Vaccine 32 (2014) 6451–6456

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Relative timing of influenza disease by age group☆

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ARTICLE INFO

Article history:
Received 31 March 2014
Received in revised form 22 July 2014
Accepted 22 September 2014
Available online 1 October 2014

Keywords:
Human influenza
Influenza A virus
Influenza B virus
Inpatient
Hospital emergency services
Epidemiology

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-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.

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].

1. Methods

1.1. 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.

1.2. 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

Abbreviations: CDC, Centers for Disease Control and Prevention; RT-PCR, reverse transcriptase polymerase chain reaction.

☆ Components of this work were presented at the Pediatric Academic Societies meeting in Washington, DC in May 2013 and have been accepted for presentation at the Pediatric Academic Societies meeting in Vancouver, Canada in May 2014.

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http://dx.doi.org/10.1016/j.vaccine.2014.09.047
0264-410X/

authorization agreement between the institutional review boards of Forsyth Medical Center and Wake Forest School of Medicine.

1.3. 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 h 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.

1.4. 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 US 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 to 2010 and from 2010 to 2011 and both study-confirmed influenza B and influenza A(H3N2) in 2010–2011 and 2012–2013.

1.5. 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 1 month apart with last dose >14 days prior to enrollment in children <9 years who had not received influenza vaccine in a prior year.

1.6. 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.

1.7. 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).

1.8. 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.