REVIEW ARTICLE

Prevention of Novel Influenza Infection in Newborns in Hospital Settings: Considerations and Strategies During the 2009 H1N1 Pandemic

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ABSTRACT

During the 2009 influenza A (H1N1) pandemic, many pregnant women experienced severe illness and some gave birth while ill with suspected or confirmed pandemic (H1N1) 2009 influenza. Because of concerns about possible transmission of this novel virus to immunologically naïve newborns, and the absence of definitive studies regarding this risk, the Centers for Disease Control and Prevention (CDC) reviewed relevant literature to understand the potential burden of disease and routes of transmission affecting newborns. This report describes the issues considered during the 2009 H1N1 pandemic as CDC developed guidance to protect newborns in hospital settings. Also presented is a framework of protection efforts to prevent novel influenza infection in fetuses/newborns before birth and in hospital settings. Although developed specifically for the pandemic, the framework may be useful during future novel influenza outbreaks.

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Key Words: influenza A virus H1N1 subtype, newborn, cross infection, vertical infectious disease transmission, prevention, and control

The Department of Health and Human Services issued a national public health emergency declaration on April 26, 2009, in response to the pandemic (H1N1) 2009 influenza (pH1N1). First identified in Mexico and the United States in the spring of 2009, the pandemic rapidly spread to become the first global influenza pandemic since 1968.[1] It was found that pregnant women were more likely to have severe illness and die than other population groups, and some were giving birth while they themselves were ill with suspected or confirmed pH1N1.[2-7] Infection with severe disease and death was also reported in early postpartum women.[5] Subsequently, there were concerns about possible transmission of pH1N1 to immunologically naïve newborns (infants aged ≤28 days), as transmission appeared to occur from person-to-person through close contact via large-particle respiratory droplets from coughing or sneezing, contact with an infectious person or surface that was contaminated with secretions, and by aerosolized small-particle droplets.[1,8] Also, viral shedding by an infected person was thought to begin one day before onset of illness and persist for five to seven days or more.[9-12]

To develop comprehensive plans for prevention and control of pH1N1 infection in newborns in hospital settings during this public health emergency, it was important to understand the potential burden of disease and routes of transmission affecting this vulnerable population. This report describes the issues considered and relevant literature reviewed during the 2009 H1N1 pandemic to support development of the Centers for Disease Control and Prevention (CDC) guidance on the management of maternal infection in intrapartum and postpartum hospital settings to protect newborns. Also included is a framework of protection efforts to prevent infection in fetuses/newborns that was used during the pandemic, which may be valuable as well during future novel influenza outbreaks.

POTENTIAL BURDEN OF DISEASE

During the pandemic, prevention of pH1N1 infection in newborns was particularly important for several reasons. First, the immune system of a newborn is immature, deriving most of its serum immunoglobulins from the transfer of maternal immunoglobulin G across the placenta during the third trimester of pregnancy.[13] In the case of pH1N1, transplacental transmission of protective antibodies against the novel virus could only occur if the mother had been vaccinated against pH1N1 or had been infected with the virus. Second, neonates are very susceptible to viral infections, having reduced cell-mediated immunity against influenza and other respiratory viruses.[14,15] Third, chemoprophylaxis and treatment options for pH1N1 infection in newborns were limited, as neither oseltamivir nor zanamivir were licensed by the US Food and Drug Administration (FDA) for use in infants younger than age one year[16]; however, an emergency use authorization for oseltamivir for pH1N1 treatment and prevention for such infants was

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issued in April 2009 for the duration of the pandemic.[17] Last, similar to seasonal influenza vaccines, the monovalent pH1N1 vaccine available during the pandemic was not approved for use in children younger than age six months.

Little had been published about pH1N1 infection in newborns, even though infants, including those younger than age six months, had been at increased risk for hospitalization and death in prior seasonal influenza seasons.[18-24] During the 2009-2010 influenza season in which pH1N1 was the predominant circulating influenza virus, the rate for newborns was not reported separately, although preliminary data from a US population-based surveillance network found young children (aged 0-4 years) had the highest laboratory-confirmed rate of influenza-associated hospitalization.[25] Data from Argentina and the Netherlands also documented greater disease burden of laboratory-confirmed pH1N1 in young children, and similarly did not report data on newborns separate from older infants and children.[26,27] In Argentina, where data were broken down into narrower pediatric age categories, results from a retrospective case series of 251 children (aged <18 years) hospitalized with laboratory-confirmed pH1N1 found that 60% of admitted children were infants younger than one year of age.[26] Moreover, rates of hospitalization were highest for younger infants; whereas the overall pediatric hospitalization rate was 20.9 per 100 000 children, the rate for infants younger than age six months was 200 per 100 000 children.[26]

Although newborn-specific data were not available, evidence suggested that overall attack rates in the pediatric population were greater than those observed with seasonal influenza. For example, the data from Argentina showed that the pediatric hospitalization rate associated with pH1N1 was twice that for the 2008 seasonal influenza season in the same population, and the rate of death was 10 times the rate associated with seasonal influenza for the same population in 2007.[26] However, the observed higher rates of hospitalization and death associated with pH1N1 may have been due in part to increased testing and reporting as a result of heightened awareness of the pandemic.

POTENTIAL ROUTES OF TRANSMISSION

The two major routes of transmission of pH1N1 to fetuses/newborns during the peripartum period considered during the pandemic were (1) transplacental transmission from an infected mother or (2) transmission during or after birth through contact with respiratory droplets from an infected individual (eg, mother, other family member, visitor, other newborn, health care personnel).

Transplacental Transmission

Although viremia and transplacental transmission appear to be rare with human influenza,[28-32] the probability of virus reaching the uterus and placenta might be greater for highly pathogenic strains of influenza or in cases of severe maternal illness. For example, evidence of transplacental transmission of avian influenza A (H5N1), as well as several other strains of influenza A virus, has been reported.[29,31,32] Limited reports of transplacental transmission may be due, in part, to the challenges in obtaining relevant specimens and appropriate documentation of emerging infections in placental and fetal tissues.[33]

During the pandemic, one report described possible placental transmission of pH1N1 to a newborn from a mother who became ill seven days before delivery.[34] The newborn was delivered by emergency cesarean section at 31 weeks' gestation after the mother experienced cardiopulmonary failure. Real-time reverse transcription polymerase chain reaction of the newborn's throat swab specimen collected after birth (timing not otherwise reported) confirmed infection with the novel virus. As the mother required intensive cardiopulmonary support at the time of delivery and was not otherwise in contact with her newborn, the authors concluded that the newborn was infected in utero. Although possible, transmission through respiratory droplets cannot be definitely ruled out, because the authors did not report how soon after birth the positive specimen was collected nor whether the newborn was exposed to other infected individuals (eg, health care worker).

Transmission During or After Birth via Contact with Infected Respiratory Droplets

Transmission of pH1N1 via exposure to infected respiratory secretions from a mother with intrapartum infection posed a potential serious risk to the newborn, given the close contact that occurs between mother and child immediately after birth and during the postpartum period. Although mother-to-child transmission of influenza during the intrapartum or early postpartum period had not been systematically examined, there were reports of newborn influenza infection that was thought to have been transmitted via an ill mother after birth. One study examined the risk of influenza during the first year of life among 209 infants enrolled at birth; one death occurred in an 11-day-old newborn with influenza A (H3N2) and pneumonitis.[35] The mother of the newborn had become ill with the influenza virus six days postpartum; the infant did not have any detectable antibody to the virus in cord serum obtained at birth. In another report, a preterm infant who developed severe respiratory distress at age 17 days tested positive for influenza B infection and died at age 33 days.[36] Although the source of infection was not definitely determined, the newborn's mother experienced symptoms of an influenza-like illness when the newborn was aged 14 days. At the time of the pandemic, only one report, conducted in Australia and New Zealand, had described findings from pH1N1 testing of neonates born to mothers admitted to an intensive care unit during pregnancy or the early postpartum period for pH1N1 illness.[7] In that report, 2 (10%) of 20 newborns of critically ill mothers tested for pH1N1 had documented infection with the novel virus. Unfortunately, no other information on the infected newborns was available, including degree of exposure to their ill mothers, timing of testing, presentation of symptoms, or course of illness.

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In addition, no reports, to our knowledge, systematically quantified the rate of influenza transmission to newborns from other infected persons such as family members or health care personnel. One case report described influenza B-associated death in a preterm newborn who was thought to have acquired infection from his ill father who visited the neonatal intensive care unit (NICU) while experiencing influenza-like illness.[37] There is also one report of pH1N1 infection in a 20-month-old oncology patient admitted to the hospital for induction chemotherapy who developed influenza symptoms and tested positive for pH1N1 after being in the hospital for one week.[38] As a contact investigation revealed that none of the patient's family members or visitors had been in recent or close contact with anyone experiencing influenza-like illness, and because health care personnel caring for the patient had also cared for pH1N1 patients, the authors concluded that transmission likely occurred through health care personnel. Any ill caregiver in close contact with newborns should be considered a potential source of infection.

Similarly, an infected newborn in a nursery may theoretically pose an infection risk to other newborns. It is estimated that 1% of infants requiring care in the NICU acquire a viral infection after admission to the NICU.[39] Most health care-associated viral infections that occur in the NICU are thought to be transmitted through respiratory droplets, contact with the contaminated hands of health care personnel or other adults, and contaminated medical equipment or supplies.[40] Specific to influenza virus, there have been several reports of health care-associated influenza virus type A respiratory infection outbreaks in NICUs.[41-43] Although the NICU patients affected in these outbreaks had underlying conditions and required prolonged hospitalizations and were not likely comparable to healthy newborns not requiring NICU care, novel virus strains for which there is no neonatal passive immunity may impact healthy newborns more readily than other strains. During the pandemic, there were no published reports on the rate of health care-associated infections with influenza viruses among healthy newborns.

PREVENTION STRATEGIES

During the 2009 H1N1 pandemic, the CDC developed a framework to prevent pH1N1 infection in fetuses/newborns before birth and in hospital settings, based on the considerations and available literature described. This framework outlines protection efforts, including immunization, provision of breast milk to the newborn, infection control practices, and treatment of illness, that could be implemented by or prevent infection in potential close contacts of newborns (Table). Developed during the H1N1 pandemic, this framework may also be useful to protect fetuses/newborns against future novel influenza viruses.

Immunization

Perhaps the most important strategy to protect fetuses/newborns from novel influenza infections, including pH1N1, is vaccination of pregnant women, household contacts of infants and pregnant women, and other individuals who will come into close contact with or care for newborns, including health care personnel. For pH1N1, the Advisory Committee on Immunization Practices identified pregnant women, persons who live with or provide care for infants younger than age six months, and health care personnel as three of five initial target groups for pH1N1 vaccination efforts.[44] Nevertheless, data collected

TABLE

Framework to Prevent Novel Influenza Infections, Including pH1N1, in Newborns Before Birth and in Hospital Settings

Protection Efforts	Potential Contact			
	Mothers	**Health Care Personnel**	**Family Members**	**Other Newborns**
Immunization	Vaccination of mothers before or during pregnancy Vaccination of mothers postpartum before hospital discharge	Vaccination of health care personnel caring for newborns	Vaccination of family members and caregivers of infants aged <6 mo	
Provision of breast milk	Breastfeeding or expression/collection of breast milk	Provide feeding assistance if mother is ill Provide lactation support	Provide feeding assistance if mother is ill	
Infection control	Respiratory hygiene and cough etiquette, hand hygiene Isolation/cohorting	Respiratory hygiene and cough etiquette, hand hygiene Work restrictions when ill	Respiratory hygiene and cough etiquette, hand hygiene Restriction on visitors Screening visitors for respiratory illness	Isolation/cohorting
Treatment of infection	Neuraminidase inhibitor	Neuraminidase inhibitor	Neuraminidase inhibitor	Consideration of oseltamivir use, as clinically indicated, under FDA emergency use authorization[a]

Abbreviation: FDA, US Food and Drug Administration.
[a]Not authorized in preterm infants during the pandemic.

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during the pandemic found low vaccination coverage rates among these target groups: 38.0% for pregnant women, 22.3% for health care personnel, and 13.9% for adults who live with or provide care for infants aged younger than six months.[45] For pregnant women, low influenza vaccination rates may be due in part to provider barriers, as findings from one survey of obstetrician-gynecologists found that although the majority would recommend influenza vaccination for a healthy pregnant woman, over one-third did not offer it in their practices.[46] Inactivated influenza vaccines have been shown to be safe and effective when administered during pregnancy.[47]

Vaccinating pregnant women not only reduces the likelihood of severe maternal illness and death but also may provide some protection against infection in newborns as a result of maternal antibodies passively transferred via the placenta.[15] One study conducted in Bangladesh randomized receipt of inactivated seasonal influenza vaccine among 340 women in the third trimester of pregnancy during the 2004-2005 influenza season. Findings showed fewer cases of laboratory-confirmed influenza among infants of mothers who received the influenza vaccine than among infants of mothers who did not.[48] In the United States, a nonrandomized, controlled, observational study was conducted during three influenza seasons during 2002-2005. Maternal influenza vaccination during pregnancy was found to be significantly associated with reduced risk of infant influenza virus infection and hospitalization for an influenza-like illness up to six months of age.[49] To improve vaccination rates among pregnant women, all health care providers are urged to provide influenza vaccine to pregnant women who present for care. Before hospital discharge, previously unvaccinated mothers should be vaccinated, and vaccine should be offered to family members and other potential close contacts of the newborn, within hospital constraints.

Provision of Breast Milk

Providing breast milk to newborns may reduce transmission of novel influenza viruses, including pH1N1, to newborns, as breast milk offers many important health benefits including protection against respiratory pathogens.[50-55] In fact, the risk of hospitalization for lower respiratory tract disease is more than 250% higher among babies who are fed formula than in those who are exclusively breastfed.[52] Because of the many benefits of breast milk, efforts to provide it to newborns are vital. Depending on the mother's severity of illness and the hospital's configuration and implementation of infection-control procedures, some newborns of mothers with intrapartum pH1N1 infection may be initially separated from their mothers and not fed directly at the breast. Ill mothers who are separated from their infants will need assistance to adequately establish lactation and express and collect their milk. Assistance should be coupled with support and encouragement from hospital staff, and staff should ensure that expressed milk is appropriately handled and stored. When possible, while the newborn is separated from the mother, all feedings should be provided by a healthy caregiver. Breast milk from an infected mother is not considered infectious,[56] and use of antiviral medication by the mother is not a contraindication to breastfeeding.[57] When the risk of maternal-to-child transmission of infection via respiratory secretions is reduced, the mother should be supported and encouraged to initiate and continue direct breastfeeding. The American Academy of Pediatrics, the World Health Organization, the American College of Obstetricians and Gynecologists, and the US Preventive Services Task Force recommend exclusive breastfeeding for about the first six months of age.[58-60]

Infection Control Practices

Another important strategy to protect newborns from infection with novel influenza viruses, including pH1N1, is implementation of hospital infection-control practices. Newborn exposure to infected secretions can be reduced through adherence to respiratory hygiene and cough etiquette (ie, use of facemasks or tissues to cover nose and mouth when coughing or sneezing), and hand hygiene performed by mothers, family members, health care personnel, and visitors. To improve adherence, facilities should ensure availability of supplies necessary to perform hand and respiratory hygiene as well as cough etiquette.

Implementing isolation/cohorting strategies as well as engineering controls (eg, physical barrier partitions), instituted by hospital policy, is also critical. In the three reports of health care-associated outbreaks of influenza A virus among NICU infants mentioned, cohorting of infected infants in a separate room[42,43] or separating infected infants from healthy infants using an acrylic wall[41] were important infection-control measures. In the event of maternal infection with pH1N1 during hospitalization for delivery, determining the best option for postpartum and newborn patient management will require careful consideration of the hospital's physical configuration, availability of isolation rooms, and number of patients in need of isolation. Recent trends in design and staffing of labor, delivery, recovery, postpartum, and newborn care units in the United States to accommodate family-centered care may create challenges to isolation of large numbers of ill mothers from their healthy newborns in a pandemic scenario. Therefore, having healthy newborns room with their infected mothers in a postpartum unit may be employed. To reduce transmission risk in this situation, separation of an infected mother from her healthy infant may require modifications to the room (eg, use of a physical barrier, keeping the newborn $\geq$6 feet from the ill mother). In addition, precautions should be taken to reduce the risk of inadvertent transmission of infection from an ill mother to other unexposed individuals that she might come into contact with during the hospital stay, such as other maternity patients, healthy term infants, and preterm or critically ill newborns in designated newborn nurseries, special care nurseries, or intensive care units.

Other infection-control measures that will provide newborns protection from novel influenza viruses in hospital settings include work restrictions for ill health care personnel and implementing hospital visitor policy restrictions. As ill health care personnel are a potential source of infection to patients, facili-

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ties should develop sick leave policies for health care personnel that are nonpunitive, flexible, and consistent with public health guidance to allow and encourage those with suspected or confirmed influenza to stay home. It is also important to ensure that health care personnel, including staff who are not directly employed by the health care facility but who provide essential daily services (eg, environmental cleaning), are aware of sick leave policies. Health care personnel who return to work following illness should be reminded that adherence to hand hygiene, respiratory hygiene, and cough etiquette after returning to work remains important, as viral shedding may occur for several days following an acute respiratory illness. Unnecessary visitors to mothers and newborns during the hospital stay should be limited, and visitors should be screened for symptoms of acute respiratory illness before being allowed to visit the postpartum mother or newborn.

Treatment of Infection

Another strategy to reduce novel influenza infection in newborns is rapid identification of infection and treatment of pregnant women and other close contacts with appropriate antiviral medications (ie, oseltamavir or zanamavir). Studies have shown that treatment with these drugs decreases viral loads and reduces the risk of severe disease and death if started within 48 hours of symptom onset.[5,11,61] Treatment will likely reduce morbidity and mortality even if started more than 48 hours after illness onset, although early treatment is most effective. For pregnant women, early identification of infection and treatment might also benefit the unborn fetus by preventing preterm delivery as a consequence of severe maternal illness. With respect to newborns themselves, although emergency use of oseltamivir, as clinically indicated, was authorized by the FDA for term infants younger than age one year for pH1N1 treatment during the pandemic,[17] data are limited on the safety and dosing of oseltamivir for this age group and offer no specific guidance for use among preterm infants (<37 weeks' gestation or corrected postmenstrual age). Moreover, chemoprophylaxis with oseltamivir is not recommended in infants younger than three months of age, unless the exposure is significant and the infant is considered at high risk of severe illness.[17]

CONCLUSIONS

Due to immune system immaturity, susceptibility to viral infections, limited antiviral treatment options, and lack of appropriate vaccine, newborns are vulnerable to novel influenza viruses, including pH1N1. After examining the potential burden of pH1N1 and routes of transmission affecting newborns during the pandemic, we developed a framework to prevent infection in fetuses/newborns that focused on protection efforts to be implemented by or prevent infection in mothers, health care personnel, family members, and other newborns. Perhaps the most important of these protection efforts included immunization; other protection efforts included provision of breast milk to newborns, implementation of infection control practices, and rapid identification and treatment of infection. Further research is needed to systematically ascertain the risks of novel influenza virus transmission to newborns, including from mother to child during the intrapartum period, in hospital settings. Information included in this report was used as the scientific foundation to develop the CDC clinical guidance on the management of maternal infection with pH1N1 in intrapartum and postpartum hospital settings,[62] and may also be a useful resource during future novel influenza outbreaks to assist in the development of comprehensive infection control plans.

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