Age-Specific Patterns of Influenza Activity in Utah: Do Older School Age Children Drive the Epidemic?

Chris Stockmann,1,2,3 Andrew T. Pavia,1 Adam L. Hersh,1 Michael G. Spigarelli,2,3 Brooks Castle,1 Kent Korgenski,4 Carrie L. Byington,1 and Krow Ampofo1

Divisions of 1Pediatric Infectious Diseases, 2Clinical Pharmacology, and 3Adolescent Medicine, Department of Pediatrics, University of Utah Health Sciences Center; and 4Primary Children’s Medical Center, Intermountain Healthcare, Salt Lake City, Utah

Corresponding Author: Chris Stockmann, Division of Pediatric Infectious Diseases, University of Utah Health Sciences Center, 295 Chipeta Way, 2S010, Salt Lake City, UT 84108. E-mail: Chris.Stockmann@hsc.utah.edu.

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Across 12 consecutive influenza seasons in Utah, medically-attended visits for laboratory-confirmed influenza infection peaked first among older children (12–18 years). Peak activity in older children preceded that of children 0–4 years by more than 2 days and that of peak activity among adults ≥65 years by more than 6 days.

Key words. age groups; disease transmission; epidemiology; infectious; influenza vaccines; population surveillance; timeliness; vaccination.

Influenza epidemics occur annually in the United States and cause substantial morbidity, mortality, and economic burden [1]. Influenza is transmitted primarily through respiratory droplets or close contact with infected persons [2]. Mathematical models have demonstrated that the transmission of influenza is highly dependent upon social contact networks and mixing patterns, which suggest that influenza epidemics are likely to spread quickly through schools [3, 4]. As early as the 1960s, studies have identified community-wide benefits from the vaccination of school age children [5]. Historically, young children were believed to be the drivers of seasonal influenza due to their high clinical attack rate [6], social contact rate within schools [3], and sustained household contact [7]. Glezen and Couch reported on interpandemic influenza from 1974 to 1976 and found that the burden of morbidity was highest among children, particularly during the early stages of the epidemic seasons [8].

To aid in considering interventions for future influenza epidemics, a retrospective ecologic study of laboratory-confirmed influenza infection in Utah from 2000 to 2011 was conducted and the relative timing of influenza infection by age group was evaluated. The objective was to define the age groups in which influenza activity first peaked, which may represent critical populations for influenza surveillance and mitigation strategies.

METHODS

This study was approved and granted a waiver of informed consent by the University of Utah and Intermountain Healthcare (Intermountain) Institutional Review Boards.

Setting and Identification of Patients With Influenza

A retrospective study of laboratory-confirmed influenza infection among patients cared for at any Intermountain facilities in Utah from July 1, 2000 through June 30, 2011 was performed. Intermountain is a large vertically integrated healthcare delivery organization that operates 20 hospitals and more than 100 ambulatory care facilities in Utah. All Intermountain facilities share a computerized record system, which was queried for cases of influenza infection, defined as a positive real-time reverse-transcriptase polymerase chain reaction (Luminex xTAG RVP; Luminex, Austin, TX), direct fluorescent antibody assay (Simulfluor respiratory screen; Light Diagnostics; Temecula, CA), or viral culture.

Seasonal Profiles

Annual influenza seasons were defined between July 1 of 1 year and June 30 of the following year. Utah experienced 2 distinct waves of the 2009 H1N1 pandemic: a spring and a fall wave [9]. Data from the 2 waves were analyzed separately due to the potential for differences in
transmission rates during the spring and fall waves. Cases identified from April to July 2009 were considered to be the first wave of pandemic H1N1, and cases from August to November 2009 were considered to constitute the second wave of pandemic H1N1.

The community-level epidemic midpoint was defined as the week when 50% of the total season’s cumulative number of infections was reached. Influenza epidemics were defined as ±5 weeks surrounding the community-level epidemic midpoint. The data were stratified by age groups, including 0–4 (infant to toddler), 5–11 (elementary school age), 12–18 (junior high/high school age), 19–25 (college age), 26–49 (young adults), 50–64 (older adults), and >65 (elderly adults) years. Distributions of influenza activity were evaluated for each season and then aggregated across all 12 seasons.

Statistical Analysis
Timeliness (lead/lag time) of influenza activity was calculated to compare the relative timing of influenza-associated presentation to healthcare by age group. This was calculated by comparing the amount of days between each age group’s peak relative to the community epidemic midpoint. For the primary analysis, timeliness was calculated for each age group across the 12 seasons. Lag time was calculated as the difference between the age-group-specific peak and the community epidemic midpoint. To examine whether the temporal patterns were more distinct in more dramatic epidemics, a secondary analysis was performed, limited to influenza seasons with well-defined epidemic peaks using prespecified criteria, as defined by Schanzer et al and Sebastian et al, including visual observation of defined epidemic peaks and a normal distribution of cases throughout the epidemic period [10, 11]. The following seasons met these criteria: 2002–2003, 2003–2004, 2005–2006, 2007–2008, and the first and second waves of 2009 H1N1. Due to potential differences in pre-existing antibody in older individuals, we also compared the relative timing by age group between seasonal and pandemic years (Supplemental Materials). The pattern of timing by age group was similar.

Mean differences in relative timing by age group were calculated and are presented graphically with error bars representing the 95% confidence intervals. Similar to Schanzer et al, nonoverlapping confidence intervals indicate a significant difference in the timing of influenza infection between 2 age groups [10]. We also used the Wilcoxon-Mann-Whitney test to perform a series of non-parametric comparisons of the median difference in the timing of influenza infection among different age groups (Supplemental Materials). For graphical purposes, influenza activity data were aggregated by week for each epidemic season. All statistical analyses were performed using Stata11.2 (StataCorp, College Station, TX).

For a sensitivity analysis, we evaluated the relative timing of peak influenza activity between age groups using both laboratory-confirmed cases of influenza infection and surveillance for influenza-like illness (ILI) activity using administrative data. The magnitude and direction of the results were in good agreement using these different methods. However, the results reported below used laboratory-confirmed influenza cases as ILI may be subject to bias due to its nonspecific nature.

RESULTS
Characterization of Influenza Seasons
The number of influenza cases exhibited strong seasonal fluctuations and varied substantially among the seasons included in these analyses (Supplementary Figure 1). From 2000–2011, 22 095 laboratory-confirmed cases of influenza infection were identified, with a median of 1742 cases per season (range: 94–4363). Ninety-two percent of the influenza seasons were predominantly due to influenza A viruses. Influenza A/H3N2 and A/H1N1 viruses predominated in 6 and 5 seasons, respectively.

Timing of Peak Influenza Activity
The average timing of influenza activity by age group is presented in Figure 1A. Influenza activity consistently occurred earlier among older school age children (12–18 years of age) when compared to other age groups, with 63% of cases occurring before/during the week of the community epidemic midpoint. Influenza activity among persons older than 65 was consistently later, with 71% of cases occurring during/after the week of the community midpoint. The patterns were similar when the analysis was restricted to the 6 seasons with more dramatic peaks. The average variation of the age specific peak from the community midpoint is shown in Figure 2A. The average lead-time for children 12–18 years was –1.8 (95% CI: –3.7 to .1) days. Peak influenza activity among adults 50–64 years was slightly later, and occurred 1.7 (95% CI: –0.8 to 4.2) days following the overall community peak (P = .10). Influenza activity peaked latest among persons ≥65, 4.5 (95% CI: 1.0–8.0) days after the community peak and 6.3 days after the peak among older school age children (P = .02). These patterns were consistent, with minor variations noted between individual influenza seasons (Supplemental Materials).

In the analysis limited to more defined seasons, the patterns were similar but the differences were more
distinct (Figure 1B). Influenza activity peaked earliest among children 12–18 years, with an average lead time of −2.5 (95% CI: −4.5 to −.5) days (Figure 2B). Influenza activity among adults 50–64 years peaked an average of 3.3 (95% CI: 1.9–4.8) days later than the community midpoint ($P = .03$). Peak influenza activity among those ≥65 years occurred even later, 5.3 (95% CI: 7–9.9) days after the overall community midpoint ($P = .03$).

**DISCUSSION**

In this study, influenza activity exhibited subtle differences in the age-specific timing of community epidemics. Influenza infection peaked earlier among older school age children (12–18 years of age). Peak activity in this age group preceded that of younger children by 2 days. Influenza activity lagged significantly among adults ≥65 years of age, lagging 6 days behind older school age children.

Due to influenza’s high clinical attack rate among young children, previous studies have suggested that they may be the first to experience influenza activity and drive the spread of disease in the community [12]. Social contact studies have found that high school students and young adults may be particularly influential in the spread of influenza epidemics due to their wide contact networks [3]. Other reports have also indicated that younger
school age children may be important in the transmission of influenza virus, perhaps as a consequence of their high attack rate [4, 12]. In a seminal cohort community study, Monto et al reported variability in the timing of peak influenza activity during the 1976–1981 influenza seasons; however, infection rates peaked among children 5–19 years and declined among older age groups [13]. Recent studies suggest that peak activity first occurs among older school age children [4, 10, 11]. Schanzer et al examined influenza seasons with a single predominant strain accounting for ≥80% of antigenically characterized cases and found that influenza epidemics peaked earliest among persons 10–19 years old. All consecutive seasons were included in the primary analysis, and demonstrated a similar pattern, albeit with smaller time differences. As expected, when this analysis was restricted, the difference in the time of peak activity among older children was greater.

Adolescents as a group have characteristics that may contribute to these findings. Individuals at this stage of life have increased interpersonal, nonfamilial contact within their own age group and typically return home to their families on a daily basis. Academically, this age group tends to change classes multiple times per day, with each class consisting of different contacts and a significant portion of time spent in small groups. Close contact of this variety (academic activities, dating, close friendship cohorts, sporting events, after-school activities, and other age-appropriate activities) could serve as a highly efficient dissemination route in which an influenza-infected individual transmits the virus to their close adolescent contacts, each of which return that infection to their families (young adults and younger children). As those family members subsequently spread the infection to their close contacts, additional adolescents will become infected and the cycle can continue.

Taken together, these studies and behaviors suggest that prioritizing influenza mitigation strategies in the population of older children might delay or decrease influenza epidemics. Nationally, only 35% of children 13–18 years of age received seasonal influenza vaccinations. It seems plausible that increasing influenza immunization coverage, particularly among older school age children, has the potential to blunt influenza transmission. Additionally, mathematical models have attempted to quantify the effects of other potential influenza mitigation strategies.

Figure 2. Timing of peak influenza activity relative to the community epidemic midpoint, presented as the mean difference across (A) 13 consecutive influenza seasons and (B) 6 nonconsecutive influenza seasons with distinct epidemic peaks. Note: Dashed gray line indicates the community-wide epidemic midpoint. Error bars represent 95% confidence intervals.
such as school closures [14–17]. Some models suggest that school closure in addition to keeping children at home may reduce the attack rate by >90% [15]; however, other models suggest a marginal effect upon epidemic size [16, 17].

This study is subject to several limitations. First, the data are derived from a single state and may not be generalizable to the entire United States. However, these data are consistent with published reports by Schanzer et al in Canada [10] and Timpka et al in Sweden [18], and are the first to confirm these findings in the United States. Second, it was not possible to account for potential age-specific differences in healthcare-seeking behavior. Third, influenza viral testing is likely to underestimate the overall burden of influenza virus in the community.

In conclusion, influenza infection in Utah displays temporal differences in peak activity across multiple seasons. Young children have conventionally been regarded as the drivers of local influenza transmission. Older school age children (12–18 years) exhibited peak influenza activity more than 6 days before peak activity occurred in the elderly. Further studies are needed to investigate influenza mitigation strategies in this age group, and their effect(s) upon community transmission. Additionally, age-specific surveillance may be useful in the early detection of emerging waves of seasonal and pandemic influenza.

Supplementary Data

Supplementary materials are available at the Journal of the Pediatric Infectious Diseases Society online (http://jpids.oxfordjournals.org). Supplementary materials consist of data provided by the author that published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

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References