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Influenza Vaccine Given To Pregnant Women Reduces Hospitalization Due To Influenza In Their Infants

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Influenza Vaccine Given to Pregnant Women
Reduces Hospitalization Due to Influenza in Their Infants

A Thesis Submitted to
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by
Isaac Benowitz
2011

INFLUENZA VACCINE GIVEN TO PREGNANT WOMEN REDUCES HOSPITALIZATION DUE TO INFLUENZA IN THEIR INFANTS

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The aim of this study was to determine whether giving influenza vaccine to pregnant women can reduce the incidence of hospitalization due to influenza in their infants in the first year of life. This was a matched, hospital-based case-control study at Yale-New Haven Children's Hospital. Case and control subjects were all aged <12 months at the time of their hospital admission from 2000 to 2009. All subjects were identified through hospital records. Cases were infants admitted due to influenza infection. Controls were infants who did not have influenza infection at the time of hospitalization, matched to cases by date of birth and date of hospitalization (both within 4 weeks before or after). We contacted parents of all subjects to collect information on the subjects' health and home setting and to get permission to review subjects' and mothers' hospital records and outpatient medical records—this was used to determine whether the subject or mother had received influenza vaccine or other vaccines and to identify underlying health conditions that could predispose to severe influenza infection. Conditional logistic regression was used to determine the relative risk of hospitalization for influenza infection for mothers who did or did not receive influenza vaccine during pregnancy or other times. The mothers of 2 (2.2%) of 91 cases and 31 (19.9%) of 156 controls aged <6 months and 1 (4.6%) of 22 cases and 2 (5.6%) of 36 controls aged \geq 6 months received influenza vaccine during pregnancy. The effectiveness of influenza vaccine given to mothers in pregnancy in preventing hospitalization in their infants aged <6 months, adjusted for potential confounders, was 91.5% (95% CI: 61.7%–98.1%, $p=0.001$). Influenza vaccine given to pregnant women was 91.5% effective in preventing hospitalization of their infants due to influenza in the first six months of life.

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INTRODUCTION

Influenza is the leading cause of vaccine-preventable death in the United States (CDC 2003), where it is responsible for 200,000 hospitalizations and 36,000 deaths per year (Thompson 2004). The highest burden of disease is in young children, pregnant women, the elderly, and people with certain chronic medical conditions. In young children, the highest incidence of hospitalization attributable to influenza is in infants aged <1 year, with those aged <6 months at highest risk (Neuzil 2000). Rates of hospitalization of healthy infants for influenza are similar to the rates in high risk adults, and are even higher for infants with underlying chronic medical conditions, in particular respiratory conditions (Neuzil 2000).

Influenza is a respiratory infection caused by the influenza virus that is transmitted through infected airborne droplets. Common symptoms of infection include fever, headache, fatigue, dry cough, sore throat, runny or stuff nose, muscle aches, and gastrointestinal upset. Complications of influenza leading to hospitalization or death can occur from direct effects of the virus, from exacerbations of pre-existing underlying or chronic medical conditions such as cardiopulmonary disease, or from causes related to pregnancy or young or old age. In infants, influenza can present with a sepsis-like picture that differs significantly from the classic presentation seen in adults. For example, infants may have fever but lack respiratory symptoms. Gastrointestinal symptoms (such as diarrhea) are another possible presentation.

Influenza is seasonal in the northern hemisphere, predominantly circulating in the fall and winter months. It typically peaks in February or March, although it may peak as late as April or May. Influenza virus has circulated in humans for thousands of years; since 1977,

three influenza virus strains have circulated globally in the human population: A H1N1, A H3N2, and B. These and other strains also circulate in avian hosts and in other mammals. Minor strain variation (antigenic drift) occurs from season to season and is associated with reinfection. Major variation (antigenic shift) occurs less frequently and is associated with pandemics (Fiore 2009).

In April 2009, a novel influenza strain appeared in the northern hemisphere that was similar to influenza strains that have circulated in swine in the past but was unlikely any one strain. This strain, 2009 influenza A H1N1, led to a pandemic with large numbers of people infected in many countries worldwide, leading to significant morbidity and mortality.

Influenza vaccine

Annual receipt of the influenza vaccine is currently the most effective method of preventing influenza infection in most individuals and this has been shown to reduce the burden of influenza infection. Two types of vaccine have been developed and are available commercially: an injectable, inactivated trivalent vaccine that can be used in any person aged ≥ 6 months, and a nasal, live-attenuated vaccine that can be used in non-pregnant, healthy persons aged 5–49 years. Either vaccine protects recipients against three influenza virus strains, one from each of the major groups. New influenza vaccine is produced yearly with the included strains selected several months prior to influenza season to allow for production, distribution, and administration. This vaccine is 70-90% effective in healthy adults in a year with good “strain match” between the vaccine strains and the circulating strains; effectiveness is lower in the elderly and in very young children and in years in

which there is poor “strain match.” Antiviral medications are also available for the prevention and treatment of influenza infection; however, these medications currently are not approved for use in persons aged <12 months (Fiore 2009). No vaccine is available for use in infants aged <6 months.

Inactivated influenza vaccine is recommended by the Centers for Disease Control and Prevention (CDC) for all people except for infants aged <6 months (for whom the vaccine is poorly immunogenic) and persons with a serious allergy to eggs (Fiore 2009, Gruber 1997). Although many influenza infections lead to only minor symptoms, more serious and life-threatening outcomes are also possible as described above. The recommendation for annual influenza vaccination is intended to reduce hospitalization and death. Strategies for the protection of groups who cannot receive influenza vaccine have included washing hands, avoiding contact with persons infected with influenza, and vaccination of close contacts (Fiore 2009). Both the CDC and the Advisory Committee for Immunization Practices recommend that household contacts of infants aged <6 months, along with their out-of-home caregivers, receive the influenza vaccine in order to form a “cocoon” of protection. However, the effectiveness of these strategies remains unknown.

CDC and the American College of Obstetrics and Gynecology (ACOG) recommend all women who will be pregnant during the influenza season receive inactivated influenza vaccination (Fiore 2008). This recommendation is based on the elevated burden of influenza-related complications, hospitalization, and death in pregnant women seen during past influenza seasons and in particular during past influenza pandemics (Fiore 2009, Naleway 2006). In general, persons aged ≥ 6 months develop high titers of influenza

antibodies after vaccination and these antibodies are protective against illness, with the degree of protection related to the similarity between the strain of influenza in the vaccine and the strain of influenza circulating in the population at the time of infection. The antibody response in children at high risk for influenza-related complications might be lower than that of healthy children (Fiore 2009).

Vaccination of pregnant women could provide protection to the infant early in life, and this suggests that a novel approach to protect young infants against influenza infection may be to vaccinate their mothers during pregnancy (Munoz 2001, GPVI 1996). Both animal and human studies support the possibility of protecting infants against influenza by immunizing the mother. Antibodies (immunoglobulin G) cross the placenta via active transport from the mother to the fetus in the final weeks of pregnancy (Kohler 1966, Hobbs 1967, Reuman 1983, Mbawuike 1990). After birth, the infant may receive antibodies (immunoglobulin A) from the mother via breastmilk (Sweet 1987) and these may provide further protection.

Review of the literature

One study showed that children aged ≤ 12 months, included those with no previous health problems, were hospitalized at a rate comparable to that in elderly (Neuzil 2000). Neuzil et al. also showed that a significant number of annual deaths attributable to influenza infection occur in infants, and that young children may have a higher risk of influenza-associated complications and hospitalization compared with healthy older children and adults aged < 65 years (Fiore 2009). Complications of influenza infection include bacterial pneumonia,

dehydration, and worsening of chronic medical conditions such as congestive heart failure, asthma, and diabetes.

Animal studies have shown that immunizing pregnant mice against influenza protected their offspring against severe influenza infection. Antibodies are transferred in breastmilk (immunoglobulin A) and across the placenta (immunoglobulin G) (Reuman 1983, Mbawuike 1990). In one study, pregnant mice received active influenza vaccine and their offspring were studied for the response to influenza infection. In another study, pregnant mice received abdominal (peritoneal) injections of inactivated influenza vaccine and their offspring, too, were protected against a challenge with a lethal dose of influenza virus (Mbawuike 1990). Results from both studies indicated that giving influenza vaccine to pregnant mice significantly decreased the incidence of influenza infection in their offspring. Both animal studies found that breastfeeding was the primary way that passive antibodies were transferred to the offspring. Although breastfeeding is thought to be a route of transfer of antibody from mother to infants, transfer across the placenta is the primordial route in humans (Sweet 1987).

In humans, maternal antibodies cross the placenta via active transport later during gestation, presumably around 32 weeks gestation. A study that measured antibody concentration (immunoglobulin G) in mothers and their infants found higher antibody concentrations in infants than in mothers, suggesting there is active transport of antibodies across the placenta (Kohler 1966). Another study measured these antibody levels in 106 premature infants in the first week of life and found a logarithmic relationship between the level of immunoglobulin G and gestational age, and suggested that infants born at 32 weeks or

earlier may have insufficient protection to fight off some infections (Hobbs 1967). No study has examined total influenza-specific antibodies from mother to the offspring.

Influenza antibodies can also be found in cord blood, indicating presence of such antibodies at birth, and antibody levels can be studied to determine whether this presence represents protection from infection. One study of inactivated influenza vaccine in 56 women in the second and third trimester of gestation found influenza antibodies in 58% of maternal sera and 42% of infant cord sera, and concluded that a sufficient dose of influenza vaccine given during pregnancy could form the basis for protection of the infant. The study also suggested that the timing of delivery relative to the influenza season might be an important determinant of antibody levels in mothers and their infants (specifically, that delivery during influenza season may be correlated with higher levels of influenza antibodies in the infant), that multiple doses of influenza vaccine might be needed in pregnancy to provide sufficient protection to the infant, and that there was no statistically significant difference between vaccinating the mother in the second trimester versus vaccinating her in the third trimester (Sumaya 1979).

Studies have shown that mothers who receive inactivated influenza vaccine during pregnancy deliver infants who have influenza antibodies that delay the onset and decrease the severity of influenza infection, with the degree of protection related to the infant's influenza antibody level at birth. Women who were naturally infected by influenza also had infants with similar or higher levels of antibodies (Sumaya 1979; Puck 1980; Reuman 1987; Englund 1993).

One study showed that giving influenza vaccine to women during pregnancy resulted in higher influenza-specific antibody concentrations in infants at birth than in their mothers at the same point in time, suggesting active transport from mother to infant. That study gave influenza vaccine to 56 pregnant women in the second or third trimester and monitored antibody concentrations in 40 mother-infant pairs after birth, and found measurable antibody titers in several of the infants, even several months after birth. They suggested that vaccination of pregnant women against influenza could help to protect infants via passive transfer of maternal antibodies against influenza (Sumaya 1979). Another study measured transplacental antibodies (immunoglobulin G) to influenza A in stored cord blood of 26 infants who had been brought to primary care facilities and had culture-positive influenza infection, and found a positive correlation between age at the time of first infection with influenza and the level of antibody found in cord serum (in other words, infants who had a higher level of influenza antibody in their cord blood at birth had a later influenza infection than infants with lower levels of antibody at birth). This suggested that these antibodies are protective, that vaccinating pregnant women could prevent symptomatic influenza infection in their infants, that breastfeeding could provide an additional level of protection, and that the antibody level wanes over time. Infection in the presence of low levels of antibody may result in attenuated illness (Puck 1980). A third study of influenza antibodies followed women and their offspring in the United States during an influenza A epidemic in 1979 and showed that the infants' concentrations of influenza antibodies at birth correlated with their mothers' antibody concentrations. Infants with higher concentrations of influenza antibodies had a delay in the onset and a decrease in the severity of influenza infection (Reuman 1987).

The active transport of antibodies from mother to infant across the placenta occurs in significant quantities and primarily after 33 weeks gestation, and infants born at an earlier gestation may be less protected by this immune protection. The presence of maternally-derived antibodies in infancy does not inhibit development of natural immunity later in life from immunization or natural infection.

There are many reasons to consider maternal vaccination as an effective strategy for the protection of infants in the first six months of life, including the immature immune systems in infants of this age and their vulnerability to common bacterial and viral infections, the adequacy of maternal vaccination, and the cost-effectiveness of giving one dose to the mother instead of several doses to the infant (Englund 1993, Munoz 2000). Immunizing women against influenza during pregnancy is a promising strategy for reducing the burden of influenza-related illness in their infants. Breastfed infants may be further protected by antibodies (immunoglobulin A) in breast milk (Munoz 2000). Indeed, vaccination of pregnant women to protect infants against childhood infection is already in widespread practice for bacterial infections such as tetanus and *Haemophilus influenzae* Type b, and for viral diseases such as polio (Munoz 2000). Several vaccines are used in mothers to decrease the incidence of diseases including pertussis and tetanus in their infants (GPVI 1996).

Inactivated influenza vaccination given to pregnant women has been shown to be safe and immunogenic in women and their infants (Naleway 2006). However, in spite of data on safety and the potential benefit to both mother and child, vaccination practices during pregnancy are poor and vary widely for different healthcare providers and regions: in the U.S. in 2006, 14% of women got influenza vaccine during pregnancy (CDC 2006). Most

obstetricians recommend influenza vaccination for pregnant women to protect those women against severe infection, yet in 2003 only one third of those recommending influenza vaccination during pregnancy offered this vaccine to their patients (CDC 2005). Studies have examined the effectiveness of flu vaccination in pregnancy on preventing or modifying influenza-related morbidity in infants, however their results have been inconsistent.

Two recent studies compared hospitalizations due to influenza in infants and rates of influenza-like illness (ILI) or medically attended acute respiratory infection (MAARI) in infants whose mothers had received influenza vaccination during pregnancy with those whose mothers had not been vaccinated. Neither study found a protective effect associated with vaccination during pregnancy; however, both studies included non-influenza infections along with influenza infections. One study of hospital admissions with principal diagnoses of influenza or pneumonia and ILI in outpatient visits during five influenza seasons from 1997 to 2002 found that women who received influenza vaccine during pregnancy had the same risk for ILI visits as unvaccinated women, and their infants had the same risks for influenza or pneumonia compared with other infants whose mothers had not received the vaccine (Black 2004). Another study that followed over 41,000 infants for MAARI (another measure that combines influenza with other diseases such as pneumonia) in outpatient, emergency department, or inpatient settings, found that maternal influenza vaccination did not delay the onset of the first respiratory illness (France 2006).

Recently, Zaman et al. conducted a trial of inactivated influenza vaccine given to pregnant women in Bangladesh found a 63% reduction in laboratory-confirmed influenza illness in

their infants up to six months old compared with administration of pneumococcal vaccine (Zaman 2008). This study was conducted outside the US in a region where influenza infection circulates year-round, unlike the seasonal pattern of influenza seen in the US in recent decades. Mothers were recruited in the third trimester of pregnancy. This study was unable to assess effectiveness on hospitalization or severe illness.

Relevance

Influenza infection has significant impacts on society including morbidity and mortality of infected individuals, impacts on their families, and healthcare utilization and costs, in the U.S. and worldwide. In children, influenza infection takes on added significance because there is no vaccine available to protect infants aged <6 months, in contrast to the rest of the population which can be protected using the vaccine, and these infants are hospitalized for influenza infection at rates similar to the elderly. Even mild cases of influenza may lead to lost productivity in society when parents miss work to care for their sick children. Children are also one of the major routes of spread of influenza in the population. The possibility of a novel approach to protect infants aged <6 months is of significant importance to the medical and public health communities. Therefore, proven effectiveness of influenza vaccine given to pregnant women will have important public health implications worldwide. If immunizing mothers is found to be effective in providing protection to their infants, this approach has the potential to improve protection of susceptible infants for whom the vaccine is not an option until later in life, and it could also further improve on the cost-effectiveness of vaccinating pregnant women (Roberts 2006) by protecting two people, mother and infant, with just one immunization. Results may also increase awareness of the

importance of influenza vaccination during pregnancy (by protecting women who are already at high risk for complications from influenza in pregnancy) and it will help overcome barriers to vaccination, potentially impacting motivations, perceptions, and attitudes of pregnant women and of their medical providers towards vaccination during pregnancy.

Statistical power

National surveys in recent years have found that only 13% of pregnant women receive influenza vaccine (NHIS 2003), with vaccination rates of pregnant women in Connecticut slightly higher, at around 30% (BRFSS 2005).

Hospital data from our institution showed that approximately 30 infants (aged <12 months) are admitted with a diagnosis of influenza each year. For this study, we initially anticipated enrolling 25 cases and 50 matched controls per season (early in the fall through the winter), a total of 75 subjects per influenza season. We also planned to enroll infants prospectively over two influenza seasons.

The statistical power to assess the vaccine's effectiveness depends on the number of discordant groups (cases and their matched controls), which in turn depends on the rate of influenza immunization among the mothers of the infants. Assuming that 30% of mothers are immunized (using the Connecticut data above), enrolling 69 cases would provide 90% statistical power to detect an effectiveness of the vaccine of 65%. Our plan was to enroll patients who had been hospitalized during the several years prior to the initiation of our

study to be able to compare across influenza seasons, and then also to continue enrolling cases in the hospital setting for two years to be able to collect nasal wash samples.

HYPOTHESIS

Giving influenza vaccine to women during pregnancy reduces hospitalization of their infants due to influenza compared to women who did not receive the influenza vaccine during pregnancy.

AIMS

To assess whether giving influenza vaccine to pregnant women protects their infants against influenza infection, leading to a lower relative risk of hospitalization before age 12 months.

METHODS

We conducted a matched case-control study of infants at Yale-New Haven Children's Hospital, an academic urban hospital in the northeastern United States.

Eligibility requirements

All subjects were infants aged <12 months, hospitalized at Yale-New Haven Children's Hospital due to laboratory-confirmed influenza between 2000 and 2009, prior to the arrival of the 2009 pandemic influenza A H1N1 in this region. Infants up to age 12 months were included because, even though they are potential candidates for influenza vaccine at age 6 months, they may not have received the vaccine and the protective effect of mother's antibodies against influenza may still be found.

We excluded infants who were adopted at birth, hospitalized for reasons unrelated to their respiratory infection (as determined by review of medical records), if their influenza infection was acquired in the hospital (nosocomial infection), if their mothers had a contraindication to inactivated influenza vaccine (e.g., egg allergy, prior adverse reaction) or were unable to consent to participate (e.g., deceased, unknown whereabouts), or if neither parent could complete the interview in English or Spanish. Infants who received influenza vaccine at least two weeks prior to hospitalization were excluded, as it would be impossible to distinguish the effect of vaccination of the mother from the effect of vaccination of the infant.

Testing for influenza

Infants hospitalized at this facility with symptoms suggesting a possible infection with a respiratory virus (including influenza, parainfluenza, and adenovirus) are routinely tested using a direct fluorescent antibody (DFA) test kit (Light Diagnostics™, Millipore; Temecula, CA) of a nasal swab sample. This test has been shown to be 96.2% sensitive and 99.0% specific for influenza compared with the polymerase chain reaction technique in our hospital's laboratory (Landry 2008). This testing is done for hospital epidemiology (e.g., to help determine the arrival of influenza in this region and to determine the extent of these infections in the hospitalized population from week to week) and for patient cohorting (i.e., patients with the same respiratory infection may sometimes be placed in a double room instead of designating two rooms for appropriate contact precautions). The test result is also available to the clinical team and may be used to guide clinical decision-making.

Identification of potential cases

Cases were infants hospitalized due to influenza with documentation of either a nasal swab or aspirate that was positive for influenza by DFA as described above. Samples deemed inadequate by the clinical virology laboratory were not included. Data collection started in June 2007. Subjects hospitalized between 2000 and May 2007 were identified historically from the clinical virology laboratory list of all tests for influenza and enrolled by telephone. During the 2007–2008 and 2008–2009 influenza seasons, research staff identified cases prospectively by reviewing both clinical virology laboratory list of all tests for influenza

and the daily list of new hospital admissions to enroll patients in the hospital setting and to collect a nasal swab sample for further testing.

Selection of controls

For each case, we identified and enrolled two matched controls, who were hospitalized for reasons other than influenza and who were infants found to be negative for influenza by DFA. Controls were identified from the same list of all hospitalized patients who had a DFA test for respiratory viruses and were negative for influenza, matched to cases by date of birth and date of hospitalization. A patient with a nasal swab sample that tested positive for another respiratory virus could still be enrolled as a control subject if they were found to be negative for influenza. Matching started with the subjects born within 2 weeks of the case (two weeks before or after the case's date of birth) and who were admitted to the hospital within 2 weeks of the case (two weeks before or after the case's date of hospital admission) and then, if necessary, proceeded to those born within 4 weeks and admitted to the hospital within 2 weeks from the case, then those born within 2 weeks and admitted to the hospital within 4 weeks from the case, and finally those born within 4 weeks and admitted to the hospital within 4 weeks from the case, until two controls were identified. We used a table of random numbers to determine the order in which to contact potential eligible subjects within each case-control group. We used risk-set sampling in our selection of cases and controls: a person could be counted as a control subject multiple times if they had more than one admission during which they met control criteria, but once a person was a case (i.e., was hospitalized for influenza) they were no longer eligible to be a control afterward (Niccolai 2007).

Collection of data and ascertainment of vaccinations

We conducted interviews with the parents of all study subjects to ask questions pertaining to demographics, possible confounders such as breastfeeding or susceptible individuals in the household, and comorbidities of the infant and the mother, and to identify all possible sources of vaccination of the mother during pregnancy or previously. Interviews were done in person when a case or control was enrolled prior to hospital discharge, or otherwise by phone call. All interviews were conducted by study personnel in either English or Spanish.

Information about vaccinations and comorbidities of the infants was obtained by reviewing medical records from their medical care providers in addition to interview data. We reviewed the mothers' medical records from their primary medical providers, obstetricians, pharmacies, and anywhere the mother stated she would have received influenza vaccine. We used this information to ascertain whether a mother had received influenza vaccine during pregnancy, whether she had received the vaccine at any time prior to that pregnancy, and whether she had received the vaccine during the same influenza season as the infant's hospital admission. A mother was considered vaccinated during pregnancy if written documentation in any record was found indicating receipt of influenza vaccine at least 14 days prior to delivery of the infant.

Clinical severity of influenza for the cases

We collected clinical data from the infants' (case subjects') hospital medical records such as vital signs suggesting a severe infection (including highest temperature and respiratory rates and lowest oxygen saturation levels), physical signs of increased work of breathing (such as retractions or nasal flaring), results of available chest radiographs, and need for mechanical ventilation and/or admission to the intensive care unit (ICU). We classified the severity of these symptoms on a scale of 0–16 points, based on our modification of a previously-validated scale of severity of respiratory symptoms in infants with respiratory infections (Table 1) (Papadopoulos 2002).

Respiratory Specimens

Respiratory samples were collected from case subjects still in the hospital at the time of enrollment, using the nasal wash technique. RNA was extracted from the clinical specimens using RNeasy Mini Kit per manufacturer instructions (Qiagen, Valencia, CA). Reverse transcription and the polymerase chain reaction were performed using primers and parameters described by the “WHO/CDC Protocol of realtime PCR for influenza A (H1N1)” (CDC 2009) and the AccessQuick RT-PCR System (Promega, Madison, WI).

Statistical Analysis

We calculated a matched odds ratio for vaccination of mothers of cases compared with matched controls. The vaccine's effectiveness was calculated as 1 minus the matched odds

ratio multiplied by 100. Conditional logistic regression was used to adjust for potential confounders including race, ethnicity, sex, age, daycare attendance, prematurity, vaccination of household contacts, breastfeeding, and relevant chronic illness (such as asthma or reactive airways disease, chronic lung disease, conditions requiring medical equipment to facilitate breathing, cardiac defects, blood disorders, seizures, metabolic or endocrine disorders, severe gastrointestinal disease, kidney disease, or spinal cord injury).

A stratified analysis was also conducted to assess for effect modification by age of the subject (aged ≥ 6 months vs. aged < 6 months) based on the CDC's recommendation to begin influenza vaccination at age 6 months and literature suggesting that maternal antibodies wane at 6–9 months. Whether the subject was identified at the time of hospitalization or historically via billing data was also evaluated as a possible confounder or effect modifier.

We also assessed the significance of the clinical severity of influenza infection of the cases using a Student's t-test or Wilcoxon rank-sum test as appropriate. Analyses were conducted using SAS[®] version 9.1.3 for Microsoft (SAS Institute; Cary, NC).

RESULTS

Enrollment of subjects

We identified a total of 220 eligible case subjects (infants aged <12 months hospitalized due to influenza) between October 2000 and April 2009. Of the 220 eligible case subjects, 36 (16%) could not be contacted by researchers (for example, because the contact telephone numbers and addresses were no longer valid). Of the remaining 184 potential case subjects contacted, parents of 27 (15%) refused to participate (for example, because the parents were not interested in participating in medical research or they did not feel comfortable releasing medical records for research purposes), and 157 (85%) were enrolled. Enrollment started in July 2007. Data presented are from October 2000 and April 2009; data collection is ongoing. Of the 157 enrolled case subjects, 33 (21%) were hospitalized between January 2008 and April 2009 and identified prospectively via active surveillance of laboratory data and hospital units and 124 (79%) were hospitalized between October 2000 and May 2007 and identified historically via laboratory data and hospital records; of these, 130 (83%) were infected with influenza A virus and 27 (17%) with influenza B. For these 157 enrolled cases, 430 potential matched controls were identified. Of these 430 potential controls, 114 (26.5%) could not be contacted. Of the 316 potential controls that we were able to reach, 45 (14.2%) refused to participate, and 271 (85.8%) were enrolled as controls.

Results presented are for the 113 cases and 192 matched controls (cases with at least one matched control) in groups with complete data for the case and matched control.

Demographic characteristics of subjects identified prospectively and historically only

differed statistically significantly on report of sick household members during the month before hospitalization (59.8% vs. 23.3%, $p < 0.001$), and length of hospital stay (5.0 ± 13.2 vs. 2.9 ± 3.7 days, $p = 0.030$).

Subject information and demographics

Characteristics of infants hospitalized with influenza and their matched controls are presented in Table 2. Cases and matched controls were comparable on most demographic characteristics and risk factors, as described below and presented in Table 2.

The majority of infants enrolled in the study (80.5% of cases and 81.2% of controls) were aged <6 months, with slightly more infants aged 0–<3 months (35.4% of cases and 35.9% of controls) than infants aged 3–<6 months (45.1% of cases and 45.3% of controls) (Table 2). There were roughly equal numbers of male and female infants enrolled as case subjects (50.4% male and 49.6% female), with slightly more male controls than female controls (52.6% male and 47.4% female). The majority of cases and controls were white (around two-thirds of each group), and approximately one-fifth of cases were black and approximately one-tenth of controls were black, with the remainder in the “other” category.

Cases came from households with a larger number of household members than controls (4.9 ± 2.0 vs. 4.4 ± 1.3 , $p = 0.015$), and they were significantly less likely to live with household members that had received influenza vaccine (32.7% cases vs. 50.0% controls for any household members vaccinated, and 10.6% cases vs. 15.1% controls for all reported household members vaccinated with influenza vaccine; $p = 0.001$). In subjects aged <6

months, the mothers of 2 (2.2%) of 91 cases and 31 (19.9%) of 156 controls had received influenza vaccine during pregnancy. In aged ≥ 6 months, the mothers of 1 (4.6%) of 22 cases and 2 (5.6%) of 36 controls had received influenza vaccine during pregnancy ($p = 0.809$).

There were no significant demographic differences between mothers who received influenza vaccine and those who did not receive influenza vaccine (Table 3). In vaccinated mothers, cases and controls did not differ significantly in the trimester of pregnancy during which vaccination occurred, with 2 (66.7%) case subjects' mothers and 26 (78.8%) of the control subjects' mothers having received vaccines in the third trimester of pregnancy.

Clinical severity of cases

The median clinical severity scores of the case subjects enrolled was 4 (moderate severity) on a scale of 0–16 (Figure 1). Case subjects aged ≥ 6 months at the time of hospitalization had a significantly higher mean severity score than those aged < 6 months (6.3 ± 3.1 vs. 4.1 ± 2.7 , $p = 0.001$), and those with chronic medical conditions had higher severity scores than those without underlying medical conditions (5.3 ± 2.5 vs. 3.5 ± 2.2 , $p = 0.003$). Differences in clinical severity scores of the cases by mother's vaccination status during pregnancy were not statistically significant.

Respiratory specimens

The nasal samples obtained from the cases identified prospectively (2007–2009) were all confirmed to be negative for 2009 pandemic influenza A H1N1. This was evaluated by comparing the respiratory specimens to known primers for the pandemic influenza strain.

Effectiveness of vaccination

The adjusted effectiveness of the vaccine of 91.5% (95% CI: 61.7%–98.1%, $p = 0.001$) for infants aged <6 months, using a final adjusted model that retained immunization of household contacts (persons other than the subject's mother residing in the household at the time of admission) (adjusted odds ratio, 0.420; 95% CI: 0.221–0.798, $p = 0.008$) and prematurity (0.375, 95% CI: 0.153–0.918, $p = 0.032$). The unadjusted effectiveness of influenza vaccine given to mothers during pregnancy in preventing hospitalization due to influenza in their infants was 90.7% (95% CI: 59.9%–97.8%, $p = 0.001$) for this age group. The effectiveness of the vaccine for infants aged ≥ 6 months was -41.4% (95% CI: -2257.3%–91.5%, $p = 0.809$). The effectiveness of the vaccine did not differ significantly when we compared subjects identified prospectively versus subjects identified historically (for historically identified subjects, effectiveness: 88.9%, 95% CI: 13.1%–98.6%, $p = 0.036$; for prospectively identified subjects, effectiveness: 92.0%, 95% CI: 37.0%–99.0%, $p = 0.016$; for the Breslow Day test for homogeneity of the odds ratios: p -value = 0.767). Also, exclusion of subjects born before 32 weeks of gestational age did not significantly affect the estimate.

DISCUSSION

Enrollment of subjects

We were able to contact most of the eligible case subjects that we had identified. Reasons that eligible cases could not be contacted included hospital records that contained only incorrect or outdated telephone numbers, people who had moved since the time of the hospitalization and for whom no updated information could be obtained through a search of hospital data systems, and people who were believed to still live in the same location but could not be reached by telephone or mail inquiries using all available contact information.

A small number of eligible case subjects and eligible control subjects who were contacted refused to participate. Although no one single reason predominated this group, some of the reasons cited included concern about the privacy of their records (e.g., they did not feel comfortable with someone reviewing the child's medical records and/or reviewing the mother's medical records for reasons unrelated to medical care), disinterest in participating in medical research, or that they did not want researchers contacting their physicians at all.

Subject information and demographics

A mother's chance of being offered influenza vaccine during pregnancy is expected to vary depending on the time of year when the pregnancy begins because the influenza vaccine is not available year-round, but rather is typically available starting shortly before the arrival of influenza virus to a region and continuing until at least partway through that season.

However, we expect that this variability did not differ significantly between cases and controls because these two groups were closely matched by the infants' dates of birth.

Clinical severity of cases

The majority of the clinical severity scores were mild to moderate (between 0 and 5 on a scale of 0–16), with only a handful of cases in the severe range (a score of 6 or greater). The ranges of clinical severity scores presented in Figure 1 (mild, ≤ 3 ; moderate, 4–5; severe, ≥ 6) were selected in order to divide the group of cases into roughly equal groups, not based on prior assumptions regarding a fixed score that would correspond to a clinically valid severity measure or that would suggest an underlying pathophysiology of disease. Eleven case subjects (9.7%) were admitted to the ICU.

Effectiveness of vaccination

Our study shows that inactivated influenza vaccine given to pregnant women is highly effective (91.5%) in preventing hospitalization due to laboratory-confirmed influenza among their infants aged <6 months. These results have great clinical relevance because they provide a strategy to confer protection to young infants, a group at high risk for the disease and for whom no vaccine is currently available. This strategy also has important public health implications as it would protect not only young infants but also their mothers, who are also in the high-risk category for severe influenza. Our results on the effectiveness of this approach in the United States, where influenza is seasonal, are consistent with

findings in a randomized trial of influenza vaccine in Bangladesh, a tropical developing country where the pattern and transmission of influenza is perennial (Zaman 2008).

Although there was inadequate statistical power to assess the vaccine's effectiveness in infants aged ≥ 6 months, an estimate of -41.4% with wide confidence intervals indicates that a null effect in this age group is plausible. This difference in protective effect between infants aged < 6 months (in which a statistically significant protective effect was found) and infants aged ≥ 6 months at hospitalization could be explained by the decline of the concentration of passively transferred antibodies, which one would expect to have dropped to negligible levels by age 6–9 months and which is supported by earlier work by other investigators. The interpretation of this effect is, however, complicated by low numbers.

Study limitations

There were several possible limitations to our study. We lacked statistical power to estimate the effectiveness of influenza vaccine for infants aged ≥ 6 months. It was also not possible to assess independently the effects of second versus third trimester vaccination because of small numbers, however the study is on-going. Women who received influenza vaccine after birth or in the final two weeks of pregnancy, and who breastfeed their infant for any period of time, are not expected to transfer influenza antibody across the placenta but they could still transfer influenza antibody in breastmilk: this effect could not be studied in our population due to the small number of women receiving influenza vaccine at this time and the low power to evaluate this question. Furthermore, our study did not have adequate power to assess the vaccine's effectiveness by influenza season, allowing us to assess for

year-to-year variability. Future prospective studies are needed to evaluate longer-term effectiveness, in subsequent influenza seasons, of this novel strategy.

We have yet to conduct complete laboratory typing of strains to determine whether influenza infections seen in case subjects were due to strains included in the vaccine or the degree of mismatch between infecting strains and vaccine strains. We also did not evaluate seasonal variability for any relationship between infecting strains and common circulating strains, which could induce immunity in the mothers even in the absence of vaccination. Further research is needed to evaluate both of these possibilities.

This study includes patients who were hospitalized over nine annual influenza seasons, but data collection, including surveys given to parents of subjects, began seven years after the earliest dates of hospitalization in these cases and controls. It is possible that recall bias could have influenced the ability of mothers to recall information that could not be verified by the medical record, such as the length of time they breastfed their infants, the number of other people living in the household and their vaccination status and age, and other information collected on the survey; we would expect that the reliability of recall for seasonal influenza vaccination and other information would decrease over successive years.

This study was conducted during years when three influenza virus strains circulated that were similar to strains that had circulated in the global human population for many decades. This was prior to the arrival of the 2009 pandemic influenza strain in this region, confirmed by laboratory analysis of collected nasal wash samples as described above. The pandemic was considered to have ended by January 2010. CDC anticipates that the pandemic strain

will circulate along with other strains. It is not known whether the presence of this strain will change the seasonal pattern of influenza infections or other aspects of the epidemiology of influenza infections in the United States. The results of this study are not anticipated to change based on an altered seasonal pattern of influenza or other factors. The possibility exists that such shifts could alter the effectiveness of this approach, for example by altering the part of the population that is infected or the age groups that are at highest risk.

Earlier studies found lower degrees of protection associated with influenza vaccination in the mother compared to our results. The restriction of the case definition to laboratory-documented influenza infection would be expected to increase the effectiveness of the maternal vaccination approach. The possibility also exists that our estimate is higher than the effectiveness in the general population because our controls were infants who were hospitalized. For example, if mothers of infants in the hospitalized population are less likely to have received influenza vaccine during pregnancy compared with mothers of infants in the general population, this could lead to an overestimate of the effectiveness in our study. Further studies could evaluate this relationship as well as possible connections between a subject's socioeconomic status and the likelihood of the mother receiving influenza vaccine.

Study implications

The CDC and the American College of Obstetrics and Gynecology recommend inactivated influenza vaccination for women who will be pregnant during the influenza season (Fiore 2009) and inactivated influenza vaccination given to pregnant women has been found safe and immunogenic (Naleway 2006). Despite data on the safety of inactivated influenza

vaccine for pregnant women and the potential benefit to both mother and infant of this strategy, rates of vaccination with influenza vaccine in pregnant women are poor and vary widely for different healthcare providers and regions (CDC 2006). Most obstetricians are aware of the recommendation for pregnant women to receive influenza vaccination as a means of protecting women against severe infection. However, in 2003 only one third of those that recommended influenza vaccination during pregnancy offered this vaccine to their patients (CDC 2005). In our sample, only 17.2% of mothers of control subjects received influenza vaccine during pregnancy. It is notable, however, that rates of influenza vaccination in pregnancy have improved steadily through recent years; 10% controls in 2000-2004, 15% controls in 2005-2007, and 35% controls in 2008-2009 were born to mothers that had received influenza vaccine during pregnancy, a similar trend to national data from these years (Fiore 2009).

The public health implications of our findings are important for several reasons. First, they provide further evidence for a novel, effective strategy for the protection of the infant in the first six months of life through vaccination of the mother during pregnancy, a novel means of protecting infants against hospitalization due to influenza and an approach that is not in widespread use nor widely known among expectant parents concerned about the health of their infant. Second, many pregnant women currently do not receive influenza vaccine in pregnancy, and this may also serve as an incentive for those women (who are also at high risk for complications from influenza) to accept influenza vaccine, and for their providers to offer it. Hopefully, this evidence could also be used in community and public campaigns to improve the overall vaccination rates in this high risk group and the degree of protection of their infants. Also, the use of influenza vaccine in pregnant women has previously been

found to be cost-effective, and this strategy improves upon that cost-effectiveness (Roberts 2006). Influenza vaccine given to pregnant women is an effective approach to reducing hospitalization due to influenza in their infants under 6 months old.

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TABLES AND FIGURES

Table 1: Clinical Severity Scale Used to Assess Severity of Influenza (Mild, 0–3; Moderate, 4–5; Severe, 6–16)			
Parameter	Point Value		
	0	1	2
Heart rate (max # of beats per min)			
<i>Age 0-7 days</i>	<130	130-160	>160
<i>Age 1-4 weeks</i>	<135	135-170	>170
<i>Age 1-6 months</i>	<140	140-170	>170
<i>Age 6-12 months</i>	<130	130-160	>160
Respiratory rate (max # of breaths per min)			
<i>Age 0-1 month</i>	<50	50-70	>70
<i>Age 1-6 months</i>	<30	30-50	>50
<i>Age 6-12 months</i>	<20	20-40	>40
Oxygen saturation (by pulse oximeter)	≥94%	–	<94%
Wheezing	No	Yes	–
Retractions (intercostal, subcostal, etc.)	No	–	Yes
Nasal Flaring	No	Yes	–
Required intubation/mechanical ventilation	No	–	Yes
Required ICU care	No	–	Yes
Abnormal chest x-ray	No	–	Yes

ICU: intensive care unit

Table 2: Characteristics of Infants Hospitalized with Influenza and Controls

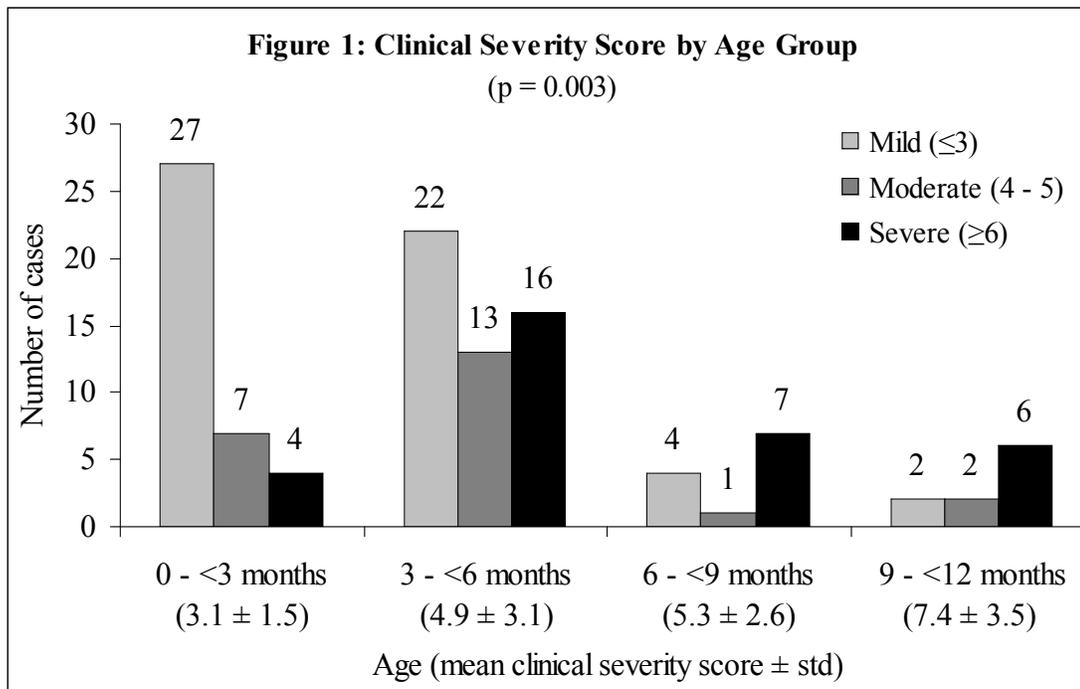
Characteristic	Cases (%) (N = 113)	Controls (%) (N = 192)	P-value
Age (months)			0.998
0-<3	40 (35.4)	69 (35.9)	
3-<6	51 (45.1)	87 (45.3)	
6-<9	12 (10.6)	19 (9.9)	
9-<12	10 (8.9)	17 (8.9)	
Mean (\pm standard deviation)	3.2 \pm 2.8	3.1 \pm 2.9	
Median	2.0	2.0	
Male gender	57 (50.4)	101 (52.6)	0.715
Hispanic ethnicity	45 (39.8)	59 (30.7)	0.106
Race			0.135
White	73 (64.6)	129 (67.2)	
Black	21 (18.6)	21 (10.9)	
Other	19 (16.8)	42 (21.9)	
Ever breastfed	59 (55.7)	115 (67.3)	0.052
Attends daycare	11 (9.8)	18 (9.4)	0.898
Environmental tobacco smoke exposure	35 (31.0)	56 (29.2)	0.739
Premature (gestational age \leq 37 weeks)	13 (11.6)	37 (19.3)	0.082
Gestational age <32 weeks	1 (0.9)	10 (3.5)	
Gestational age 32-36 weeks	12 (10.7)	27 (14.1)	
Chronic medical conditions ¹	41 (36.3)	74 (38.5)	0.695
Respiratory conditions	25 (22.1)	25 (24.5)	0.640
Type of residence			0.028
Single family home	56 (49.6)	110 (57.3)	
Multi-family home	22 (19.5)	26 (13.5)	
Apartment	31 (27.4)	56 (29.2)	
Other setting ²	4 (3.5)	0 (0.0)	
Mean number of people at home, including subject, \pm standard deviation; median	4.9 \pm 2.1 5.0	4.4 \pm 1.3 4.0	0.015
Household contacts who had received influenza vaccine			0.001
None	64 (56.6)	67 (34.9)	
Some	37 (32.7)	96 (50.0)	
All	12 (10.6)	29 (15.1)	

¹ Includes respiratory conditions (asthma, reactive airways disease, chronic lung disease, and conditions requiring medical equipment to facilitate breathing) as well as heart defects, blood disorders, seizures, metabolic or endocrine problems, severe stomach problems, kidney disease, and spinal cord injuries.

² Other settings include dormitories, shelters, and mobile homes.

Table 3: Effectiveness of Influenza Vaccine Given to Mothers During Pregnancy in Preventing Hospitalization Due to Influenza in their Infants		
	Subjects aged <6 months Cases (%) / Controls (%)	Subjects aged ≥6 months Cases (%) / Controls (%)
Mother Vaccinated	2 (2.2) / 31 (19.9)	1 (4.6) / 2 (5.6)
Mother Not vaccinated	89 (97.8) / 125 (80.1)	21 (95.5) / 34 (94.4)
Unadjusted		
Vaccine Effectiveness [95% CI]	90.7% [59.9% – 97.8%] p = 0.001	-41.4% [-2257.3% – 91.5%] p = 0.809
Adjusted ¹		
Vaccine Effectiveness [95% CI]	91.5% [61.7% – 98.1%] p = 0.001	.
¹ Adjusted model for subjects aged <6 months retained vaccination of household contacts and prematurity.		

Table 4: Receipt of Influenza Vaccine by Subjects' Mothers			
	Cases (N = 113)	Controls (N = 192)	P-value
Vaccination status during pregnancy			<0.001
Not vaccinated	110 (97.4)	159 (82.8)	
Vaccinated	3 (2.7)	33 (17.2)	
<i>During hospitalization season</i>	2 (1.8)	32 (16.7)	
<i>During prior season</i>	1 (0.9)	1 (0.5)	
For those vaccinated during pregnancy, timing of vaccination in pregnancy			0.541
First trimester	0 (0.0)	0 (0.0)	
Second trimester	1 (33.3)	7 (21.2)	
Third trimester	2 (66.7)	26 (78.8)	
During influenza season when infant was hospitalized, mother			<0.001
Not vaccinated	109 (96.5)	155 (80.7)	
Vaccinated	4 (3.5)	37 (19.3)	



STUDY PERSONNEL

I worked with Dr. Marietta Vázquez and Dr. Eugene Shapiro for the first 18 months of the study. Dr. Vázquez and Dr. Shapiro provided oversight. I identified case and control subjects using data from hospital records, made phone calls to enroll participants, and enrolled cases and controls in the hospital during 2007-2008. In August 2008, Daina Esposito took over management of this study: she identified case and control subjects, enrolled additional participants, reviewed records and conducted much of the data analysis. Kristina Gracey, Nancy Holabird, Marcella Mignosa, Heather Yates, Matthew Burke and other personnel assisted with enrolling cases and controls, reviewing records, building an electronic database for results, and other study tasks. RT-PCR analysis of nasal wash samples was done by Madison Hustedt and Dr. Richard Martinello.

APPENDIX

PATIENT INTERVIEW FORM

INFANT INFORMATION

“First I would like to ask some general questions about [child].”

1. “What is your relationship to [child]?”

- 1 Mother/stepmother
 2 Father/stepfather
 3 Grandparent
 4 Other* *If OTHER, specify: _____
 5 Guardian

2. “Is [child] Hispanic or Latino?”

- 1 Yes
 0 No
 9 Unknown

3. “Which one or more of the following is [child] race?” (Check all that apply)

- 1 White
 2 Black or African American
 3 Asian
 4 Native Hawaiian or Other Pacific Islander
 5 American Indian or Alaska Native
 6 Other* *Specify: _____
 7 Don't know/Not sure
 9 Declined to answer

4. “Is [child] an adopted child or living in foster care?”

- 1 Yes
 0 No
 9 Unknown

5. “What was [child]’s birth weight?”

___ lbs ___ ozs (OR) _____ grams

6. “Was [child] born early (prematurely)?”

- 1 Yes *If YES: “At how many weeks/days was he/she born?”
 0 No _____ weeks +
 9 Unknown _____ days

7. Did [child] have to stay in the hospital more than 4 days after birth?

- 1 Yes *If YES, “How many days?”
 0 No _____ days
 9 Unknown

8. **“Was [child] ever breastfed?”**

- Yes* 1*
 No 0
 Unknown 9
 Still BF 11

*IF YES: **“How many months old was [child] when all breastfeeding stopped?”** ____ ____
 (# complete months – mark “99” if unknown)

“For how many weeks was [child] breastfed exclusively?” ____ ____

“Next, I am going to ask several questions about a specific period of time. This period is the 30 days right before your child was hospitalized, which is from __/__/____ to __/__/____.”

I will refer to this as the reference period. [The reference period begins 30 days prior to date of admission (or the child’s date of birth, whichever comes later, and ends on the date of admission.]

“I’d like to begin by asking some general questions about your household during the reference period that I just mentioned.

9. **“I’m going to read a list of different types of residences. Can you please tell me which best describes the type of residence in which [child] lived during the reference period?”**

- Single family house 1
 Duplex or Multi-family house 2
 Apartment/Condominium 3
 Mobile home/Trailer 4
 Dormitory 5
 Shelter 6
 Other 7
 Don’t know/Refuse 9

10. **“So, during the reference period of _____, how many people were living or staying in this household? Include you, your child, foster children, roomers, housemates, people staying here that had no other place to stay, long-term visitors, and people living here most of the time while working, even if they had another place to live.”**

____ ____ (# of people - mark “99” if unknown)

11. **“Please tell me the ages of all the people who lived in the household, including you but not counting [child] and tell me their relationship to [child]. I would like to know the ages during the reference period. Please also tell me if each person smoked at least once during the reference period. Finally, if you recall that any of these people were sick during the reference period, please let me know that information, too.”**

(record responses in table on next page)

Note: Please fill out table below for each person living in the house. Circle where appropriate. Do not include the case/control child. Cigars and pipes should also be included for smoking data.

Relationship codes: 1=mother/stepmother, 2=father/stepfather, 3=sibling, 4=grandparent, 5=aunt/uncle, 6=cousin, 7=friend of family, 8=other.

Relation to [child]	Age during ref. period	Unit of age Years or Months	Smoker? (yes, no, unknown)	Received seasonal flu vaccine by end of ref period?	Received H1N1 flu vaccine by end of ref period?	Slept in same room as child during ref. period?	Was person sick during ref. period?	Notes
				Type: Nasal (live intra-nasal) IM (attenuated intra-muscular)				
		Yr Mo	Yes No UK	Nasal IM No UK	Nasal IM No UK	Yes No UK	Yes No UK	
		Yr Mo	Yes No UK	Nasal IM No UK	Nasal IM No UK	Yes No UK	Yes No UK	
		Yr Mo	Yes No UK	Nasal IM No UK	Nasal IM No UK	Yes No UK	Yes No UK	
		Yr Mo	Yes No UK	Nasal IM No UK	Nasal IM No UK	Yes No UK	Yes No UK	
		Yr Mo	Yes No UK	Nasal IM No UK	Nasal IM No UK	Yes No UK	Yes No UK	
		Yr Mo	Yes No UK	Nasal IM No UK	Nasal IM No UK	Yes No UK	Yes No UK	
		Yr Mo	Yes No UK	Nasal IM No UK	Nasal IM No UK	Yes No UK	Yes No UK	
		Yr Mo	Yes No UK	Nasal IM No UK	Nasal IM No UK	Yes No UK	Yes No UK	

Note: check the total household members against Question 10; clarify any potential discrepancies

12. “So, during the reference period, there were ____ [count from above] people under the age of 18 sleeping in the same room as [child]?” (Fix numbers if there is a discrepancy)

13. “Which best describes the highest level of education that the child’s caretaker has received?”

- No high school 1
- Some high school 2
- High school graduate/GED 3
- Technical school 4
- Some college 5
- College graduate 6
- Post graduate/professional 7
- Don’t know/refused 8

14. “Which of the following categories best describes your total household income?”

- Up to \$15,000 1
- \$15,000 to \$30,000 2

- | | |
|----------------------|----------------------------|
| \$30,000 to \$45,000 | <input type="checkbox"/> 3 |
| \$45,000 to \$60,000 | <input type="checkbox"/> 4 |
| More than \$60,000 | <input type="checkbox"/> 5 |
| Refused | <input type="checkbox"/> 6 |
| Don't know | <input type="checkbox"/> 7 |

“Now, I would like to ask you some questions about [child]’s daycare during the reference period. The definition of daycare for this evaluation is any setting outside of your home where your child regularly spent 4 or more hours per week with at least 2 other children of any age under the care of an adult. Include preschool if your child attended for more than 4 hours/wk. If child care is provided in your home for others, think of your child as attending day care if care is provided for at least 2 unrelated children for 4+ hrs/wk with [child].”

15. **“During the reference period, did [child] attend any daycare, as we have just defined it?”** *(If child attended >1 daycare, have respondent answer in relation to the site where the child spent the most time during the week.)*
- Yes 1
 No 0 *(Skip to Q. 22)*
 Unknown 9 *(Skip to Q. 22)*
16. **“How many hours per week did [child] attend daycare during the reference period?”** *(Add total hours per week for all daycare ctrs.)*
 _____ = Total hours/week (mark “999” if unknown)
17. **“For how many months before hospitalization did [child] attend this daycare?”** *(If child attended >1 daycare, instruct respondent to answer question in relation to the site where the child spent the most time during week.)*
 _____ (# months – mark “99” if unknown, or “00” if less than 1 month)
18. **“What type of daycare did [child] attend during the reference period? I will read several options.”** *(If child attended >1 daycare, instruct respondent to answer in relation to the site where the child spent the most time during week)*
- Daycare center* 1*
 Preschool* 2*
 Home daycare 3
 Other 4
 Don't know 9
- *If response is either Daycare center (1) or Preschool (2), then also ask Question 19:
19. **“During the reference period, how many children, including [child], were in the same classroom or daycare setting as [child]?”** *(If child attended >1 daycare, instruct respondent to answer in relation to the site where the child spent the most time during the week)*
 _____ (# of children – mark “99” if unknown)

20. **During the reference period, how many children, including [child], attended the same daycare facility as [child]?”** (If child attended >1 daycare, instruct respondent to answer in relation to the site where the child spent the most time during week)
 _____ (# of children – mark “99” if unknown)

21. **“Were cigarettes smoked inside any facility or home where [child] attended day care?”**
 Yes 1
 No 0
 Unknown 9

“Now I would like to ask you a few questions about [child]’s general health. I will read a list of health problems. Some terms may be unfamiliar to you because they do not apply to your family. I will be happy to repeat or explain any terms. I will ask you to indicate if you were ever told by a physician that [child] had any of these conditions. Please answer Yes, No, or Don’t know. Answer Yes only if the condition started before the end of the reference period.”

CASES: “Answer NO if the condition started as part of your child’s influenza infection.”

CONTROLS: “Answer NO if the condition started as part of your child’s hospitalization.”

22. **“Sickle cell disease?”** (Note: SS or SC disease, not SC trait or being a carrier)
 Yes 1 *If YES, specify _____
 No 0
 Unknown 9

23. **“Kidney or renal disease?”**
 Yes* 1* *If YES, specify type _____
 No 0
 Unknown 9

***IF YES: “Does the child require dialysis?”**

- Yes 1
 No 0
 Unknown 9

24. **“Heart problems?”**
 Yes* 1* *If YES, specify type _____
 No 0
 Unknown 9

25. **“Any chronic problems with the immune system, including any immune system problem your child was born with?”**
 Yes 1* *If YES, specify type _____
 No 0
 Unknown 9

26. “Asthma, reactive airways disease, or >1 episode of wheezing?”

Yes* 1* *If YES, specify type _____
 No 0
 Unknown 9

IF YES: “From birth to hospitalization, how many times did [child] go to the doctor or emergency room for an attack of asthma, reactive airways disease, or wheezing?” _____ (# of visits – mark “99” if unknown)

27. “Other chronic lung condition/s?”

Yes* 1* *If YES, please specify type _____
 No 0
 Unknown 9

28. “A birth defect or chronic condition that makes breathing or swallowing difficult?”

Yes* 1* *If YES, please specify type _____
 No 0
 Unknown 9

29. “A condition that needs medical equipment to make breathing or handling secretions easier, such as receiving supplemental oxygen, or for which an operation was done, such as a tracheostomy (a ‘trach’)?”

Yes* 1* *If YES, please specify type _____
 No 0
 Unknown 9

30. “Spinal cord injury?”

Yes* 1* *If YES, please specify type _____
 No 0
 Unknown 9

31. “A seizure disorder or epilepsy?”

Yes* 1*
 No 0
 Unknown 9

*IF YES: “Are seizures only with fever?”

Yes 1
 No* 0* *If NO, please specify type _____
 Unknown 9

32. “Severe developmental delay or mental retardation?”

Yes 1* *If YES, please specify type _____
 No 0
 Unknown 9

33. **“Any neurologic or neuromuscular problems?”**
 Yes* 1* *If YES, please specify type _____
 No 0
 Unknown 9
34. **“Any metabolic or endocrine problems?”**
 Yes* 1* *If YES, please specify type _____
 No 0
 Unknown 9
35. **“Any serious stomach problems?”**
 Yes* 1* *If YES, please specify type _____
 No 0
 Unknown 9
36. **“Any other chronic illnesses?”**
 Yes* 1* *If YES, please specify type _____
 No 0
 Unknown 9

“Now, I would like to ask you some questions regarding medicines that [child] may have taken during the reference period.”

37. **“During the reference period, did [child] ever take aspirin for more than a month?”**
 Yes 1
 No 0
 Unknown 9
38. **“During the reference period, did [child] take any steroid medications, such as Prelone, prednisilone, prednisone, Decadron, dexamethasone or Orapred, either by mouth as pills or liquid or by injection? These medications are sometimes given for asthma or other illnesses.”** [Note: don't include inhaled steroids.]
 Yes* 1* *If YES: How many days? ____ ____
 No 0
 Unknown 9
39. **“During the reference period, did [child] use any medications for wheezing, reactive airways disease, or asthma?”**
 Yes 1* *If YES, please specify type _____
 No 0 (*Skip to Q. 42*)
 Unknown 9
40. **“During the reference period, how many different breathing medications did [child] use on an average day?”**
 ____ # different medications

41. **“How many doses per day on average did [child] use these medications? For example, if [child] took two medicines twice a day, that would be 4 doses. Please include inhaled doses, pills, or liquids taken through a nebulizer.”**

Less than 1 0 1 or 2 times 1
3 or more times 2 Don't know 9

42. **“Did [child's name] get at least one flu shot?”**

Yes 1* *If Yes, number of doses: 1 2 Unknown
No 0
Unknown 9
Child <6 mo 11

INFORMATION ABOUT THE MOTHER

“Now I want to ask you information about your pregnancy and your health.”

- 43. “Did you routinely visit a doctor/healthcare provider while pregnant?”** (*prenatal care*)

Yes* 1*
 No 0
 Unknown 9

***If YES: “Approximately how many weeks pregnant were you when you went to visit a doctor/healthcare provider for the first time?”**

_____ weeks

- 44. “Did you visit >1 one clinic/office when pregnant, including any other primary care physicians?”** [If you already specifically asked about this during earlier data collection, skip.]

Yes* 1 * If YES, record other doctors on the cover page.
 No 0

- 45. “Approx. how many times did you visit the doctor while pregnant?”**

Approximate # visits
 “Normal” number (1/mo early, 2- 3 visits/month in 3rd trimester)

- 46. “Were you ever hospitalized during this pregnancy?”**

Yes* 1* *If YES, explain: _____
 No 0

- 47. “Do you have asthma or chronic obstructive pulmonary disease (COPD)?”**

Yes 1* *If YES, explain: _____
 No 0
 Unknown 9

- 48. “Do you have any long-standing/chronic medical problems?”**

Yes* 1* *If YES, explain: _____
 No 0
 Unknown 9

- 49. “Do you smoke?”**

Smoking
 details: _____
 Yes* 1 (*past/present*) _____
 No 0

(Compare response against data from question 11. This should reflect status at hospitalization.)

50. "Did you smoke during the pregnancy?"

Yes 1
No 0

51. "With this child, were you pregnant with more than one child?"

Yes* 1* If YES, specify: _____
No 0 (i.e., twins, triplets)

52. "How many children do you have now (only count live children)?"

_____ (# of children – mark "99" if unknown)

53. "Did your doctor/healthcare provider recommend you get flu vaccine when you were pregnant?"

Yes 1
No 0
Unknown 9

54. "Did you receive influenza vaccine (the flu shot) during this pregnancy?" (check with response to #11)

Yes* 1* If yes, give details: _____
No 0 (year, location) _____
Unknown 9 _____

55. "Other than when you were pregnant, did you EVER receive flu vaccine (before your child was hospitalized)?" (check with response to #11)

Yes* 1* If yes, give details: _____
No 0 (year, location) _____
Unknown 9 _____

56. Have you ever received ANY vaccines (other than the flu shot) outside of your primary care physician or obstetrician, for example at a pharmacy, at work or at a public health department?"

Yes* 1* If yes, give details: _____
No 0 (year, location) _____
Unknown 9 _____

HOSPITAL RECORD DATA FORM

Study ID _____

Checked by: _____ Date checked: _____

Admission date ____/____/____
MM/DD/YYYY

DOB ____/____/____

Age at hospitalization (wks) _____

Sample (check all that apply):

Research team; date collected ____/____/____

Leftover sample; date sent ____/____/____

Reviewer's initials ____ Date of record review _____

Hospital Medical Record Extraction Form

1. Vitals: T_{max} ____C Axillary Rectal HR_{max} ____ RR_{max} ____ O₂Sat_{min} ____ on RA

2. Labs

WBC _____ Diff: ____G ____L ____M ____E ____Bands

DFA _____

H1N1 PCR _____

hMPV PCR _____

Sputum Culture _____

Blood Culture _____

ABG _____

CSF results

Culture/gm stain _____

Cell counts: ____rbc ____nuc cells (____G ____L ____M)

Virology _____

Urine culture _____

Other _____

3. Wheezing on exam Yes No Not recorded

Nasal flaring on exam Yes No Not recorded

Retractions on exam Yes No Not recorded

Details _____

4. Imaging

CXR _____

Chest CT _____

5. Treatments given for this sickness at PCC, ED and/or hospital

Require O₂: Yes No If YES, details _____

6. Diagnoses: _____

7. Reasons for admission: _____

- 8. Hospital admission Yes No
 8a. If admitted, type: Floor ICU
- 9. Require ICU care Yes No
- 10. Length hospital stay _____ days
- 11. Intubation Yes No
- 12. Death Yes No

Pre-existing medical conditions/co-morbidities:

Also note the presence/absence of these symptoms:

Recording method:

- | | | | |
|-----------------|-------------------------------|------------------------------|----------------------------------|
| Sneeze | <input type="checkbox"/> Yes | <input type="checkbox"/> No | <input type="checkbox"/> Unknown |
| Cough | <input type="checkbox"/> Yes | <input type="checkbox"/> No | <input type="checkbox"/> Unknown |
| Rash | <input type="checkbox"/> Yes | <input type="checkbox"/> No | <input type="checkbox"/> Unknown |
| Nasal discharge | <input type="checkbox"/> Yes | <input type="checkbox"/> No | <input type="checkbox"/> Unknown |
| Appearance: | <input type="checkbox"/> Well | <input type="checkbox"/> Ill | <input type="checkbox"/> Toxic |

____ *Observed by
study personnel*
 ____ *Information is
from records*

Other pertinent clinical information: (be sure to note recent antibiotic use if any)

RESPIRATORY CLINICAL SEVERITY SCALE

Date: ___/___/___ *Time:* ___:___ [am/pm]

Scored by: _____ (initials)

	0 pts	1 pt	2 pts
1. Heart Rate (max): _____ beats/min			
<i>Age 0-7 days</i>	<130	130 – 160	>160
<i>Age 1-4 weeks</i>	<135	135 – 170	>170
<i>Age 1-6 months</i>	<140	140 – 170	>170
<i>Age 6-12 months</i>	<130	130 – 160	>160
2. Respiratory rate (max): _____ breaths/min			
<i>Age 0-1 month</i>	<50	50 – 70	>70
<i>Age 1-6 months</i>	<30	30 – 50	>50
<i>Age 6-12 months</i>	<20	20 – 40	>40
3. Oxygen saturation: _____%	≥94%	—	<94%
4. Wheezing present?	No	Yes	—
5: Retractions present?	No	—	Yes
6. Nasal flaring present?	No	Yes	—
7. Require intubation?	No	—	Yes
8. Require ICU care?	No	—	Yes
9. Abnormal chest x-ray?	No	—	Yes
TOTAL SCORE (0-16): _____			

OUTPATIENT MEDICAL GROUP INFORMATION

Clinic or group:	_____		
Physician(s):	_____		
Address:	_____		
Phone number:	(____) ____ - ____	(voice) /	(____) ____ - ____ (fax)
Type:	<input type="checkbox"/> Pediatrics	<input type="checkbox"/> Family	<input type="checkbox"/> Hospital
	<input type="checkbox"/> Ob/gyn	<input type="checkbox"/> PMD	<input type="checkbox"/> L&D
			<input type="checkbox"/> Other: _____
Date of this interview:	____/____/____	Reviewer initials:	____
Interviewee	_____		

1. Have you ever given the flu vaccine in this office or in any other office of this medical group?

- Yes **If YES, when did you start/stop offering the vaccine?** _____
- No

2. If YES for at least one season:

Do physicians in this office recommend flu vaccine to their patients?

- Yes, for children as per CDC recommendations
- Yes, for pregnant women as per CDC recommendations
- Other: _____
- No

If the flu vaccine is offered to pregnant women, when is the vaccine administered?

- 1st trimester
- 2nd trimester
- 3rd trimester

How was the vaccination information recorded?

- In the patient's medical records
- In the medical group's billing records
- Other: _____

How can the vaccination information be obtained? _____

3. If NO for at least one season:

If a patient had asked for flu vaccine in these seasons, what would have happened?

- The patient would have been directed elsewhere: _____
- We would not have provided any further information or assistance

OUTPATIENT MEDICAL RECORD REVIEW – INFANT

Subject's Name: _____

Notes about practice _____ Faxed info:

Type: Pediatrics Family Hospital Other: _____

Infant DOB: ____/____/____ Last time seen: ____/____/____

Admit Date of case/control: ____/____/____ Flu season: ____ - ____

Date of this record review: ____/____/____ Reviewer initials: ____

Insurance Provider: No ___ Yes ___ If yes: _____
Public Private Company

VACCINATION RECORD

DTaP

- Dose 1: ____/____/____
- Dose 2: ____/____/____
- Dose 3: ____/____/____
- Dose 4: ____/____/____
- Dose 5: ____/____/____

Hepatitis B

- Dose 1: ____/____/____
- Dose 2: ____/____/____
- Dose 3: ____/____/____
- Dose 4: ____/____/____

Polio (IPV)

- Dose 1: ____/____/____
- Dose 2: ____/____/____
- Dose 3: ____/____/____
- Dose 4: ____/____/____
- Dose 5: ____/____/____

Haemophilus influenzae B (Hib)

- Dose 1: ____/____/____
- Dose 2: ____/____/____
- Dose 3: ____/____/____
- Dose 4: ____/____/____
- Dose 5: ____/____/____
- Dose 6: ____/____/____

Hepatitis A Vaccine

- Dose 1: ____/____/____
- Dose 2: ____/____/____

Pevnar

- Dose 1: ____/____/____
- Dose 2: ____/____/____
- Dose 3: ____/____/____
- Dose 4: ____/____/____

Influenza vaccine

- Dose 1: ____/____/____
- Dose 2: ____/____/____
- Dose 3: ____/____/____
- Dose 4: ____/____/____
- Dose 5: ____/____/____
- Dose 6: ____/____/____
- Dose 7: ____/____/____

MMR

- Dose 1: ____/____/____
- Dose 2: ____/____/____

Varicella Vaccine

- Dose 1: ____/____/____
- Dose 2: ____/____/____

Rotateq

- Dose 1: ____/____/____
- Dose 2: ____/____/____
- Dose 3: ____/____/____

RotaRix

- Dose 1: ____/____/____
- Dose 2: ____/____/____

Common Combination Vaccines

(please circle and add dates)

Pediarix (DTaP, Hep B, IPV)

Comvax (HepB and Hib)

TriHIBit (DTaP and Hib)

ProQuad (MMR + Varicella-MMRV)

Pentacel (DTaP, Hib, IPV)

Other vaccine notes:

(continued)

Date of birth: ____ / ____ / ____ Weeks gestation: ____

Birthweight: ____ lbs ____ oz OR ____ grams

Place of Birth: _____

Child's other physicians, if listed _____

*Please list all medications and pre-existing medical conditions.***All pre-existing medical conditions:****Specifics to look for:**

- Sickle cell disease
- Kidney/renal disease
- Heart problems
- Chronic immune problems
- Asthma, reactive airways disease, or wheezing
- Birth defects
- Conditions requiring med equip for breathing
- Spinal cord injury
- Other chronic illnesses
- Seizures or epilepsy
- Developmental delay or mental retardation
-

All chronic or recent medications before acute illness: (route + dose)**Specifics to look for:*****Steroid medications***

- Prelone, Prednisolone, Prednisone, Decadron, Dexamethasone, Orapred

Medications

- Albuterol
 - Aspirin (long term)
- Be sure to include the type, route and dose for all medications listed here.

Acute illness – brief history

visits to clinic or practice for acute illness ____

Other pertinent information noted in medical record:

(continued)

Any prior long-standing/chronic medical problems: (i.e. asthma, COPD, diabetes) Yes No Unknown/no information available**Any medications?** Yes No Unknown/no information available**Any complications during this pregnancy: (especially conditions requiring hospitalization)** Yes No Unknown/no information available**Did mom ever smoke?** Yes No Unknown/no information available

If YES, details

Other information: