Incidence of symptomatic A(H1N1)pdm09 influenza during the pandemic and post-pandemic periods in a rural Indian community

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SUMMARY

Background—Data on influenza illness rates with population denominators are needed to quantify overall morbidity and to prioritize public health intervention strategies.

Methods—The rates of influenza A(H1N1)pdm09 infection during pandemic phases were determined in a longitudinal community cohort study as part of an influenza vaccine study in a rural community of North India.

Results—During the 711 731 person-weeks of surveillance, a total of 1410/7571 (19%) febrile acute respiratory illness cases were positive for influenza. Of these, 749 (53%) were influenza A(H1N1)pdm09, 643 (46%) influenza B, and 18 (1%) influenza A (H3N2). The overall incidence rate of influenza-associated febrile acute respiratory illness was 128/1000 person-years. The incidence rates of influenza A(H1N1)pdm09 were high during both the pandemic phase (179/1000 person-years; November 2009 to January 2010) and post-pandemic phase (156/1000 person-years; August to October 2010), with children <18 years of age being at the greatest risk of influenza infection in the community.

Conclusions—These findings provide important information for planning clinical and public health intervention strategies to mitigate the impact of influenza epidemics.

Keywords

Incidence; Influenza A(H1N1)pdm09; Epidemiology; Cohort; Rural India

1. Introduction

A novel pandemic strain of influenza virus, A(H1N1)pdm09, emerged in April 2009 and spread rapidly worldwide.[1] Understanding the transmission dynamics and incidence of influenza, especially in resource-constrained countries, where different co-morbidities might lead to a different burden and epidemiology, are important factors in devising public health responses and mitigation strategies for pandemic influenza control.[1,2]

Serological surveys during the early part of the pandemic suggested that the majority of naive populations would be susceptible to A(H1N1)pdm09 infection.[3] Indeed, several studies established a consistent pattern of higher rates of A(H1N1)pdm09 infection in school-aged children relative to younger adults, with the lowest rates observed in older adults.[4–7] The majority of the serological approaches to estimate the incidence of influenza A(H1N1)pdm09 have used a non-cohort-based design by the testing of longitudinal paired sera from pre- and post-pandemic phases or a cross-sectional design where a cut-off threshold was established to estimate exposure and/or infection.[5–7] These studies underscore the need to have better indicators for understanding the incidence rates (IRs) of an epidemic along with population denominators to quantify overall morbidity and to prioritize public health intervention strategies.[2] Modeling studies may have an important role in early estimates of cumulative incidence; however, prospective cohort studies, such as the one described here, are needed to provide the actual community estimates of influenza incidence.

Population-based weekly active surveillance implemented soon after the emergence of pandemic influenza in a rural community in India[8] provided an opportunity to determine the overall incidence of A(H1N1)pdm09 during the first influenza pandemic of the 21st century. This information on magnitude, age distribution, and seasonality of A(H1N1)pdm09 will be useful for modeling disease burden, advocacy, and health system planning.

2. Methods

2.1. Study population

During November 1, 2009 to October 31, 2010, all members of the households residing in three villages located in the Ballabhgarh sub-district of Faridabad, Haryana State in North India, were eligible to enroll in the febrile acute respiratory illness (FARI) surveillance component of an influenza vaccine trial of children aged 6 months to 10 years within the same villages.[8] The vaccine trial is an ongoing prospective, longitudinal, phase IV, household-randomized, controlled, observer-blinded 3-year study (2009–2011) designed to measure the direct and indirect protective effects of immunizing children aged 6 months through 10 years with seasonal inactivated trivalent influenza vaccine (TIV) or a control vaccine (http://www.ClinicalTrials.gov, NCT00934245).[8] The 2009 northern hemisphere influenza vaccine administered in December 2009 through January 2010 included strains: A/Brisbane/59/2007 (H1N1), A/Brisbane/10/2007 (H3N2), and B/Brisbane/60/2008. Pandemic virus was not a component of this vaccine.

Members of 2806 households (enrollment rate >90% of eligible cases) in the villages were enrolled in the FARI surveillance and received weekly home visits, represented as epidemiologic weeks (EW) throughout the year (no surveillance occurred in EW48 and EW53 of 2009 due to vaccination efforts). If a household member who was to be surveyed was not present at the time of the home visit by the study trained surveillance officer, proxy information about possible FARIs was collected from an available adult in the household. Possible FARI cases identified by the study surveillance officers were visited by nurses for confirmation of case definition, clinical assessment, and collection of specimens for influenza testing. The study population was a dynamic study cohort under weekly surveillance, with changes in the household composition (marriages/moves and births/deaths) recorded in the study database as reported throughout the year.

Written informed consent was obtained from each household member for enrollment into the study. For children, consent from their parents was obtained, and where appropriate, assent from the child. Institutional review board approval was obtained from the All India Institute of Medical Sciences, New Delhi, India, the University of Alabama at Birmingham, Birmingham, and the Centers for Disease Control and Prevention, Atlanta.

2.2. Case definition

FARI was defined as a history (current or in the preceding week) of fever with any of the following respiratory complaints: cough, sore throat, congestion/runny nose, earache, or difficulty in breathing.

2.3. Specimen collection and influenza detection

For each FARI episode, combined throat and nasal swabs were collected from children 1 year of age and adults, and nasopharyngeal swabs were collected from infants <1 year of age. US Centers for Disease Control and Prevention real-time RT-PCR protocols were used for the detection and subtyping of influenza viruses, as described previously.[9]

2.4. Data analysis

Clinical and demographic information on FARI cases was collected on paper forms at the weekly household visits. Laboratory results were linked to the FARI surveillance information in the study database. FARI IRs were calculated by taking the total number of FARI cases identified in the age-group for the numerator, and the total person-time contributed by individuals who were surveyed each week in the specific age-group for the denominator. The proportions of samples positive for each influenza subtype in each age group were calculated for each time period. This positive proportion was then applied to the FARI IRs to calculate the influenza IRs overall and by subtype. This yielded influenza IRs adjusted for FARI cases from whom either no respiratory tract samples were obtained or whose samples were inadequate for testing (unsampled cases). IRs and 95% confidence intervals (95% CI) were calculated for pandemic influenza. All statistical analyses were performed using SAS software version 9.2 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Incidence rates for FARI

The total study population under surveillance for at least 1 week during the 1-year study period was 18 220 individuals. The study included 14 229 individuals enrolled into the cohort at the beginning of the study, an additional 3991 individuals who enrolled during the course of the study, and 1359 cohort members who dropped out during the study year (withdrawals, deaths, and migrations). The final population under surveillance on October 31, 2010 was 16 861 individuals. Overall, 9395 incident FARI episodes were recorded with 711 731 person-weeks of observation completed (Table 1). Weekly surveillance of an average 13 687 household members over the year revealed two distinct peaks of FARI episodes (EW45–EW52 in 2009 and EW32–EW40 in 2010), although FARI cases occurred throughout the study period (Figure 1). Over 50% of the incident FARI episodes occurred in children aged 0–18 years, with 30% occurring in children 0–5 years of age. The overall IR for FARI was 686/1000 person-years. The FARI rate was highest in children 0–5 years of age (1672/1000 person-years), followed by children 6–18 years of age (657/1000 person-years) (Table 2).

3.2. Incidence rates for A(H1N1)pdm09 influenza

A total of 81% of incident FARI (7571/9395) cases were tested for influenza. Among the FARI cases unavailable for influenza testing, 56% were adults (19 years) and 44% children (<19 years), and there was no difference in any of the demographic characteristics of those tested vs. not tested. Of the 7571 specimens tested, 1410 (19%) were positive for influenza. Of these, 749 (53%) were influenza A(H1N1)pdm09, 643 (46%) influenza B, and 18 (1%) influenza A (H3N2) (Table 1). There were two distinct peak periods of influenza positivity at EW45–EW52 (November–December) of 2009 and EW32–EW40 (August–October) of 2010, with co-circulation of influenza B viruses throughout the study period (Figure 1). The first peak during the pandemic period was almost exclusively due to influenza A(H1N1)pdm09 virus. The IR for influenza A(H1N1)pdm09 was greatest during the first pandemic phase in November–December 2009 (179/1000 person-years), followed by a second peak in the post-pandemic phase in August–October 2010 (156/1000 person-years) (Figure 2; Table 1).

Age-wise distribution of pandemic A(H1N1)pdm09 revealed the greatest IR in children aged 0–5 years (120/1000 person-years) and 6–18 years (93/1000 person-years) when compared with adults (Table 2). Children aged 0–5 years and 6–18 years were more likely to have A(H1N1)pdm09 (incidence rate ratio (IRR) 2.5, 95% CI 2.1–3.0; and IRR 1.9, 95% CI 1.7–2.2, respectively) than adults aged 19 years and older, indicating that children aged 0–18 years have the greatest IRs for pandemic influenza in the community.

4. Discussion

Understanding the incidence of pandemic influenza is important for devising public health responses and mitigation strategies for pandemic influenza control. Our study demonstrated high IRs of A(H1N1)pdm09 in the rural community during the peak pandemic and post-

pandemic periods in the year following the emergence of pandemic influenza in North India. The IR of FARI estimated to be 686/1000 person-years using a population-based study in a rural village in North India, is at least 10 times higher than estimated influenza-like illness rates in a southern province of China.[10] The difference in IRs may be explained partly by the survey methods (active population survey in the current study vs. multi-stage stratified cluster sampling in the latter) or the timing of the survey (current surveillance implemented during the pandemic in 2009 vs. 2007 in the China survey). Prospective analysis of FARI cases over the study period demonstrated circulation of both pandemic 2009A/H1N1 and influenza B (influenza A (H3N2) was limited) throughout the year. Additionally, pandemic 2009A/H1N1 revealed atypical seasonality, with a peak in November–December 2009, whereas seasonal influenza peaks are typically observed in the monsoon season in the Delhi area.[9]

Another unique aspect of our study was the ability to determine IRs for pandemic A(H1N1)pdm09 during the pandemic and post-pandemic phases. Using the numbers of persons in the cohort as the denominator, the overall influenza A(H1N1)pdm09 incidence of 6.8% for all age groups identified in our prospective cohort-based study is lower than the 11% summary attack rate for all ages reported in a Hong Kong serosurvey[5] and the 16–18% incidence observed in serosurveys in England.[4] The difference in our cohort-based pandemic influenza incidence and the serosurvey-based rates may be due to the study definition (FARI case definition with laboratory confirmed infection vs. the presence of an antibody response indicating infection, subclinical infection, and/or cross-reactive antibodies), difference in study populations (rural vs. urban), or study design (prospective cohort-based vs. pre–post cohort design). Further we demonstrated that although the incidence of A(H1N1)pdm09 was highest during the late 2009 pandemic phase, comparable high rates were also observed during the post-pandemic period from August to October 2010.

In our study population, children (0–18 years) had significantly higher IRs of symptomatic A(H1N1)pdm09 influenza than adults. During the first wave of pandemic influenza, analysis of multiple published studies estimated influenza IRs to be 34–43% among school-aged children and 10% in adults in eight countries from four continents.[7,11] Familial clustering studies have shown that influenza incidence is greater in children than in adults, and observational studies have shown that living with children increases the risk of influenza infection.[7,11] Recent data suggest that the reduced incidence and severity of infection with A(H1N1)pdm09 virus in the adult population during the 2009–2010 influenza season may have been a result of previous exposure to seasonal influenza A viruses.[12,13] Our results suggest that exposure to children should be taken into account for influenza research studies, especially for influenza vaccine efficacy trials in adults with known familial exposure to children.[2]

This study has several limitations. First, our use of self-reported fever in the FARI case definition may have captured a wide range of febrile illnesses and overestimated the incidence of true febrile respiratory illness. However, influenza incidence was not likely to be overestimated as the majority of the FARI incident cases were tested for influenza by molecular methods. Second, the overall influenza rates reported here may have been influenced by the fact that almost one-half of the children had received influenza vaccine

from November 2009 to January 2010.[8] While the 2009 seasonal vaccine did not contain pandemic virus, recent studies have shown that prior infection with influenza A (H1N1),[12,13] or immunization with seasonal live attenuated influenza vaccine, may confer some cross-protection against the A/(H1N1)pdm09 virus.[14,15] Thus, we believe that the current study likely represents a minimal estimate of IRs for pandemic influenza. It is plausible that the true incidence of A(H1N1)pdm09 may even be greater than the IR we reported for the pandemic period, since the initial pandemic influenza peak was observed during August 2009 in this region but was not captured because the study reported here had not yet begun.[8]

The results of this large-scale community-based household surveillance are important for quantifying influenza risk at the population level. These data can contribute to global efforts to estimate burden of seasonal and pandemic influenza, which are useful for advocacy for strengthening influenza prevention and control efforts. At a national level, such studies provide important information for planning clinical and public health intervention strategies to mitigate the impact of influenza epidemics.

Acknowledgments

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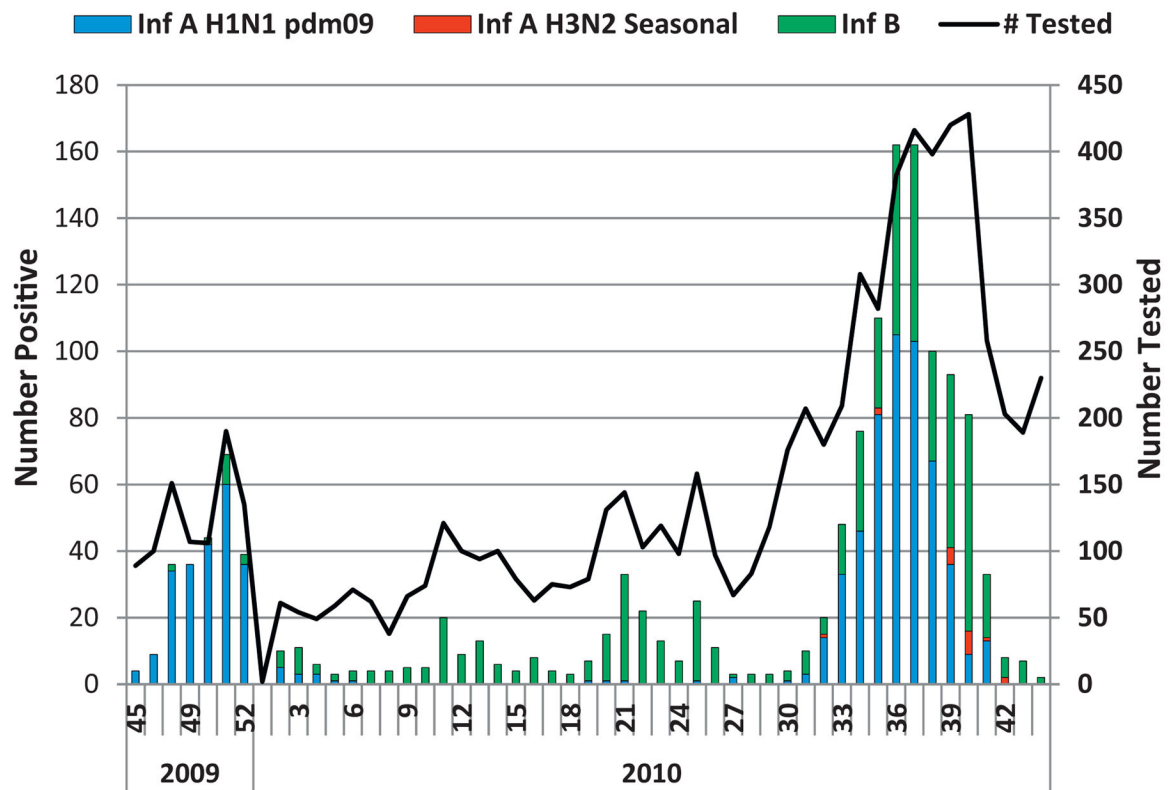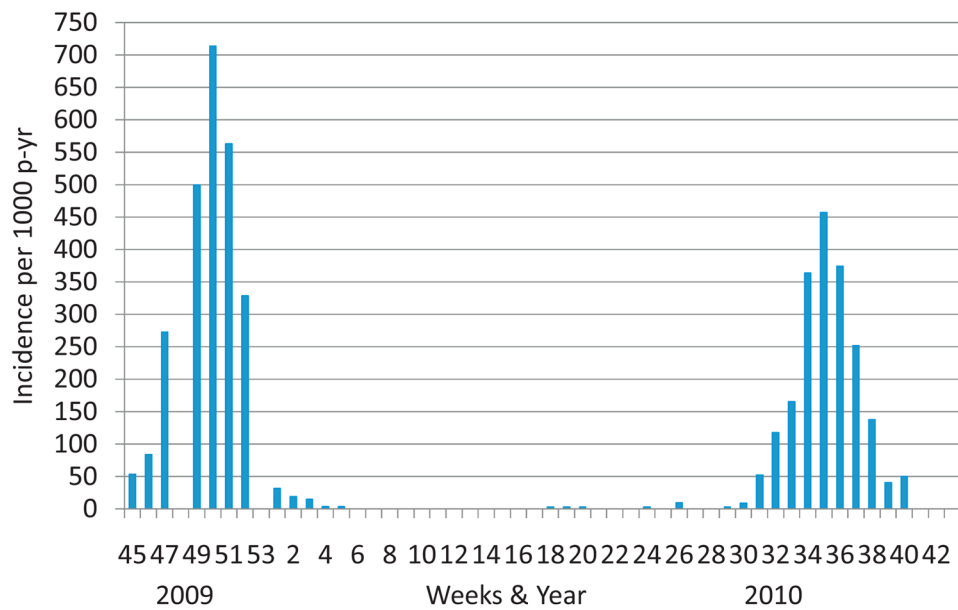
Figure 1.
Weekly trend of influenza positivity during active surveillance in a community-based study from November 2009 to October 2010 in rural India. The left axis shows the number positive for seasonal influenza (red bar: A(H3N2); green bar: influenza B) and pandemic A(H1N1)pdm09 (blue); the total number of samples tested (line) is shown on the right axis. Children aged 6 months to 10 years received either trivalent seasonal influenza vaccine (intervention) or inactivated polio vaccine (control).[10]

Figure 2.
Incidence rate/1000 person-years for pandemic influenza A(H1N1)pdm09 in a rural
community in North India during the pandemic phase (until July 2010) and post-pandemic
phase (since August 2010). The incidence rates for A(H1N1)pdm09 were greatest during the
first pandemic wave from November 2009 to January 2010 (179/1000 person-years),
followed by a second peak in the post-pandemic phase in August–October 2010 (156/1000
person-years), with very low rates observed (3/1000 person-years) during the inter-
pandemic period from February to July 2010.

Table 1

Quarterly influenza data for the study population, November 2009 to October 2010

	Nov 09–Jan 10 Q1	Feb 10–Apr 10 Q2	May 10–Jul 10 Q3	Aug 10–Oct 10 Q4	Total
Persons-weeks under surveillance	95 414	191 532	211 637	213 148	711 731
FARI identified	1515	1158	1789	4933	9395
Total influenza positives (%)	24	9	10	23	19
2009A/H1N1 positivity (%)	231 (21)	1 (0)	10 (1)	507 (13)	749 (10)
Seasonal influenza positivity (%)[a]	34 (3)	88 (9)	143 (9)	396 (10)	661 (9)
Incidence rate of influenza[b] (95% CI)	205 (185–227)	28 (23–34)	43 (37–50)	278 (262–294)	128 (122–134)
Incidence rate of influenza A(H1N1)pdm09[b] (95% CI)	179 (160–199)	0 (0–1)	3 (1–5)	156 (144–168)	68 (64–72)
Incidence rate of influenza B[b] (95% CI)	26 (19–35)	28 (23–34)	40 (34–47)	116 (106–127)	58 (54–62)

FARI, febrile acute respiratory illness; CI, confidence interval.

[a]Overall only 2.7% of seasonal influenza was influenza A (H3N2); 97.3% was influenza B.

[b]Per 1000 person-years.

Table 2

Person-weeks under surveillance, febrile acute respiratory illness incidence rates, and pandemic A(H1N1)pdm09 in rural India from November 2009 to October 2010

Age groups,[a] years	Person-weeks under surveillance	Incident FARI cases, n	FARI IR per 1000 person-years (95% CI)	Laboratory specimens tested, n (%)	Influenza virus positive, n (% among tested)	Influenza A(H1N1)pdm09 virus positive, n (% among tested)	Influenza A(H1N1)pdm09 IR per 1000 person-years (95% CI)
0–5	86 352	2776	1672 (1610–1735)	2460 (89)	371 (15)	177 (7)	120 (104–138)
6–18	186 239	2352	657 (630–684)	1864 (79)	494 (26)	265 (14)	93 (83–104)
19–29	156 183	1357	452 (428–476)	1008 (74)	231 (23)	134 (13)	60 (51–69)
30–44	149 061	1314	458 (434–484)	1004 (76)	171 (17)	89 (9)	41 (34–49)
45–59	83 512	953	593 (556–632)	724 (76)	96 (13)	67 (9)	55 (44–68)
60+	50 384	643	664 (613–717)	511 (79)	47 (9)	17 (3)	22 (13–33)
Total	711 731	9395	686 (673–700)	7571 (81)	1410 (19)	749 (10)	68 (64–72)

FARI, febrile acute respiratory illness; IR, incidence rate; CI, confidence interval.

[a] Age groups are inclusive.