DRL 2008-003

The findings in this report are subject to at least three limitations. First, identification of hospitalizations for pneumonia and nonpneumonia ARI was based on ICD-9-CM codes and might be subject to misclassification, despite internal quality control and validation for consistency within the Nationwide Inpatient Sample. Second, establishing the etiology of pneumonia is difficult. Nationwide Inpatient Sample data are deidentified before public release and chart reviews cannot be performed to confirm recorded diagnoses. Because most pneumococcal pneumonias are classified as pneumonias without further characterization, this report provides an estimate of the effect of PCV7 on all-cause pneumonia without regard to pneumococcal serotypes. Furthermore, serotyping is not part of routine diagnostic work-ups, and this information would not be recorded in medical charts. However, the decrease in nonpneumonia ARI hospitalizations among children aged <2 years suggests that the decreases in pneumonia hospitalizations were unlikely to result from a shift in coding of pneumonia to nonpneumonia ARI codes. Finally, factors other than shifts in coding could affect hospitalization rates. Reduced clinician concerns for severe pneumococcal disease among immunized children, for example, might lead to outpatient treatment rather than hospitalization. However, other data indicate that ambulatory-care visits for pneumonia among children aged <2 years also have decreased since introduction of PCV7 (*5*). In addition, the proportion of all hospitalizations that were attributable to pneumonia or nonpneumonia ARI decreased significantly, suggesting that the declines were unlikely to result from a secular reduction in overall hospitalization rate.

Despite the substantial morbidity associated with childhood pneumonia, no pneumonia-specific prospective population-based surveillance system exists for monitoring trends in the incidence of pneumonia hospitalizations or pneumonia-related ambulatory-care visits in the United States. Monitoring childhood pneumonia is important for the evaluation of effects of current and future pneumococcal immunization programs. Increases in pneumococcal disease caused by serotypes not included in PCV7 could result in some increase in pneumonia, even though observed increases in non-PCV7 serotype IPD have been modest thus far (*9*). In addition, extended-valency pneumococcal conjugate vaccines are expected to be licensed by late 2009 to early 2010 and might further reduce pneumonia rates. Finally, vaccination of children against influenza, as recommended by the Advisory Committee on Immunization Practices, is increasing and also might reduce pneumonia hospitalization rates (*10*).

References

1. McIntosh K. Community-acquired pneumonia in children. N Engl J Med 2002;346:429–37.
2. CDC. Preventing pneumococcal disease among infants and young children: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2000;49(No. RR-9).
3. CDC. Invasive pneumococcal disease in children 5 years after conjugate vaccine introduction—eight states, 1998–2005. MMWR 2008;57:144–8.
4. Grijalva CG, Nuorti JP, Arbogast PG, Martin SW, Edwards KM, Griffin MR. Decline in pneumonia admissions after routine childhood immunisation with pneumococcal conjugate vaccine in the USA: a time-series analysis. Lancet 2007;369:1179–86.
5. Zhou F, Kyaw MH, Shefer A, Winston CA, Nuorti JP. Health care utilization for pneumonia in young children after routine pneumococcal conjugate vaccine use in the United States. Arch Pediatr Adolesc Med 2007;161:1162–8.
6. Agency for Healthcare Research and Quality. Introduction to the HCUP Nationwide Inpatient Sample (NIS), 2006. Rockville, MD: Agency for Healthcare Research and Quality; 2006. Available at http://www.hcup-us.ahrq.gov/db/nation/nis/NIS_Introduction_2006.jsp.
7. Dagan R, Sikuler-Cohen M, Zamir O, Janco J, Givon-Lavi N, Fraser D. Effect of a conjugate pneumococcal vaccine on the occurrence of respiratory infections and antibiotic use in day-care center attendees. Pediatr Infect Dis J 2001;20:951–8.
8. Madhi SA, Klugman KP; Vaccine Trialist Group. A role for *Streptococcus pneumoniae* in virus-associated pneumonia. Nat Med 2004;10:811–3.
9. Hicks LA, Harrison LH, Flannery B, et al. Incidence of pneumococcal disease due to non-pneumococcal conjugate vaccine (PCV7) serotypes in the United States during the era of widespread PCV7 vaccination, 1998–2004. J Infect Dis 2007;196:1346–54.
10. CDC. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2007. MMWR 2007;56(No. RR-6).

Possible Congenital Infection with La Crosse Encephalitis Virus — West Virginia, 2006–2007

La Crosse encephalitis virus (LACV) is a mosquitoborne bunyavirus of the California encephalitis serogroup (*1*). During 2003–2007, West Virginia had the greatest number of cases (95) and highest incidence of LACV disease (5.1 cases per 100,000 population) of any state.* The majority of persons infected with LACV either have no symptoms or a mild febrile illness; a limited number experience encephalitis (*2*). Although only 1%–4% of those infected with LACV develop any symptoms, children aged <16 years are at highest risk for severe neurologic disease and possible long-term sequelae (*2,3*). The effects of LACV infection during pregnancy and the potential for intrauterine transmission and adverse birth or developmental outcomes are unknown. This report describes the first known case of LACV infection in a pregnant woman, with evidence of possible congenital infection with LACV in her infant, based on the presence of immunoglobulin M (IgM)

*Confirmed and probable California serogroup viral (mainly La Crosse) encephalitis cases, human, United States, 1964–2007, by state. Available at http://www.cdc.gov/ncidod/dvbid/arbor/pdf/cal_lac.pdf.

antibodies in umbilical cord serum at delivery. The infant was born healthy with normal neurologic and cognitive functions and no LACV symptoms. Further investigation is needed to confirm the potential for intrauterine LACV transmission and to identify immediate and long-term health risks posed to infants. Because of the potential for congenital infection, pregnant women in areas where LACV is endemic should be advised to avoid mosquitoes; health-care providers should monitor for LACV infection and sequelae among infants born to women infected with LACV during pregnancy.

In August 2006, a previously healthy woman aged 43 years in week 21 of her pregnancy was admitted to a West Virginia hospital after experiencing severe headaches, photophobia, stiff neck, fever, weakness, confusion, and a red papular rash. The patient had reported a 3-month history of severe headaches, which were diagnosed initially as migraines and treated with morphine for pain. Two previous pregnancies had proceeded without complication, and each resulted in delivery of a healthy infant. The patient's medical history included anxiety, depression, and hypothyroidism, for which she received ongoing thyroid hormone replacement therapy.

After hospital admission, analysis of cerebrospinal fluid revealed an elevated white blood cell count (556 cells/mm^3 [94% lymphocytes, 5% monocytes, and 1% polymorphonuclear neutrophilic leukocytes]), elevated protein (66 mg/dL), and normal glucose (55 mg/dL). A diagnostic panel for viral encephalitis was performed, and the patient's serum was determined positive for the presence of LACV-specific IgM and immunoglobulin G (IgG) antibodies by immunofluorescence assay and for IgM by capture enzyme-linked immunosorbent assay (ELISA) (Table). The patient's serum was negative for IgM and IgG antibodies to the other three diseases in the diagnostic panel: eastern equine encephalitis, western equine encephalitis, and St. Louis encephalitis. A diagnosis of La Crosse encephalitis was made, and supportive therapy was initiated. During hospitalization, the patient experienced a low-grade fever and exhibited panleukocytosis (absolute neutrophil count: 12,800/μL), which persisted after discharge despite resolution of clinical signs.

After reporting the case to the West Virginia Department of Health and Human Resources, active follow-up of the patient and her fetus was initiated in collaboration with the patient's primary-care providers and CDC. With her consent, the patient's medical and prenatal histories were reviewed. Because guidelines for evaluating pregnant women infected with LACV do not exist, interim guidelines for West Nile virus were used to direct maternal and infant follow-up (*4*). Specifically, collection of blood and tissue products at time of delivery was arranged with the patient's obstetrician. Umbilical cord serum and maternal serum were tested for LACV-specific antibodies by ELISA and serum-dilution plaque-reduction neutralization test (PRNT). Sera also were tested for neutralizing antibodies to the closely related Jamestown Canyon virus by PRNT to rule out potential cross-reactivity. Umbilical cord and placental tissue were tested for LACV RNA by reverse transcription–polymerase chain reaction (RT-PCR). Data were collected regarding the infant's health at delivery and through routine well-child visits during the first 6 months of life.

The patient had a normal, spontaneous, vaginal delivery of a healthy girl at approximately 40 weeks gestation. The child

TABLE. Summary of laboratory test results during investigation and follow-up of possible congenital infection with La Crosse encephalitis virus (LACV) — West Virginia, 2006–2007

Collection date	Specimen	Test	Result
August 20, 2006	Maternal serum	LACV IgM* capture ELISA†	Positive
	Maternal serum	LACV IgM IFA§	Positive
	Maternal serum	LACV IgG¶ IFA	Positive
	Maternal serum	LACV neutralizing antibodies PRNT**	Positive
	Maternal serum	JCV†† neutralizing antibodies PRNT	Negative
January 5, 2007	Placental tissue	LACV RNA RT-PCR§§	Negative
	Umbilical cord tissue	LACV RNA RT-PCR	Negative
	Umbilical cord serum	LACV IgM capture ELISA	Positive
	Umbilical cord serum	LACV IgG capture ELISA	Equivocal
	Umbilical cord serum	LACV neutralizing antibodies PRNT	Positive
	Umbilical cord serum	JCV neutralizing antibodies PRNT	Negative
March 23, 2007	Maternal serum	LACV IgM capture ELISA	Negative
	Maternal serum	LACV IgG capture ELISA	Positive

* Immunoglobulin M.
† Enzyme-linked immunosorbent assay.
§ Immunofluorescence assay.
¶ Immunoglobulin G.
** Plaque-reduction neutralization test.
†† Jamestown Canyon virus.
§§ Reverse transcription–polymerase chain reaction.

had normal birth weight (2,970 g), length (52 cm), and head circumference (33 cm). Apgar scores at 1 minute and 5 minutes postpartum were within normal limits (8 and 9, respectively). LACV-specific IgM antibodies were detected in umbilical cord serum, although no evidence of LACV RNA was detected in umbilical cord tissue or placental tissue by RT-PCR (Table).

The mother declined collection of additional specimens of infant serum for confirmation of congenital LACV infection. Maternal serum collected at 11 weeks postpartum was positive for LACV IgG antibodies but negative for IgM. Except for intermittent nasal congestion associated with upper respiratory infections, the infant remained healthy and exhibited appropriate growth and development through the first 6 months of life. No neurologic abnormalities or decreased cognitive functions were observed.

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Editorial Note: This report summarizes the first case of symptomatic LACV infection identified during pregnancy. Congenital LACV infection of the fetus was suggested through identification of IgM antibodies in umbilical cord serum, although the newborn was asymptomatic and development was normal. Although unlikely to cross the placental barrier, LACV IgM antibodies detected in cord serum might have been attributable to transplacental leakage induced by uterine contractions that disrupt placental barriers during labor, which has been documented for anti-*Toxoplasma* IgM antibodies (*5*). Because specificity of standard laboratory techniques used to detect LACV IgM antibodies in cord serum or newborn serum is unknown, a follow-up evaluation of infant serum is necessary to confirm congenital infection. However, in this case, the mother declined collection of any additional specimens from her infant.

Certain infectious diseases have more severe clinical presentations in pregnant women (*6*). Symptomatic LACV infection is rare among adults; therefore, effects of pregnancy on the risk for or severity of illness are unknown. Because LACV-specific IgM can be present for as long as 9 months after infection (*1*), LACV might not have been responsible for the symptoms reported during this woman's pregnancy. However, the woman resided in an area where LACV is known to be endemic; during 2006, 16 (24%) of 67 LACV cases in the United States reported to CDC occurred in West Virginia, including three other cases from the same county as this patient.† Although antimicrobial treatment of pregnant women often is controversial because of limited information regarding efficacy and risk to the developing infant (*7*), certain in vitro evidence indicates that the antiviral agent ribavirin might be useful for treating LACV infection in nonpregnant patients (*2*). However, supportive treatment continues as the standard of care for managing all LACV patients (*2*).

Congenital infection with other arboviral diseases has been reviewed and documented previously (*8*). Although no human congenital infection with a bunyavirus of the California serogroup has been reported, congenital infection with other bunyaviruses of the Bunyamwera serogroup has been associated with macrocephaly. In addition, animal studies have determined that infection with LACV during pregnancy can cause teratogenic effects in domestic rabbits, Mongolian gerbils, and sheep (*9,10*).

Pregnant women in areas where LACV is endemic should take precautions to reduce risk for infection by avoiding mosquitoes, wearing protective clothing, and applying a mosquito repellent to skin and clothing. Additionally, health-care providers serving areas where LACV is endemic should consider LACV in the differential diagnosis of viral encephalitis. As a nationally notifiable disease, all probable and confirmed cases of LACV should be reported to the appropriate state and local public health authorities. When LACV infection is suspected in a pregnant woman or infant, appropriate serologic and virologic testing by a public health reference laboratory is recommended. Testing breast milk for the presence of LACV also might be reasonable to evaluate the potential for maternal-infant transmission and to determine the suitability for continued breastfeeding. Additional investigations are needed to confirm the potential for congenital infection with LACV and to identify immediate and long-term health risks LACV poses to infants.

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References

1. McJunkin JE, Minnich LL, Tsai TE. La Crosse encephalitis and other *California serogroup viruses. In: Feigin RD, Cherry JD, eds. Textbook* of pediatric infectious diseases. 5th ed. Philadelphia, PA: W.B. Saunders; 2004:2403–11.
2. McJunkin JE, Khan RR, Tsai TF. California-La Crosse encephalitis. Infect Dis Clin North Am 1998;12:83–93.
3. Kappus KD, Monath TP, Kaminski RM, et al. Reported encephalitis associated with California serogroup virus infections in the United States, 1963–1981. In: Thompson WH, Calisher CD, eds. California serogroup viruses. New York, NY: Alan R. Liss; 1983:31–41.

† La Crosse encephalitis, human: cumulative 2006 data. Available at http://diseasemaps.usgs.gov/2006/lac_us_human.html.

4. CDC. Interim guidelines for the evaluation of infants born to mothers infected with West Nile virus during pregnancy. MMWR 2004; 53:154–7.
5. Pinon JM, Dumon H, Chemla C, et al. Strategy for diagnosis of congenital toxoplasmosis: evaluation of methods comparing mothers and newborns and standard methods for postnatal detection of immunoglobulin G, M, and A antibodies. J Clin Microbiol 2001;39:2267–71.
6. Jamieson DJ, Theiler RN, Rasmussen SA. Emerging infections and pregnancy. Emerg Infect Dis 2006;12:1638–43.
7. Cono J, Cragan JD, Jamieson DJ, Rasmussen SA. Prophylaxis and treatment of pregnant women for emerging infections and bioterrorism emergencies. Emerg Infect Dis 2006;12:1631–7.
8. Tsai TF. Congenital arboviral infections: something new, something old. Pediatrics 2006;117:936–9.
9. Osorio JE, Schoepp RJ, Yuill TM. Effects of La Crosse infection on pregnant domestic rabbits and Mongolian gerbils. Am J Trop Med Hyg 1996;55:384–90.
10. Edwards JF, Karabatsos N, Collisson EW, de la Concha Bermejillo A. Ovine fetal malformations induced by in utero inoculation with Main Drain, San Angelo, and LaCrosse viruses. Am J Trop Med Hyg 1997;56:171–6.

Updated Guidelines for the Use of Nucleic Acid Amplification Tests in the Diagnosis of Tuberculosis

Guidelines for the use of nucleic acid amplification (NAA) tests for the diagnosis of tuberculosis (TB) were published in 1996 (*1*) and updated in 2000 (*2*). Since then, NAA testing has become a routine procedure in many settings because NAA tests can reliably detect *Mycobacterium tuberculosis* bacteria in specimens 1 or more weeks earlier than culture (*3*). Earlier laboratory confirmation of TB can lead to earlier treatment initiation, improved patient outcomes, increased opportunities to interrupt transmission, and more effective public health interventions (*4,5*). Because of the increasing use of NAA tests and the potential impact on patient care and public health, in June 2008, CDC and the Association of Public Health Laboratories (APHL) convened a panel of clinicians, laboratorians, and TB control officials to assess existing guidelines (*1,2*) and make recommendations for using NAA tests for laboratory confirmation of TB. On the basis of the panel's report and consultations with the Advisory Council for the Elimination of TB (ACET),* CDC recommends that NAA testing be performed on at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB for whom a diagnosis of TB is being considered but has not yet been established, and for whom the test result would alter case management or TB control activities, such as contact investigations. These guidelines update the previously published guidelines (*1,2*).

Background

Conventional tests for laboratory confirmation of TB include acid-fast bacilli (AFB) smear microscopy, which can produce results in 24 hours, and culture, which requires 2–6 weeks to produce results (*5,6*). Although rapid and inexpensive, AFB smear microscopy is limited by its poor sensitivity (45%–80% with culture-confirmed pulmonary TB cases) and its poor positive predictive value (50%–80%) for TB in settings in which nontuberculous mycobacteria are commonly isolated (*3,6,7*).

NAA tests can provide results within 24–48 hours. The Amplified *Mycobacterium tuberculosis* Direct Test (MTD, Gen-Probe, San Diego, California) was approved by the Food and Drug Administration (FDA) in 1995 for use with AFB smear-positive respiratory specimens, and in a supplement application, an enhanced MTD test was approved in 1999 for use with AFB smear-negative respiratory specimens from patients suspected to have TB. In addition, the Amplicor *Mycobacterium tuberculosis* Test (Amplicor, Roche Diagnostics, Basel, Switzerland) was approved by FDA in 1996 for use with AFB smear-positive respiratory specimens from patients suspected to have TB. NAA tests for TB that have not been FDA-approved also have been used clinically (e.g., NAA tests based on analyte specific reagents, often called "home-brew" or "in-house" tests) (*8,9*).

Compared with AFB smear microscopy, the added value of NAA testing lies in its 1) greater positive predictive value (>95%) with AFB smear-positive specimens in settings in which nontuberculous mycobacteria are common and 2) ability to confirm rapidly the presence of *M. tuberculosis* in 50%–80% of AFB smear-negative, culture-positive specimens (*3,7–9*). Compared with culture, NAA tests can detect the presence of *M. tuberculosis* bacteria in a specimen weeks earlier than culture for 80%–90% of patients suspected to have pulmonary TB whose TB is ultimately confirmed by culture (*3,8,9*). These advantages can impact patient care and TB control efforts, such as by avoiding unnecessary contact investigations or respiratory isolation for patients whose AFB smear-positive specimens do not contain *M. tuberculosis*.

Despite being commercially available for more than a decade (*1*), NAA tests for TB have not been widely used in the United States largely because of 1) an uncertainty as to whether NAA test results influence case-management decisions or TB control activities; 2) a lack of information on the overall cost-effectiveness of NAA testing for TB; and 3) a lack of demand from clinicians and public health authorities. However, recent

*Additional information regarding ACET is available at http://www.cdc.gov/maso/facm/facmacet.htm.

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識別番号・報告回数			報告日	第一報入手日 2009 年 1 月 13 日	新医薬品等の区分	厚生労働省処理欄

一般的名称	①献血アルブミン-Wf ②献血アルブミン(5%)-Wf ③ノイアート ④ノイアート静注用 1500 単位 ⑤ハプトグロビン注-ヨシトミ ⑥コンコエイト-HT	研究報告の公表状況	OIE/2008/12/23	公表国 フィリピン
販売名 （企業名）	①②人血清アルブミン ③④乾燥濃縮人アンチトロンビンⅢ ⑤人ハプトグロビン ⑥乾燥濃縮人血液凝固第Ⅷ因子			

研究報告の概要

ブタにおける Ebola-Reston ウイルスの初めての検出：
フィリピンにおいて，ブタから Ebola-Reston ウイルスが検出されたことを受けて，フィリピン政府が国連 FAO，OIE および WHO に専門家の派遣を要請したことが発表された。
2007 年および 2008 年に Nueva Ecija および Bulacan の農場においてブタの死亡が増加したことから調査が開始され，2008 年 5 月，6 月および 9 月に病気のブタのサンプルが研究所に送付され，10 月に豚繁殖・呼吸器障害症候群（RRRS）および Ebola-Reston ウイルス感染が確認された。
ブタにおいて Ebola-Reston ウイルスが検出されたのは世界的に初めてである。フィリピンのサルにおいては 1989-1990 年，1992 年および 1996 年にアウトブレイクしたことが確認されている。
フィリピン保健当局は，感染したブタと接触したと思われる人における初期検査は Ebola-Reston ウイルス感染陰性であったと報告した。
フィリピンの農務省動物産業局（BAI）は感染した家畜はすべて破棄され、埋められるか焼却され、施設は消毒されたこと、また、感染地域は厳しい検疫と管理体制の下にあることを OIE に報告した。

使用上の注意記載状況・その他参考事項等

使用状の注意にヘパリン由来の感染症に関連する記載なし。

報告企業の意見	今後の対応
フィロウイルス科エボラウイルス属には、エボラ・アイボリーコーストウイルス、エボラ・ザイールウイルス、エボラ・スーダンウイルス、エボラ・レストンウイルスの４種がある。エボラレストンウイルスは、長径 800～1,500nm、短径 80～100nm のエンベロープを有する RNA ウイルスであり、人にも感染するが重病や死に至る危険性はないと言われている。ヘパリンからのエボラウイルス感染に関する報告は、入手していない。 万一、ブタ原料にエボラ・レストンウイルスが混入したとしても、BVDをモデルウイルスとしたウイルスバリデーション試験成績から、ヘパリンの製造工程中の過酸化水素処理、加熱処理工程で十分に不活化・除去されると考えている。	本報告は本剤の安全性に影響を与えないと考えるので、特段の措置はとらない。

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