding in older age groups.[13] Influenza B infection, unlike influenza A, was not observed among adults >30. The most likely explanation is due to the relative conservation of influenza B immunity in older individuals, as previously reported.[14,15] The incidence of entero/rhinovirus and coronavirus infection in older individuals was relatively higher than that of other viruses, consistent with previous studies.[16] Our study has several limitations. First, the respiratory virus test is performed only within symptomatic participants during the influenza season, and the respiratory virus shedding in asymptomatic control is not evaluated. Second, because the study is performed during the 2008–2009 influenza season, it potentially underestimates the annual incidence of respiratory viruses other than influenza which may have different season or which may cause biannual epidemic. Third, it is performed in Hutterite colonies that do not represent the general population of Canada. Another limitation is that there were three colonies dropped out of the study after randomization. However, as the characteristics of these colonies do not differ from those of the 46 colonies that participated the study, we consider this did not affect the results.

In conclusion, there were multiple co-circulating viruses over the influenza season. Age-specific incidence of respiratory viruses was highest in young children but with unexpected high incidence of entero/rhinovirus in this group.

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Addendum

Tae Hyong Kim[a,b] wrote this manuscript as first author and involved in data collection and analysis. Margaret L. Russell[c] and Kevin Fonseca[d] designed the study and involved in data collection, the writing and major revision of this manuscript, final approval. Gregory Horsman[f], Paul Van Caeseele[e,g], Khami Chokani[h], Mark Voight[I], Lorraine Moss[a] Richard Webby[k], and Cassandra Howse[a] involved with data collection, writing, and major revision. Lorne Babiuk[j], David J. D. Earn[l,m,n], Pardeep Singh[a], and Fred Aoki[e] involved with analysis, writing, and major revision.

Mark Loeb[a,l,m,n,o] designed the study and involved in data collection, the writing and major revision of this manuscript.

All authors gave final approval.

[a]Department of Pathology and Molecular Medicine, McMaster University, Hamilton, Ontario, Canada. [b]Division of Infectious Diseases, Departments of Internal Medicine,

Soon Chun Hyang University Seoul Hospital, Seoul, Republic of Korea. [c]Department of Community Health Sciences, University of Calgary, Alberta, Canada. [d]Provincial Laboratory for Public Health and Department of Microbiology and Infectious Diseases, Calgary, Alberta, Canada. [e]Department of Medical Microbiology, University of Manitoba, Winnipeg, Manitoba, Canada. [f]Department of Disease Control Laboratory, Saskatoon, Saskatchewan, Canada. [g]Cadham Provincial Laboratory, Winnipeg, Manitoba, Canada. [h]Cypress Health Region, Swift Current, Saskatchewan, Canada. [i]Saskatchewan Health, Five Hills, Moose Jaw, Saskatchewan, Canada. [j]University of Alberta, Edmonton, Alberta, Canada. [k]St. Judes Children's Research Hospital, Memphis, Tennessee, USA. [l]Department of Mathematics and Statistics, McMaster University, Hamilton, Ontario, Canada. [m]Michael G. DeGroote Institute for Infectious Disease Research, McMaster University, Hamilton, Ontario, Canada. [n]Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Cananda. [o]Departments of Medicine, McMaster University, Hamilton, Ontario, Canada.

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