Back-to-School Upper Respiratory Infection in Preschool and Primary School-Age Children in Israel

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Background: Increased upper respiratory infection (URI) among children at the beginning of school year is well known to parents and pediatricians. However, this phenomenon is not well documented or characterized.

Methods: Computerized datasets from a large health maintenance organization in Israel were used to calculate the weekly rates of URI among children 3–14 years old for the years 2007–2012. In addition, nasopharyngeal swabs were collected in 2010–2012 from children with URI symptoms and controls during school opening time. Swabs were tested by real-time polymerase chain reaction for the presence of respiratory viruses.

Results: Time-series analysis demonstrated a peak of URI in September each year. The peaks reached their height 2 weeks after school opening and returned to baseline within 4–7 weeks. The main 3 viruses detected both in URI patients and in healthy controls during the first weeks of school opening were rhinovirus, adenovirus and enterovirus. The detection rate of any respiratory virus, and of rhinovirus in particular, was significantly higher among cases than among controls (54% vs. 16%, P < 0.001 for any virus, and 35% vs. 6.0%, P < 0.01 for rhinovirus). When adjusting for age and sex cases had 5.8 times more viral detection when compared with controls. Upper respiratory symptoms were significantly more prevalent among the virus-positive cases when compared with negative ones.

Conclusions: Back-to-school illness consisting of URI has a distinct epidemiological pattern demonstrating a rapid rise peaking within 2 weeks of school opening and is associated predominantly with rhinovirus.

Key Words: upper respiratory infection, school, surveillance

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the study. Sample collection started 2 days from school opening date and included the entire month of September. In 2010 only cases were studied, and in 2011 and 2012 both cases and controls were studied.

Sample and Data Collection
Nasopharyngeal swab samples were obtained from symptomatic children who presented with fever (>37.8°C) along with at least one of the following symptoms: sneezing, nasal congestion, coryza, cough, sore/dry throat or hoarseness (cases). To be included in the study, time from symptoms onset to nasopharyngeal swabbing of cases should not exceed 3 days. Samples were collected only on working days.

If samples were collected from more than one symptomatic family member, only one that was randomly selected was included in the study. A short questionnaire was filled out by the patients’ physicians (for cases) or by a designated nurse (for controls). The questionnaire included demographic data as well as medical information about the current illness (for cases) and any febrile illness during the past month (for controls). Follow-up of cases or controls after sample collection was not performed as part of this study.

Laboratory Analysis
Viral genome was extracted from nasopharyngeal samples using NucliSENS easyMAG (BioMerieux, France). The presence of respiratory viruses was determined by TaqMan Chemistry using the ABI 7500 instrument. The detection of RNA viruses was performed using a panel of real-time reverse transcription-polymerase chain reaction (rRT-PCR) assays as previously described: Influenza A and B, influenza A(H1N1)pdm09, RSV, human metapneumovirus, enterovirus, rhinovirus and parainfluenza 3 viruses. For detection of adenovirus (DNA virus), RT-PCR was performed, as previously described.

Statistical Analysis
For the generation of time-series, the daily computerized datasets of URI form Maccabi Health Services were aggregated into weekly data. Weekly rates of URI among patients 3–14 years old were calculated as the number of outpatient visits per 10,000 enrolled members. Demographic characteristics of cases and controls were compared using t test or χ² test. Comparisons between viral detection rate by age and sex in cases and controls were done using the χ² test. Logistic regression model was used to control for confounders. A 2-tailed P value of <0.05 was considered statistically significant. All analyses were performed using SPSS (version 21.0.0. SPSS Inc., Chicago, IL), SAS (SAS 9.1, SAS Institute Inc, Cary, NC) and Excel softwares.

Ethical Considerations
Approval was obtained by the ethics committee of the Sheba Medical Center and the clinical trials department of the Ministry of Health, Israel. Samples were collected from patients as part of the routine of care. Informed consent to participate in the study was signed by parents of control individuals. The consent was obtained by a nurse designated for this study.

RESULTS
Increased URI Rates at the Beginning of School Year
Weekly rates of outpatient URI visits per 10,000 HMO enrolled members among 3 to 14-year-old were analyzed and plotted on a time-series graph (Fig. 1). As shown in Figure 1, a narrow peak of URI was clearly observed during the month of September of each year, shortly after the beginning of the school year. These September peaks are later followed by separate, larger increases in URI rates lasting until April. Figure 2 demonstrates the September URI peaks of each year in greater detail. The URI peaks lasted 4–7 weeks (with an average of 5 weeks) following school openings (Fig. 2). URI reached its highest rate usually during the second epidemiological week following school opening of each year. A 3 days school intermission for the Jewish New Year occurred at different times during the month of September of each year. These intermissions were not associated with changes in the timing of URI maximal rate, even in the years 2007 and 2010, when these intermissions occurred within 11 and 7 days from school opening, respectively. There was some variability in the magnitude of the peaks over the years, with

FIGURE 1. Time series demonstrating URI rate per 10,000 HMO members aged 3–14 years, Israel 2007–2012. The month of September is highlighted in grey, and school-opening is marked with an arrow.
an average visit rate at the height of the peaks of 173.3 visits per 10,000 HMO members aged 3–14 years (SD = 34.2). When excluding 2009, the year of H1N1 influenza A pandemic, the average height of the peak was 159.2 visits per 10,000 HMO members aged 3–14 years (SD = 14.7).

**Study Participants**

A total of 220 cases and 133 controls were included in nasopharyngeal viral identification during school opening time. The characteristics of the study participants according to the study year are described in Table 1.

**FIGURE 2.** Detailed look at the yearly time series demonstrating URI rate per 10,000 HMO members aged 3–14 years, during school opening, Israel 2007–2012. ▲ represents school year opening; ♦, starting date of Jewish holiday intermission: (A) 2007; (B) 2008; (C) 2009; (D) 2010; (E) 2011; and (F) 2012.

**TABLE 1.** Characteristics of Study Participants, Israel 2010–2012
Viral Detection and Clinical Presentation

Cases and control samples were tested for the presence of influenza A, influenza B, H1N1pdm, RSV, human metapneumovirus, parainfluenza 3, rhinovirus, adenovirus and enterovirus. The main three viruses detected in cases were rhinovirus, adenovirus, and enterovirus (Table 2). Among the cases, at least one virus was detected in 50.0%, 57.7% and 49.1% of samples in 2010, 2011 and 2012 respectively. Viral detection in the years 2011 and 2012 was significantly more frequent in cases when compared with controls (54.0% vs. 15.8% \( P < 0.001 \)). When adjusting for age and sex cases had 5.8 times more viral detection when compared with controls. Of the URI cases who had a positive viral sample, 75.7%, 21.7% and 2.6% were found to have 1, 2 or 3 viruses, respectively.

The same main 3 viruses that were detected in cases were also detected in controls (Table 2). Among the controls, at least one virus was detected in 15.9% and 15.7% of samples from 2011 and 2012 respectively.

Both in 2011 and 2012, the rate of viral detection and specifically the detection of rhinovirus were significantly higher among cases when compared with controls (Table 2). Enterovirus and adenovirus were detected more often in cases than in controls without statistically significant differences.

Cough, pharyngeal erythema and nasal congestion/coryza were reported more frequently among the virus-positive cases when compared with virus-negative cases (\( P < 0.01 \), \( P < 0.05 \) and \( P = 0.07 \) respectively).

### DISCUSSION

In the present study, our surveillance data clearly demonstrated an increase in the rate of outpatient visits because of URI among children aged 3–14 years upon the beginning of school year. Thus far, there have been no reports describing and characterizing this phenomenon in community outpatient clinics. One report demonstrated an increased number of emergency department and acute care center visits because of respiratory illness, among children 5–19 years of age at the start of the school year,1 and several reports showed an increase in the rate of September hospital admissions and emergency department visits because of asthma exacerbation.14-16

In Israel, official school opening day for nursery school to high school occurs each year on the same day throughout the country (up until the year 2011 the school year in Israel started on September 1; in 2012, the school opening date was changed and the school year has started on August 27). This situation provides a clear advantage for analysis and interpretation of the time-series. It is important to note that several short school intermissions lasting between 2 and 7 days start during the month of September due to the Jewish holidays. These intermissions may commence in the beginning, the middle or the end of September because they are determined by the Jewish calendar, a lunisolar calendar, rather than the Gregorian calendar. Our data demonstrate a consistent pattern of URI peaks regardless of when the first short school intermission for the Jewish holidays began.

Information regarding the rate of respiratory pathogens propagation in schools is scarce. A recent study demonstrated high attack rate of influenza among children, exceeding that of adults, particularly in schools,17 suggesting that the transmission of respiratory viruses is enhanced in school settings. Another study demonstrated that a 2-week school closure due to elementary school teachers’ strike that took place during influenza season was associated with a significant decrease in pediatric outpatient doctors’ visits, respiratory infections, emergency department visits and the purchase of medications.18 These
studies provide strong support for the enhanced transmission of respiratory viruses in school settings. In Israel, the first school intermission lasts 3 days, which may not be sufficient to reduce virus circulation and therefore not influencing URI peak timing. During September 2009, URI rates were higher than URI rates found in the other years included in our analysis (Fig. 2). This may be attributed to cocirculation of 2009 H1N1 influenza A pandemic strain along with the 3 viruses, which we found to be most prevalent at this time of the year.

Rhinovirus, adenovirus and enterovirus were the most prevalent viruses isolated in our preschool and school aged study subjects at the beginning of the school year. The finding that rhinovirus was the most prevalent virus found in our study is consistent with viral isolation among children presenting to emergency departments with asthma exacerbations during the month of September, after returning to school, in Ontario, Canada.14 This study coupled with our findings provides strong evidence for the contribution of rhinovirus to respiratory illness at the beginning of the school year.19

Furthermore, the fact that these viruses were isolated more often in cases as compared with controls suggests that they were the cause of illness in cases during the study period. The presence of these viruses in controls may be because of prolonged viral shedding after infection, colonization or incubation before disease. All of which support the fact that these viruses circulate during the beginning of school year but may not always cause disease. Human rhinovirus is a known cause of URI.20,21 Although URI is usually a mild illness, rhinovirus has been associated with severe illness, such as lower respiratory infections and asthma exacerbations, both of which can lead to hospitalizations.22

Our study has several limitations. One of them is that virus was detected in only 47.7% of our cases. However, this is consistent with the findings of others who detected viruses from nasopharyngeal swabs in 48–49% of study patients.23,24 We tested the samples for 7 viruses that are known to be involved in children’s URI. Other viruses, such as corona, parainfluenza 1, 2 and 4 or Boca may account for additional cases that were negative for viral infection in our study.25,26 Recall bias, which may have led to earlier or later swabbing than desired, may have also accounted for some false-negative results.

Although viral detection from controls can be attributed to carrier state, it is also possible that virus can be isolated in a preclinical stage. Since no follow-up of controls was included in this study, we have no knowledge regarding the appearance of URI in controls, following our sampling. In addition, the severity of illness could not be assessed from our questionnaire. Additional studies are required to assess the association between severity of symptoms and viral detection and to conduct a follow-up of both cases and controls.

Our study characterizes a circumscribed period of time during the year. It would be beneficial to compare these findings to viral detection during other periods throughout the year.

Finally, the URI surges described here are visual in nature, as no formal time series analysis was conducted in the present study to evaluate the observation. Additional studies are required to further analyze the phenomena described here.

In conclusion, we identified and characterized the nature of rise in URI outpatient visits among children in the beginning of the school year and identified the viruses that are associated with this epidemiologic observation. The characterization of this rise in URI visits is of paramount importance for the surveillance of respiratory illness and the distinction from the subsequent rise in respiratory illness, which leads into the winter. Our findings have several implications for public health. First, they provide an important layer to the understanding of the role of school environment for the propagation and transmission of respiratory viruses. Second, to the best of our knowledge, there was no previous identification of the respiratory viruses involved in school morbidity during school opening. Third, although vaccines are not available against the viruses involved in the “September URI peak,” our findings may provide further support for the need to vaccinate school children against respiratory viruses for which a vaccine is available, such as influenza.

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REFERENCES


**APPENDIX**

The Israel Pediatric Upper Respiratory Infection Network (IPURIN) included the following:

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**Ramat Aviv Pediatric Clinic:** Yoseph Laks, MD, Nitza Vadas, MD, Idit Meshulach, MD and Gary Robinson, MD.

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