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## Relative Timing of Influenza Disease by Age Group

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### Abstract

A detailed understanding of influenza movement in communities during yearly epidemics is needed to inform improved influenza control programs. We sought to determine the relative timing of influenza presentation and symptom onset by age group and influenza strain.

Prospective, laboratory-confirmed surveillance was performed over three moderate influenza seasons in emergency departments and inpatient settings of both medical centers in Winston-

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Salem, NC. Influenza disease presented first in school age children through community epidemics of influenza A(H1N1)pdm09 and influenza B, and first in persons 5–49 years old for influenza A(H3N2). This finding indicates that influenza prevention in persons 5–49 years of age may be particularly important in influenza epidemic control.

## Keywords

human influenza; influenza A virus; influenza B virus; inpatient; hospital emergency services; epidemiology

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Influenza virus is an important cause of illness, outpatient visits and hospitalizations among persons of all ages.[1–7] Globally, influenza virus caused an estimated 508,000 deaths in 2010.[8] The importance of influenza epidemic control is recognized as an international public health priority.[9] An improved understanding of influenza spread within communities is needed to inform design of influenza prevention and control programs.

Despite the large annual influenza disease burden, a detailed understanding of how influenza spreads through communities is lacking. Literature suggests that children are important to the spread of influenza infection.[10–15] This important work has highlighted the need for additional studies that further examine the spread of influenza within communities.[16–18] This prospective, laboratory-confirmed influenza surveillance study was designed to address this gap by using prospective data to determine the relative timing of influenza disease by serotype and age group. We tested the hypothesis that influenza disease occurs first in school age children during annual influenza epidemics. Defining which age groups seek medical attention for influenza early in annual seasonal epidemics is important to inform the debate about universal influenza vaccination.[19–24]

## Methods

### Study Overview

Prospective, laboratory-confirmed surveillance for influenza was performed throughout each respiratory season among persons of all ages presenting to the emergency department or inpatient wards of the two large medical centers, including the children's hospital, located in Winston-Salem, North Carolina. More than 94% of all Forsyth County residents that are seen in the emergency department or are hospitalized receive care at these surveillance hospitals.

### Approval

Eligible persons were approached for enrollment, and written informed consent and assent, when appropriate, were provided. This study was approved by the Wake Forest School of Medicine Institutional Review Board and performed under an authorization agreement between the institutional review boards of Forsyth Medical Center and Wake Forest School of Medicine.

## Study population

Patients of all ages who resided in Forsyth County or a contiguous North Carolina county and presented to any surveillance emergency department or inpatient setting with fever (by report or documentation) or any acute respiratory symptoms were study-eligible. Patients were eligible for enrollment if they presented with fever, cough, nasal congestion, difficulty breathing, ear pain, sore throat, and/or wheezing and if admitted were enrolled within 24 hours of hospitalization. Patients who presented with only fever were eligible unless they had an identified non-respiratory source of fever, i.e. cellulitis or urinary tract infection.

## Influenza seasons

Surveillance was systematically conducted each year from November through April and began earlier or extended later if influenza was detected in the hospital laboratories or reported regionally. Enrollment was performed during daytime hours from Monday through Thursday during four consecutive influenza seasons from 2009–2010 through 2012–2013. Regional and national data from the CDC indicates three of these four seasons had moderate influenza circulation in the U.S and 2011–2012 was a mild influenza season; all three moderate influenza seasons had sufficient influenza-positive observations and were included in this analysis.[25] We enrolled fewer than half the number of patients with study-confirmed influenza in 2011–2012 than any other study years, and these 26 influenza-positive patients were divided among three serotypes. Thus, 2011–2012 was excluded given too few influenza-positive observations to compute an epidemic curve.

Regional data was evaluated to determine the circulating influenza viruses identified during each study season.[26] Influenza A(H1N1)pdm09 comprised 98% of all isolates from August 30, 2009 through April 17, 2010. From October 31, 2010 through April 30, 2011, the proportions of all typed influenza isolates were 21% influenza A(H1N1)pdm09, 58% influenza B, and 21% influenza A(H3N2) virus. From October 28, 2012 through April 27, 2013, the proportions of all typed influenza isolates were 59% influenza B, 37% seasonal influenza A (H3N2), and 2% influenza A(H1N1)pdm09. Hence, we included all study-confirmed influenza A(H1N1)pdm09 from 2009–2010 and 2010–2011 and both study-confirmed influenza B and influenza A(H3N2) in 2010–2011 and 2012–2013.

## Patient/Parental Questionnaire

Patients or their guardians completed a standardized questionnaire to obtain demographic information and medical history. The date of birth was used to compute age at the time of enrollment. The age groups were determined *a priori* to be 0–4 years (preschool age), 5–17 years (school age), 18–49 years, and ≥ 50 years. We obtained the number of symptom days at enrollment from the patient or guardian with a cut-off maximum of 14 days. The date of symptom onset was computed by subtracting the number of symptom days from the date of enrollment.

High-risk medical conditions included all conditions with a specific CDC recommendation to receive the 2009–2010 influenza vaccine.[27] They include cardiopulmonary diseases, metabolic diseases, renal diseases, hemoglobinopathies, primary or secondary immunodeficiency, cognitive or neurologic conditions that can compromise respiratory

functioning, pregnancy and children on long-term aspirin therapy. High-risk conditions were included because of their association with an increased risk of severe influenza disease.

Influenza vaccination status was obtained by patient/guardian report and verified in the North Carolina Immunization Registry or practice, when available. Most children < 6 months (99.7%) and 83% adults > 18 years had their vaccination status verified. Full vaccination was one of the following: receipt of one dose of influenza vaccine >14 days prior to enrollment for all persons > 9 years of age, receipt of one dose of influenza vaccine >14 days prior to enrollment and history of influenza vaccination in prior year for children 1–8 years of age, and receipt of two doses of influenza vaccine one month apart with last dose >14 days prior to enrollment in children <9 years who had not received influenza vaccine in a prior year.

### Nasal/Throat Swabs

A mid-turbinate nasal specimen and a throat specimen were obtained from enrolled subjects using flocked swabs. Both specimens were placed in one vial of viral transport media and transported on ice to the study laboratory.

### Detection of Influenza

All nasal and throat swabs were cultured for influenza viruses on R-Mix Too™ cells (Diagnostic Hybrids). Detection of influenza culture was performed by direct fluorescence microscopy using type-specific antibodies (Diagnostic Hybrids). Reverse transcriptase polymerase chain reaction (RT-PCR) testing for influenza A(H3N2), influenza A(H1N1)pdm09, and influenza B without lineage delineation was performed using a RT-PCR analysis protocol developed at the CDC and kindly made available under a Material Transfer Agreement (Stephen Lindstrom, PhD, CDC). A human RNase P gene RNA was detected in parallel for each specimen as an internal control for human subject specimen adequacy.

A specimen was classified as influenza A(H1N1)pdm09 positive if the RT-PCR for influenza A(H1N1)pdm09 was positive. A specimen was classified as influenza B positive if type-specific RT-PCR or viral culture was positive. A specimen was classified as influenza A(H3N2) positive if the RT-PCR or viral culture was positive for influenza A(H3N2).

### Statistical Analyses

By identifying the enrollment date of all influenza A(H1N1)pdm09 positive specimens obtained by prospective influenza surveillance for each season, we determined the influenza A(H1N1)pdm09 epidemic midpoint. The epidemic midpoint was defined as the date when the cumulative distribution of study-confirmed influenza A(H1N1)pdm09 infections reached 50% of the total for each season.[10] The demographic characteristics of persons enrolled on or before the epidemic midpoint were compared to those persons enrolled after the epidemic midpoint using the chi-square test. The cumulative proportion of study-confirmed influenza A(H1N1)pdm09 infections for each age group was plotted by time in weeks, relative to the overall epidemic midpoint for each season. The rank sum days of influenza A(H1N1)pdm09 infection for each age group were compared by Kruskal-Wallis test. These calculations and analysis were repeated using date of symptom onset instead of enrollment date to address

the possibility that the timing of presentation to the hospital or emergency department varied by age group.

The analysis for both study-confirmed influenza B and influenza A(H3N2) used the same approach for each strain during the 2010–2011 and 2012–2013 seasons.

## Results

Among 4083 approached and eligible patients presenting with fever or acute respiratory symptoms to the emergency department or inpatient setting in 2009–2010, 2010–2011 or 2012–2013, 3373 (83%) were enrolled. The gender and age group of persons who were approached and enrolled or not enrolled were similar. The study population comprised all 447 persons who had any of three study-confirmed influenza serotypes, 97% of all influenza positive persons from these study years. The study population comprised 447 (13%) persons who had any of three strains of study-confirmed influenza--93 persons with study-confirmed influenza A(H1N1)pdm09 in 2009–2010 or 2010–2011, 187 persons with study-confirmed influenza B in 2010–2011 or 2012–2013, and 177 persons with study confirmed influenza A(H3N2) in 2010–2011 or 2012–2013. Ten persons were co-infected with two influenza strains; 7 had influenza B and influenza A(H1N1)pdm09 and 3 had influenza B and influenza A(H3N2). By year for study-confirmed influenza A(H1N1)pdm09, 56 (6%) of 977 enrolled persons in 2009–2010 had influenza A(H1N1)pdm09 infection (epidemic midpoint 11/03/2009 by timing of enrollment) and 37 (3%) of 1020 enrolled persons in 2010–2011 had infection (epidemic midpoint 2/10/2011). For influenza B, 125 (12%) of 1020 enrolled persons in 2010–2011 had influenza B infection (epidemic midpoint 1/31/2011) and 62 (5%) of 1376 enrolled person in 2012–2013 (epidemic midpoint 3/6/2013). For influenza A(H3N2), 44 (4%) of 1020 enrolled persons in 2010–2011 had influenza A(H3N2) infection (epidemic midpoint 2/16/2011) and 133 (10%) of 1376 enrolled person in 2012–2013 (epidemic midpoint 12/10/2012).

For each influenza strain, the demographic characteristics of persons enrolled before or on the epidemic midpoint were compared to those enrolled after the epidemic midpoint (Table 1). For influenza A(H1N1)pdm09 and influenza A(H3N2), more children 5–17 years and adults 18–49 years were enrolled before or on the epidemic midpoint than after the epidemic midpoint. For influenza B, more children 0–4 years and 5–17 years were enrolled before or on the epidemic midpoint than after the epidemic midpoint. There were no significant differences before and after the midpoint by year, sex, high-risk conditions, insurance, full influenza vaccination status or hospitalization for any strain. Duration of symptom at time of presentation with influenza A(H1N1)pdm09 were similar for patients seen before and after the epidemic midpoint with an overall mean of 3.8 days for influenza A(H1N1)pdm09, 4.2 days for influenza B, and 4.3 days for influenza A(H3N2).

The cumulative proportion of all study-confirmed influenza A(H1N1)pdm09 infections from 2009–2010 and 2010–2011 was plotted by time in weeks, relative to the overall influenza A(H1N1)pdm09 epidemic midpoint for each season as determined by date of enrollment in prospective influenza surveillance. The median of influenza A(H1N1)pdm09 and influenza B infection (cumulative proportion of 0.5 or 50<sup>th</sup> percentile) was earliest for children 5–17

years of age. Children 5–17 years of age presented with study-confirmed influenza A(H1N1)pdm09 infection at least 10.5 days earlier all other age groups (Table 2,  $p=0.006$  by Kruskal-Wallis test) and closely resembled Figure 1A. Also with influenza A(H1N1)pdm09, adults 18–49 years presented after school age children but prior to the epidemic midpoint. For study-confirmed influenza B, children 5–17 years presented at least 15 days earlier than all other age groups (Table 2,  $p=0.0003$  by Kruskal-Wallis test) and closely resembled Figure 1B. Children 0–4 years of age also presented prior to the epidemic midpoint with influenza B and all adults presented after the epidemic midpoint. For study-confirmed influenza A(H3N2), both adults 18–49 years and children 5–17 years presented prior to the epidemic midpoint with adults presenting 1.5 days earlier than school age children (Table 2,  $p=0.04$  by Kruskal-Wallis test) and closely resembled Figure 1C.

These analyses were repeated by plotting the date of reported symptom onset among persons with each strain of study-confirmed influenza, relative to its epidemic midpoint for each season (as recalculated based on symptom onset to a maximum of 14 days). The results were similar to the analysis based on enrollment date. School age children had the earliest onset of symptoms with influenza A(H1N1)pdm09 and influenza B. Children 5–17 years of age reported onset of symptoms with study-confirmed influenza A(H1N1)pdm09 infection at least 10 days earlier than all other age groups (Table 2,  $p=0.008$  by Kruskal-Wallis test, Figure 1A). Following the same pattern as with influenza A(H1N1)pdm09 enrollment, adults 18–49 years had onset of symptoms after school age children but prior to the epidemic midpoint. Children 5–17 years of age reported onset of symptoms with study-confirmed influenza B infection at least 15.5 days earlier than all other age groups (Table 2,  $p=0.0002$  by Kruskal-Wallis test, Figure 1B). Similarly, children 0–4 years of age had onset of symptoms with influenza B prior to the epidemic midpoint. Symptom onset for study-confirmed influenza A(H3N2) followed the trend observed for presentation; adults 18–49 years reported onset of symptoms 1 day prior to children 5–17 years and both were before the epidemic midpoint (Table 2,  $p=0.14$  by Kruskal-Wallis test, Figure 1C).

## Discussion

In this study using prospective, laboratory-confirmed influenza surveillance data over three seasons, school age children 5–17 years of age presented to the emergency department or inpatient setting earlier with influenza A(H1N1)pdm09 and influenza B disease than patients 0–4, 18–49 or 50 years of age. School age children also presented early, but not first, with influenza A(H3N2) disease during these seasons, presenting 1.5 days after adults 18–49 years of age, and before younger children or older adults. Notably, the median time of presentation for school age children preceded the epidemic midpoint for all three influenza strains. These findings suggest that influenza disease transmission among school age children is an important determinant in the spread of influenza disease throughout the community. Annual influenza vaccination of school age children provides community-wide protection.[11;28–33] These findings support recommendations that all school age children receive the influenza vaccine each year.[34] Although there are many logistical challenges to vaccinating school age children,[35–37] programs that enhance the vaccination coverage of school age children may be especially successful in reducing influenza disease.

This study is novel in that it utilizes prospective surveillance with culture and RT-PCR to determine patients who are influenza-positive by serotype, avoiding the bias associated with physician-ordered testing and lack of test specificity for influenza A serotypes associated with rapid influenza tests. Study results using this distinct approach complement the literature suggesting that influenza community epidemics are disproportionately driven by disease transmission in school age children. Glezen et al. found that the large burden of influenza B infection in 1976–1977 among school age children in Houston, Texas preceded most of the identified cases among preschool children and adults.[38] By examining 11 years of Canadian national surveillance data from physician-ordered influenza tests, Schanzer et al. showed that children 10–19 years and adults 20–29 years had positive influenza tests 1 week earlier than other age groups; and that positive tests in children 10–19 years of age peaked 3 days earlier than in younger children and young adults during the influenza A(H1N1)pdm09 epidemic.[10]

Community adoption of programs to vaccinate school age children results in measurable benefits in disease reduction in both vaccine recipients and unvaccinated community members, as well as other indirect benefits including increased school attendance. [11;30;31;39;40] Reichert et al. showed that the population of Japan showed marked increases in rates of excess mortality following discontinuation of a countrywide program to promote influenza vaccination of schoolchildren.[32] Copeland et al. found that a Texas school district that closed all public schools for 8 days during the peak of the influenza A(H1N1)pdm09 epidemic had lower rates of self-reported acute respiratory illness or influenza-related emergency department visits than nearby communities with schools that remained mostly open.[33]

Another important finding in this study is that median time of influenza presentation and symptom onset in adults 18–49 years preceded the epidemic midpoint for both influenza A strains but not influenza B strains. Influenza A strains have been shown to evolve in humans approximately 2-fold to 3-fold faster than influenza B strains.[41–43] It may be that protective immunity following exposure to influenza B strains persists longer than that following influenza A exposure, given more rapid influenza A evolution. More adults than children enrolled in our study may have been exposed to influenza B strains of both Yamagata and Victoria lineages that have circulated since the early 1980s,[44] and consequently may have had more pre-existing immunity to circulating influenza B strains. It is interesting to speculate that prior strain-specific immunity may partially explain the relative timing of influenza A and influenza B to the epidemic midpoint for adults 18–49 years of age.

Since implementation of the universal childhood influenza vaccination recommendation in 2008,[45] influenza vaccination coverage for U.S. children 0.5–17 years of age was 55% for either seasonal or monovalent H1N1 vaccine in 2009–2010.[46] Influenza vaccine coverage was highest for young children and lowest for adolescents,[47] and these rates reflect the many logistical challenges in vaccinating school age children.[37] Barriers to increased vaccination of school age children include, but are not limited to, vaccine supply limitations, need for extra office visits to get the yearly vaccine each season, and challenges of

communication between primary care providers, subspecialists, schools, health departments, pharmacists and other influenza vaccine providers.[35;37;48]

An important strength of our study is that prospective surveillance of persons of all ages was performed over multiple years, and influenza detection for circulating strains was not influenced by physician-ordered influenza testing patterns. This approach was particularly important during the 2009–2010 season given reports of poor rapid influenza diagnostic test detection of influenza A(H1N1)pdm09 and recommendations discouraging the use of rapid influenza diagnostic tests that season.[49;50] The majority of approached patients were enrolled with a range of mild to severe influenza disease. All major influenza serotypes circulating during these study years were available for analysis.

There are several limitations to this study. Surveillance was limited to one community, however our findings remain consistent over multiple seasons and is consistent with retrospective studies. There may be systematic differences between persons with influenza who were and were not enrolled. Enrolled patients sought medical care in the emergency department or were hospitalized with influenza infection, though most influenza disease is managed in the non-hospital setting.[4;51] Many pediatric and adult emergency department visits are for minor complaints;[52–54] approximately 10% of emergency department visits by persons <65 years in 2007 were non-urgent, with similar rates of non-urgent visits among uninsured, publicly insured and privately insured patients.[55] This study enrolled patients of all ages with a range of mild to severe influenza disease.

## Conclusion

This study demonstrated that school age children acquired influenza A(H1N1)pdm09 and influenza B disease earlier than younger and older persons. The pattern for influenza A(H1N1)pdm09 and influenza A(H3N2) was children and adults 5–49 years of age presented prior to the epidemic midpoint. Each year our communities are besieged by influenza, relentless and lethal. Strongest defenses must stand before children; influenza strikes them first.

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## Abbreviations

<b>CDC</b>	Centers for Disease Control and Prevention
<b>RT-PCR</b>	reverse transcriptase polymerase chain reaction



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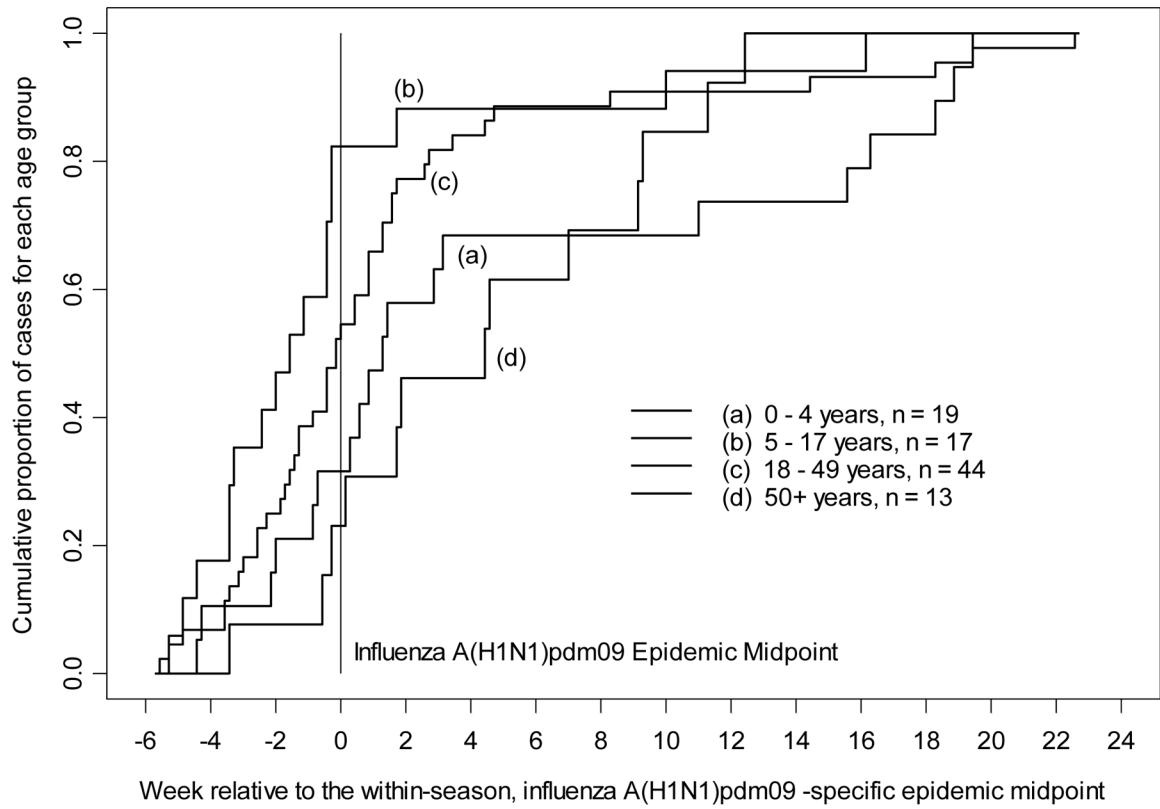
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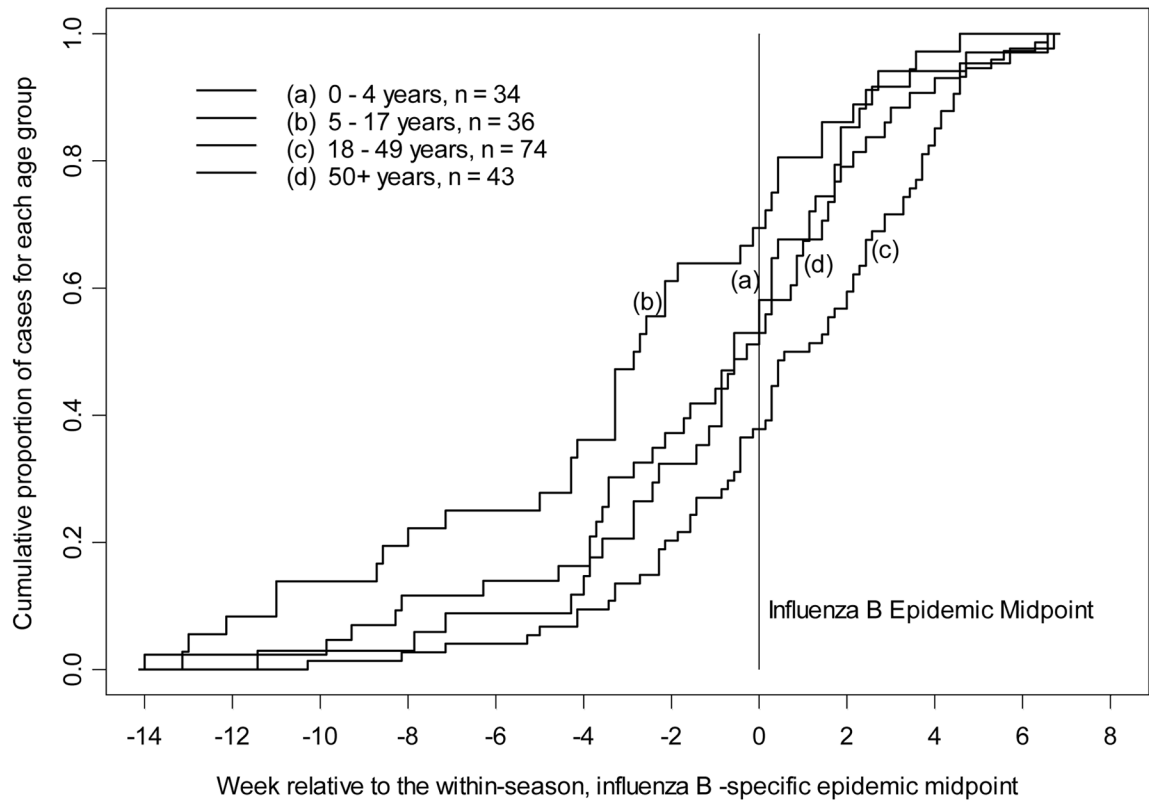
### Highlights

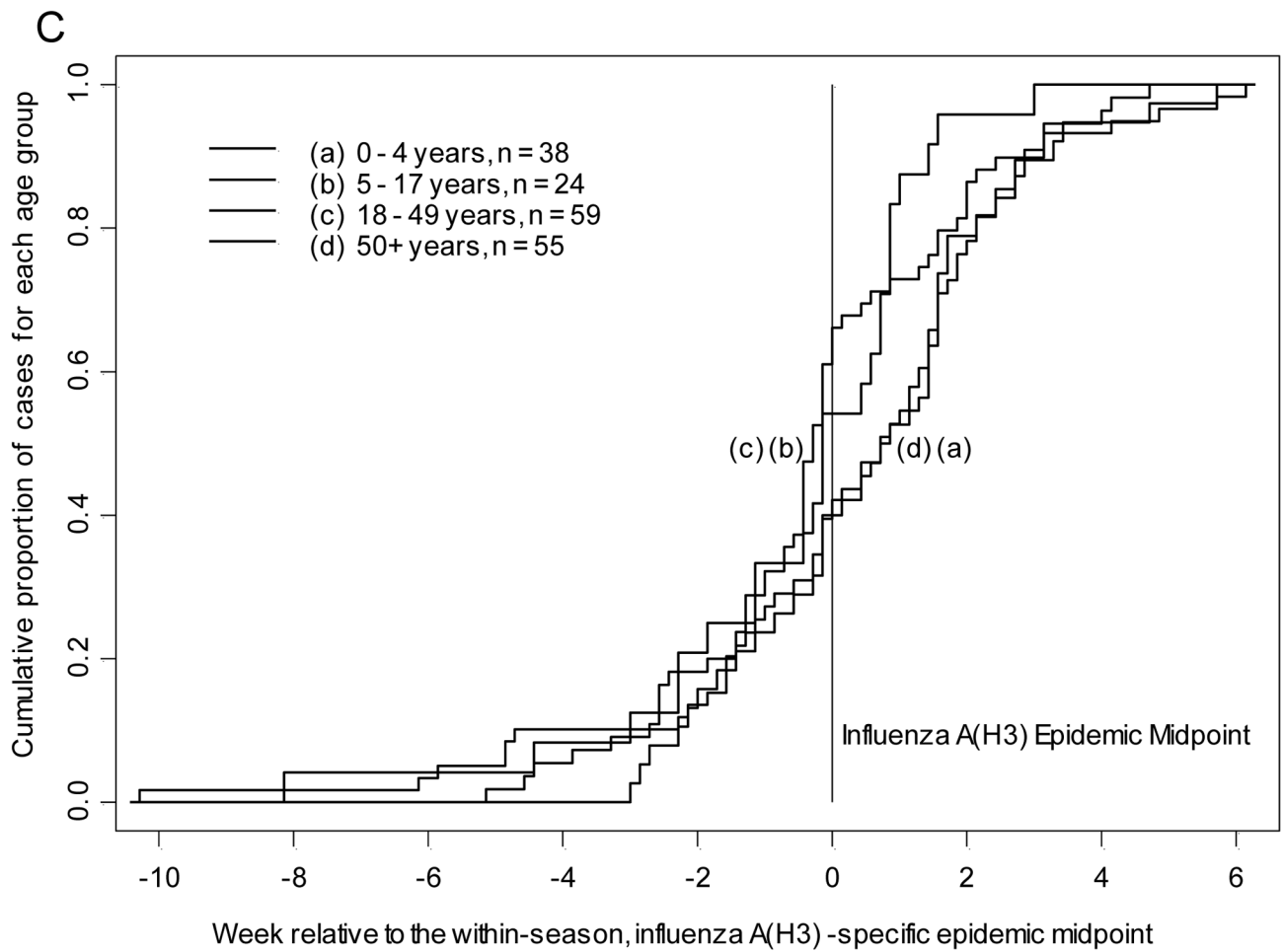
- We prospectively measured relative timing of laboratory-confirmed influenza.
- Influenza occurred earliest in children 5–17 years for influenza A(H1N1) and B.
- Influenza occurred earliest in persons 5–49 years for influenza A(H3N2).
- Yearly influenza occurs in school age children before the very young and elderly.

A



**B**





**Figure 1.** Timing of symptom onset for laboratory-confirmed influenza by age group and strain with A) influenza A(H1N1)pdm09, B) influenza B, and C) influenza A(H3N2).

**Table 1**  
Demographic characteristics of persons by influenza strain and enrollment date relative to the epidemic midpoint

Characteristics	Timing of influenza infection for each circulating strain											
	Influenza A(H1N1)pdm09				Influenza B				Influenza A(H3)			
	At or before Midpoint	After Midpoint	P-value*	n (row %)	At or before Midpoint	After Midpoint	P-value*	n (row %)	At or before Midpoint	After Midpoint	P-value*	n (row %)
<b>Age group</b>			0.008				0.04				0.04	
0-4 years	6 (32%)	13 (68%)		21 (62%)	13 (38%)		16 (42%)	22 (58%)				
5-17 years	14 (82%)	3 (18%)		26 (72%)	10 (28%)		14 (58%)	10 (42%)				
18-49 years	24 (55%)	20 (41%)		34 (46%)	40 (54%)		38 (64%)	21 (36%)				
50 years	4 (31%)	9 (69%)		20 (47%)	23 (53%)		23 (41%)	33 (59%)				
<b>Sex</b>			0.37				0.84				0.85	
Male	17 (46%)	20 (54%)		52 (55%)	43 (45%)		41 (51%)	40 (49%)				
Female	31 (55%)	25 (45%)		49 (53%)	43 (47%)		50 (52%)	46 (48%)				
<b>Insurance</b>			0.07				0.09				0.46	
Public Only	31 (61%)	20 (39%)		59 (61%)	37 (39%)		46 (51%)	44 (49%)				
Private	9 (33%)	18 (67%)		29 (48%)	31 (52%)		29 (48%)	32 (52%)				
None	8 (53%)	7 (47%)		13 (42%)	18 (58%)		15 (63%)	9 (38%)				
<b>Year</b>			0.97				0.64				0.83	
2009-2010	29 (52%)	27 (48%)		NA	NA		NA	NA				
2010-2011	19 (51%)	18 (49%)		69 (55%)	56 (45%)		22 (50%)	22 (50%)				
2012-2013	NA	NA		32 (52%)	30 (48%)		69 (52%)	64 (48%)				
<b>High-risk condition</b>			0.94				0.88				0.39	
Yes	22 (51%)	21 (49%)		40 (53%)	35 (47%)		46 (48%)	49 (52%)				
No	26 (52%)	24 (48%)		61 (54%)	51 (46%)		45 (55%)	37 (45%)				
<b>Full vaccination<sup>†</sup></b>			0.48				0.63				0.87	
Yes	3 (38%)	5 (63%)		15 (50%)	15 (50%)		15 (50%)	15 (50%)				
No	45 (53%)	40 (47%)		86 (55%)	71 (45%)		76 (52%)	71 (48%)				
<b>Hospitalized</b>			0.23				0.14				0.12	



Characteristics	Timing of influenza infection for each circulating strain											
	Influenza A(H1N1)pdm09				Influenza B				Influenza A(H3)			
	At or before Midpoint	After Midpoint	P-value*		At or before Midpoint	After Midpoint	P-value*		At or before Midpoint	After Midpoint	P-value*	
n (row%)	n (row %)			n (row%)	n (row %)			n (row%)	n (row %)			n (row %)
Yes	7 (39%)	11 (61%)			20 (44%)	25 (56%)			25 (43%)	33 (57%)		
No (ED only)	41 (55%)	34 (45%)			81 (57%)	61 (43%)			66 (55%)	53 (45%)		
<b>Symptoms</b>			0.17				0.81				1.00	
Fever only	0	0		0	0	0		1 (50%)	1 (50%)			
Respiratory only <sup>††</sup>	9 (69%)	4 (31%)		19 (56%)	15 (44%)			11 (52%)	10 (48%)			
Both	39 (49%)	41 (51%)		82 (54%)	71 (46%)			79 (51%)	75 (49%)			
<b>Symptom Days</b>			0.64								0.80	
2 days	18 (49%)	19 (51%)		33 (65%)	18 (35%)		0.07	24 (53%)	21 (47%)			
>2 days	30 (54%)	24 (46%)		68 (50%)	68 (50%)			67 (51%)	64 (49%)			
Mean (SD)	3.9 (2.8)	3.7 (2.4)		4.0 (2.6)	4.5 (3.0)			3.7 (2.3)	4.9 (3.6)			
Range	1-14	2-14		1-14	1-14			1-14	1-14			

\* P-value for comparison of the characteristic between persons enrolled at or before the epidemic midpoint and those enrolled after the epidemic midpoint.

<sup>†</sup> Full vaccination for H1N1 monovalent vaccine in 2009-2010 only and seasonal vaccine for all subsequent years.

<sup>††</sup> Report of any respiratory symptoms--cough, nasal congestion, difficulty breathing, ear pain, sore throat or wheezing.

**Table 2**

Median day of enrollment or symptom onset relative to epidemic midpoint by age group and strain.

	Influenza A(H1N1) pdm09	Influenza B	Influenza A(H3)
<b>Median day of enrollment relative to epidemic midpoint<sup>‡</sup></b>			
<b>0–4 years</b>	6 days	-5 days	3.5 days
<b>5–17 years</b>	-11 days	-20 days	-3.5 days
<b>18–49 years</b>	-0.5 days	5.5 days	-5 days
<b>50 years</b>	32 days	2 days	7.5 days
<b>p-value*</b>	0.006	0.0003	0.04
<b>Median day of symptom onset relative to epidemic midpoint<sup>‡</sup></b>			
<b>0–4 years</b>	9 days	-4 days	5.5 days
<b>5–17 years</b>	-11 days	-19.5 days	-1 days
<b>18–49 years</b>	-1 days	6 days	-2 days
<b>50 years</b>	31 days	-2 days	5 days
<b>p-value*</b>	0.008	0.0002	0.14

<sup>‡</sup> Negative numbers are medians before the epidemic midpoint, and positive numbers are medians after the epidemic midpoint.

\* P-value was computed using the Kruskal-Wallis Test.