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World Hepatitis Day — July 28, 2013

Established by the World Health Assembly in 2010, the third annual World Hepatitis Day will be observed July 28, 2013. Viral hepatitis is a leading cause of infectious disease mortality globally, each year causing approximately 1.4 million deaths (*1*). Most of these deaths occur among the approximately 400 million persons living with chronic hepatitis B virus (HBV) or hepatitis C virus infection who die from cirrhosis or liver cancer years and decades after their infection. In addition to HBV, hepatitis A virus is a leading cause of vaccine-preventable death globally (*1*). Hepatitis E virus (HEV) also causes significant morbidity and mortality, particularly in Asia and Africa.

HBV and HEV infection are important yet largely neglected causes of maternal and infant morbidity and mortality in resource-constrained settings. This issue of *MMWR* includes a report describing the investigation of a hepatitis E outbreak among refugees in South Sudan, where a significant proportion of affected pregnant women died from HEV infection. A second report from Laos describes missed opportunities for vaccination of newborns to protect them from mother-to-child transmission of HBV.

Prevention of both new infections and mortality from viral hepatitis are the goals of global control efforts. Additional information on viral hepatitis for health professionals and the public is available at http://www.cdc.gov/hepatitis.

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Investigation of Hepatitis E Outbreak Among Refugees — Upper Nile, South Sudan, 2012-2013

During the week of July 2, 2012, the deaths of two pregnant women and one child were reported by household mortality surveillance in Jamam refugee camp, Maban County, Upper Nile State, South Sudan. All were reported to have yellow eyes before death. During July 27–August 3, 2012, three adult males with acute onset jaundice were admitted to the Médecins Sans Frontières (MSF) hospital in Jamam camp; two died within 4 days of admission. The Republic of South Sudan Ministry of Health, United Nations High Commissioner for Refugees (UNHCR), CDC, and humanitarian organizations responded through enhanced case surveillance, a serosurvey investigation, and targeted prevention efforts. As of January 27, 2013, a total of 5,080 acute jaundice syndrome (AJS) cases had been reported from all four Maban County refugee camps (Doro, Gendrassa, Jamam, and Yusuf Batil). Hepatitis E virus (HEV) infection was confirmed in a convenience sample of cases in each camp. A cross-sectional serosurvey conducted in Jamam camp in November 2012 indicated that 54.3% of the population was susceptible to HEV infection. Across all camps, an AJS case-fatality rate (CFR) of 10.4% was observed among pregnant women. The outbreak response has focused on improving safe drinking water availability, improving sanitation

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and hygiene, conducting active case finding, and optimizing clinical care, especially among pregnant women. Sustaining these improvements, along with strengthening community outreach, is needed to improve outbreak control. Further investigation of the potential role for the newly developed HEV vaccine in outbreak control also is needed (*1*).

Refugees began fleeing armed violence in Blue Nile State, Sudan, in late 2011, initially settling in Doro, the oldest camp. By July 2012, the Maban County refugee camp population surged to 110,000, coinciding with the onset of heavy rains and flooding. Flooding disproportionately affected large sections of Jamam camp, forcing refugee relocation to Gendrassa camp, 12 miles (20 kilometers) away. Yusuf Batil camp, 2 miles (3 kilometers) from Gendrassa, also was rapidly settled during the 2012 population displacement. An acute humanitarian emergency ensued, with crude mortality rates exceeding the emergency threshold of one per 10,000 per day in July and August; diarrheal disease was a leading cause of morbidity and mortality.

UNHCR and World Health Organization consider AJS to be a priority syndrome for communicable disease surveillance in humanitarian emergencies (*2*). The South Sudan Ministry of Health case definition for AJS is acute onset of jaundice and severe illness in any person. The etiologies and outcomes of AJS are varied and represent multiple diseases of outbreak potential, including HEV. HEV is endemic in Sudan and South Sudan; however, the extent of immunity is unknown. Transmission is fecal-oral, with an incubation period of 2–8 weeks. Globally, the overall CFR for HEV has been reported to range from 0.2% to 4%; mortality in pregnant women can be as high as 10%–25% (*3*). No unique clinical manifestations of hepatitis E distinguish it from other viral AJS etiologies, such as hepatitis A or yellow fever.

Following the initial cluster of AJS cases in July 2012, active surveillance was implemented in each camp by training community health workers on detection and referral of jaundiced patients to MSF health facilities. Clinician-confirmed AJS cases were documented using standardized line lists. No diagnostic testing for HEV was available at the field level. The etiologic cause of the outbreak was confirmed as HEV in August 2012 by the CDC-Kenya Medical Research Institute laboratory in Nairobi, Kenya, after six of eight initial AJS cases from Jamam camp were positive by reverse transcription–polymerase chain reaction (rt-PCR) for HEV. Blood specimens were tested for alternative acute infectious hepatitis etiologies, specifically yellow fever and viral hemorrhagic fevers. All eight were negative for these alternative etiologies. Subsequent AJS cases from the three other camps also were confirmed as HEV positive by rt-PCR. After alternate etiologies were excluded and HEV was confirmed in each camp (38 of 62 [61.3%] AJS cases tested were rt-PCR positive for HEV), cases of AJS recognized clinically were considered probable cases of HEV. Dipstick testing for bilirubinuria was used as a diagnostic adjunct when a finding of yellow eyes was in doubt.

As of January 27, 2013, a total of 5,080 AJS cases were reported: 3,291 in Yusuf Batil, 1,261 in Jamam, 474 in

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Gendrassa, and 54 in Doro (Figure 1). During the first weeks of 2013, a large increase in cases was reported from Yusuf Batil, with a second peak observed in Jamam and Gendrassa. The initial peak had occurred in August 2012. Possible explanations for this second peak include: 1) less than optimal water, sanitation, and hygiene interventions, both at the community and household levels; 2) the long incubation period of HEV, resulting in an increase of cases well after control measures had been put in place; and 3) alternative modes of transmission, including person-to-person transmission. Median patient age was 25 years, and 52.5% were female. Among pregnant women, 211 AJS cases and 22 deaths were reported (CFR = 10.4%). UNHCR population estimates were used to calculate age-specific attack rates and risk ratios for AJS death among pregnant women. Approximately 2,027 women (3% of the total Jamam, Yusuf Batil, and Gendrassa population) were estimated to be pregnant, based on an assumed crude birth rate of 39 per 1,000 (*4*). The risk for death from AJS among pregnant women was estimated to be 4.8 times that for nonpregnant women aged 18–59 years in the three most affected camps (Jamam, Gendrassa, and Yusuf Batil). The overall attack rate in the three most affected camps was 7.4%; persons aged 18–59 years had the highest attack rates (Figure 2). As of January 27, 2013, a total of 576 (11.3%) AJS patients identified by surveillance had been hospitalized in the three most affected camps, with a cumulative hospital CFR of 17.5% (Figure 3). Of the 101 hospitalized patients who died, 51.5% were female; the median age was 29 years. Hospital data for Doro patients were limited.

The surge of AJS patients required a sustained medical response in challenging field conditions. MSF's clinical response focused on supportive management. In addition to individual symptom management, all outpatients received multivitamins, supplemental nutrition, soap, and hygiene education. A concerted effort to improve community outreach was implemented. Outpatients were reassessed every 7 days until symptoms resolved. Patients with severe fever, anorexia, vomiting, diarrhea, bleeding, agitation, or coma were admitted, as were patients with a positive malaria rapid diagnostic test, hypoglycemia, or pregnancy. A low-threshold approach to hospitalization was taken, including admission of all jaundiced pregnant women for observation, because of challenges in predicting clinical course.

Critically ill patients had confusion, agitation, coma, hypoglycemia, or suspected electrolyte imbalances. These patients required intensive care in a resource-limited setting to manage

FIGURE 1. Acute jaundice syndrome (AJS) cases, by surveillance week — Jamam, Gendrassa, and Yusuf Batil refugee camps, South Sudan, 2012–2013

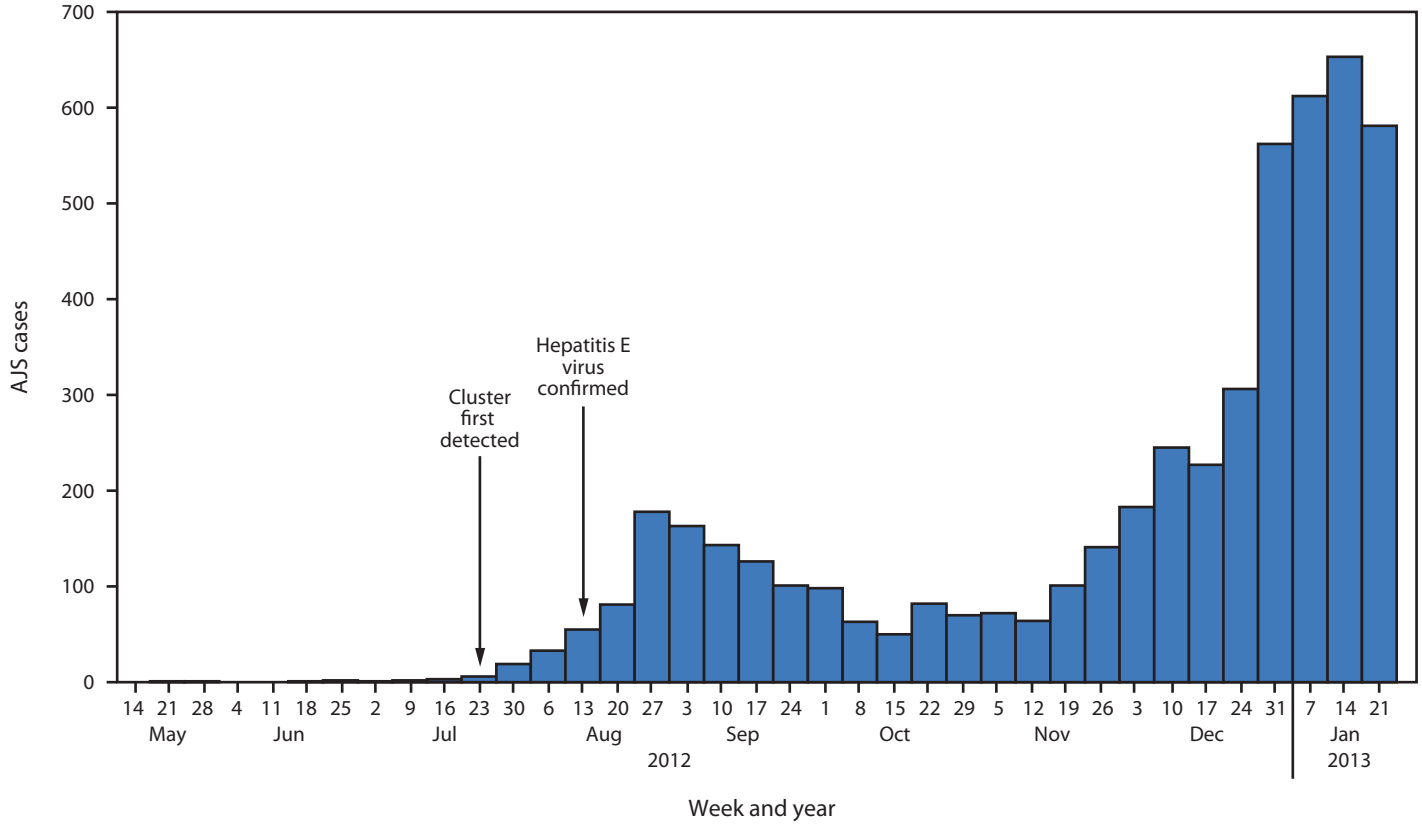
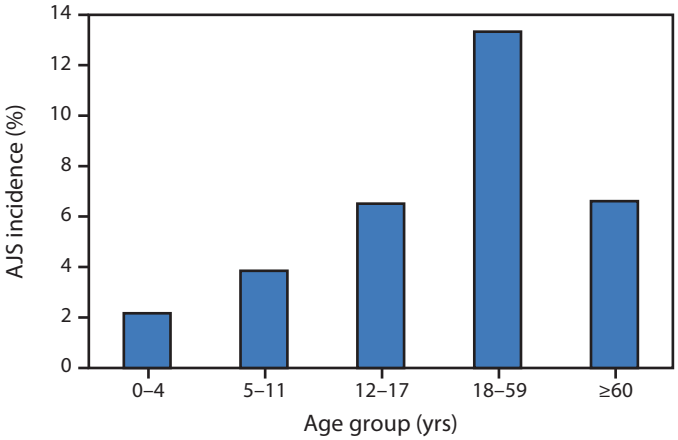


FIGURE 2. Cumulative acute jaundice syndrome (AJS) incidence, by age group — Jamam, Gendrassa, and Yusuf Batil refugee camps, South Sudan, July 2012–January 2013



fluid balance and complications of hepatic encephalopathy. Initial treatment included antibiotics and intravenous fluids. Metronidazole was administered if the mental status changed, and ceftriaxone was administered if fever or suspected bacterial infection was present. Intravenous dextrose and saline fluid were alternated to prevent hypoglycemia and hyponatremia, respectively, when enteral feeding was not feasible. Adjunctive haloperidol for agitation and vitamin K for coagulopathy were provided.

A cross-sectional serosurvey was conducted in Jamam camp during November 6–10, 2012, to estimate population susceptibility and understand potential outbreak evolution. A total of 443 randomly selected persons aged ≥3 years from households sampled by simple and systematic random sampling provided consent for anti-HEV antibody testing. The CDC-Kenya Medical Research Institute laboratory used enzyme immunosorbent assay kits to detect anti-HEV immunoglobulin M (IgM) and anti-HEV immunoglobulin G (IgG) among participants. Serology results were weighted for age, based on UNHCR population data, to be representative of the Jamam population at the time of the survey. Overall, 21.7% (CI = 17.6–25.7) had IgM anti-HEV, representing recent exposure to HEV, and 54.3% (CI = 49.2–59.3) had no serologic evidence of recent or prior HEV infection (i.e., both IgM and IgG negative).

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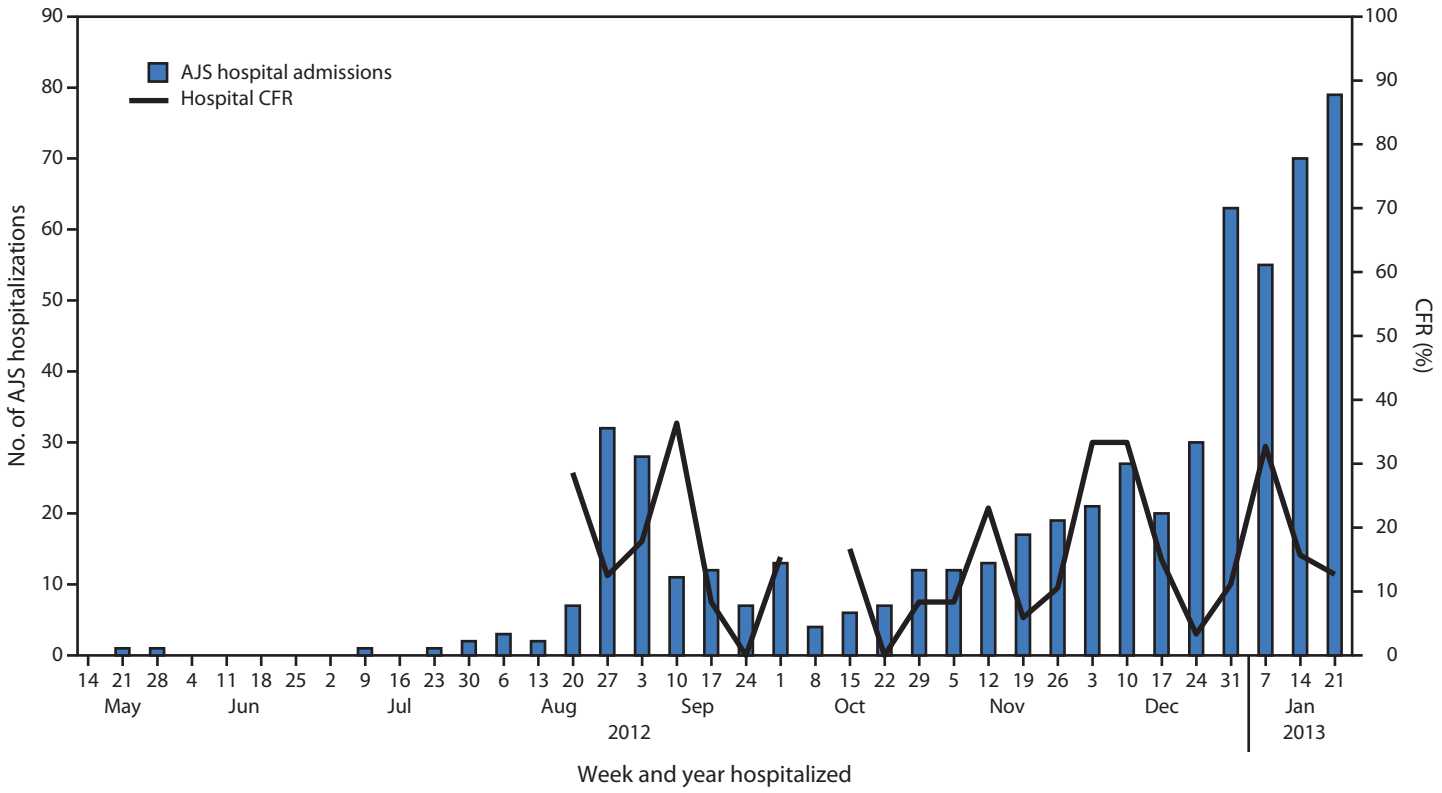
Editorial Note

Globally, an estimated 20 million HEV infections occur annually, resulting in 3.4 million cases of acute hepatitis and 70,000 deaths (*5*). HEV is the most common cause of acute viral hepatitis globally. Recent large outbreaks have occurred among displaced persons in Sudan, Chad, and Uganda (*6*). The first such outbreak documented in Africa occurred among Angolan refugees in Namibia in 1983 (*7*). The current outbreak in South Sudan shares similar epidemiologic characteristics with other HEV outbreaks. Similar to a 2007 outbreak in northern Uganda, this outbreak started during the rainy season and has had high attack rates among young adults and high mortality among pregnant women (*8*). The serosurvey conducted during this outbreak showed that more than half of Jamam camp residents had no evidence of recent or past HEV infection, suggesting that these persons remained uninfected and were still susceptible to HEV infection 3 months after the implementation of control measures.

Since the South Sudan Ministry of Health declared the HEV outbreak in September 2012, efforts to improve water, sanitation, and hygiene conditions have been ongoing. Health and hygiene promoters have been trained on HEV prevention and active case finding. HEV preventive hygiene education has been conducted during household visits, at health facilities, and in community forums. UNHCR and partner agencies have scaled up water, sanitation, and hygiene activities, including increasing the availability of treated drinking water, increasing latrine coverage, distributing soap and water storage vessels, installing handwashing stations, and expanding hygiene promotion activities. Further water, sanitation, and hygiene improvements are needed to address ongoing transmission.

Implementing outbreak control measures in displaced persons camps often is extremely challenging. Scaling up water, sanitation, and hygiene interventions takes time. In addition, the long HEV incubation period often complicates response because transmission can occur for weeks before symptomatic cases first appear. This was witnessed in the current Maban County outbreak, where despite an apparent decrease in HEV cases following the scaling up of water, sanitation, and hygiene measures, a second peak was observed several months later. A cross-sectional survey conducted in Jamam camp in November 2012 revealed that 54.3% of the Jamam population was

FIGURE 3. Acute jaundice syndrome (AJS) hospital admissions and weekly hospital case-fatality rate (CFR), by week of hospitalization — Jamam, Gendrassa, and Yusuf Batil refugee camps, South Sudan, 2012–2013*



* Hospital CFR not reported if the number of AJS hospital admissions in a given week was ≤5.

susceptible to HEV, after the initial peak already had occurred. The high proportion of nonimmune persons, in conjunction with potential alternative routes of transmission (e.g., person-to-person), might explain the prolonged nature of this outbreak. Crowded living conditions also might facilitate multiple transmission routes, resulting in the need for improved hygienic conditions at the community and household levels (*9*). Unlike single-source waterborne outbreaks, HEV outbreaks in such settings can display a prolonged multimodal course (i.e., multiple peaks, each attributed to separate modes of transmission) and might not abate rapidly with targeted water, sanitation, and hygiene interventions. However, such interventions remain the main strategy to interrupt transmission. Given the difficulty in controlling HEV outbreaks in emergency settings, additional interventions, such as vaccination, need further consideration.

A recombinant, 3-dose series HEV vaccine is available but has not yet been prequalified by the World Health Organization. The vaccine has been shown to prevent symptomatic HEV infection and proven to be safe and effective in persons aged 16–64 years (*1*). Limited vaccine safety data in 37 pregnant women receiving 57 doses has been reported (*10*); however, further research is needed, and safety for children is unknown. The vaccine is expected to be protective against HEV genotype 1, the strain associated with most waterborne outbreaks in Africa and Asia. Several questions regarding duration of immunity and prevention of subclinical infection remain. The effectiveness and implementation logistics of a 3-dose vaccine in an outbreak setting, particularly a challenging setting such as a displaced persons camp, also needs investigation. Genotype testing on serum samples collected for the cross-sectional serosurvey has not been performed to date.

Large HEV outbreaks have occurred among crowded displaced populations. These outbreaks result in appreciable morbidity and mortality, particularly among pregnant women. Despite enhancing water, sanitation, and hygiene control measures, outbreaks often are prolonged and necessitate a sustained prevention and control response. The role of vaccination in the context of outbreak control urgently needs to be examined.

What is already known on this topic?

Hepatitis E virus (HEV), which is transmitted via the fecal-oral route, is the most common cause of acute viral hepatitis globally. Large HEV outbreaks have been documented in crowded settings that have poor water, sanitation, and hygiene conditions. Pregnant women suffer disproportionately high mortality from hepatitis E.

What is added by this report?

A hepatitis E outbreak in South Sudan has demonstrated ongoing transmission, possibly including person-to-person transmission, among refugees in crowded living conditions with poor water, sanitation, and hygiene conditions. Following the initial peak, 54.3% of the Jamam camp population remained susceptible to HEV infection, despite having traveled from a region where HEV is believed to be endemic. The outbreak has strained existing local and humanitarian relief health facilities, and additional resources are needed.

What are the implications for public health practice?

Given that HEV transmission has continued among refugees in South Sudan despite improvements in water, sanitation, and hygiene conditions, further consideration should be given to alternative methods of HEV outbreak control and response efforts. This outbreak also underscores the need for investigation of a possible role for an HEV vaccine.

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Hepatitis B Vaccine Birthdose Practices in a Country Where Hepatitis B is Endemic — Laos, December 2011–February 2012

Chronic hepatitis B virus (HBV) infection causes approximately 325,000 deaths from cirrhosis and liver cancer each year in the Western Pacific Region of the World Health Organization (WHO) (*1*). With an estimated infection prevalence of >8%, HBV is considered highly endemic in Laos (*2*) and is most commonly transmitted from mother to child during birth and early childhood. A hepatitis B vaccine birth dose (HepB-BD) is needed to prevent mother-to-child HBV transmission (*3*). To assess gaps in coverage and identify possible remedies for improvement of coverage, during the 3-month period December 2011–February 2012, the Laos Ministry of Health and WHO staff members surveyed 37 health facilities in five provinces in Laos, inquiring about HepB-BD knowledge and practices among health-care providers and estimating HepB-BD coverage provided by the facilities. For facility-based births, the median HepB-BD coverage was 74% (interquartile range: 39%–97%). Hepatitis B vaccine was not in stock at 18 (49%) of the 37 facilities on the day they were visited. Of the 37 facilities, 17 (46%) assisted with home births, and 23 (62%) conducted postnatal home visits. Of the 17 facilities that assisted with home births, seven (41%) included HepB-BD vaccination as part of the service; of the 23 that conducted postnatal home visits, 15 (65%) provided HepB-BD as part of the visit. However, among those reporting that they provided these outreach services, only 48 births were recorded as attended, and only 81 postnatal visits were recorded as conducted during the 3-month period. Health facilities can help prevent mother-to-child HBV transmission in Laos by ensuring vaccine availability, vaccinating all infants born in the facility, and enhancing outreach services for home births.

Despite having only 28% of the world's population, approximately half of all HBV-attributable deaths globally occur in the WHO Western Pacific Region (*4*). To control HBV transmission, the region adopted a goal of reducing chronic hepatitis B prevalence to <2% by 2012 among children aged ≥5 years and to <1% in a target year yet to be determined (*5*).

Administration of the hepatitis B vaccine birth dose followed by timely completion of the hepatitis B vaccine series is 70%–95% effective in preventing mother-to-child HBV transmission (*6,7*). During 2006–2011, reported HepB-BD coverage in Laos increased from 3% to 34% (*8*). Despite this increase, the country continues to have the lowest coverage in the region, largely because only 37% of women in Laos give birth with the assistance of a skilled birth attendant.*

This assessment was conducted in five of 24 provinces selected on the basis of accessibility and larger population size. In each of the five provinces, the central or provincial hospitals were selected, along with a sample of two district hospitals and four health centers to ensure representation of facilities with both high and low rates of HepB-BD coverage. One district health office that offered vaccination services also was included.

At each of the 37 health facilities, a standardized questionnaire was administered by in-person interview with one to three staff members, including administrators, staff members in charge of the delivery ward, and vaccination department personnel. Information collected by interview concerned staffing; job descriptions and training; policies and practices with regard to administering HepB-BD; administration of HepB-BD as part of outreach service delivery; and availability, supply, and storage of hepatitis B vaccine in the facility and for outreach delivery. Birth and vaccination registries were reviewed to obtain total birth and vaccination data for all births recorded by these facilities occurring during the 3-month period December 2011–February 2012. Data were extracted for newborns delivered in the 37 facilities and those receiving HepB-BD; among newborns receiving HepB-BD, information regarding birth setting (i.e., health facility or home) was obtained when available.

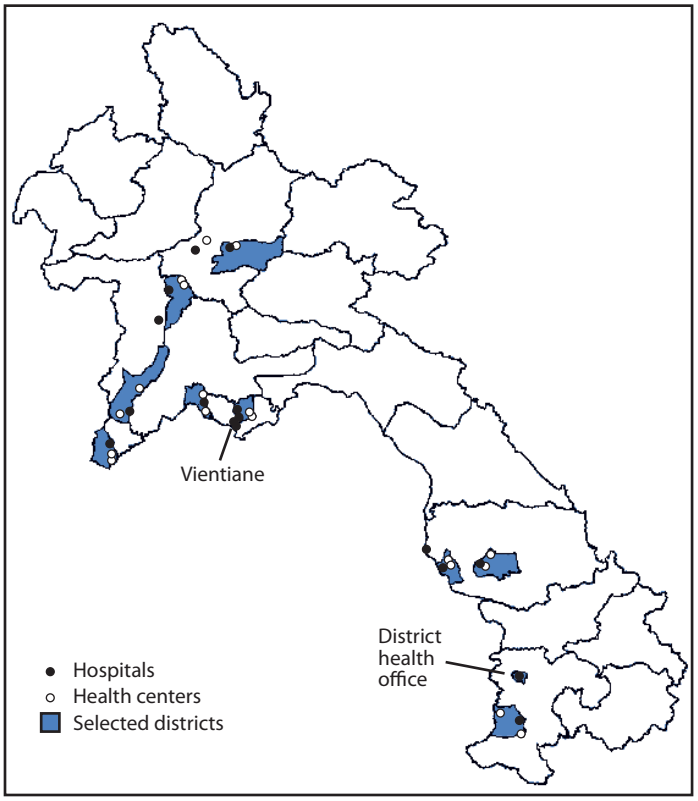
HepB-BD vaccination was defined as administration of the monovalent hepatitis B vaccine within the first 7 days of life, per the Laos vaccination schedule. For health-care facilities providing onsite delivery services, HepB-BD coverage was calculated by dividing the number of newborns who received HepB-BD in the facility by the total number of births in that facility. The median and interquartile ranges of facility-specific coverage rates also were calculated. A total of 37 facilities known to have reported HepB-BD vaccinations in 2011 were selected to visit during the study period (Figure). These facilities included seven central or provincial hospitals, nine district hospitals, one district health office, and 20 health centers.

Facility-Based Births

Thirty-one (84%) of the 37 facilities reported providing birthing services onsite (Table). These 31 facilities had a total of 5,072 onsite births recorded during the 3-month assessment period, and all reported providing HepB-BD. At these facilities, 3,541 (70%) newborns received HepB-BD; median HepB-BD coverage was 74% (interquartile range: 39%–97%). HepB-BD was administered by skilled birth attendants at 19 (61%) of the 31 facilities. Four additional facilities without onsite birthing

*Additional information available at http://www.moh.gov.la/index.php?option=com_phocadownload&view=category&id=9%3Aresearch&download=51%3Astatistic-him&Itemid=59&lang=en.

FIGURE. Location of selected districts and 37 health facilities surveyed regarding delivery services and hepatitis B vaccine birth dose (HepB-BD) practices — Laos, December 2011–February 2012



* Includes seven central or provincial hospitals, nine district hospitals, one district health office, and 20 health centers.

TABLE. Delivery services and hepatitis B vaccine birth dose (HepB-BD) practices at 37 health facilities* — Laos, December 2011–February 2012

Services/Practices	Total facilities asked	No.	(%)
Birthing			
Deliveries on site	37	31	(84)
SBAs not available at all times to deliver births	31	11	(35)
Length of stay after delivery >24 hrs	31	9	(29)
Vaccination			
Administers HepB-BD	37	35	(95)
Vaccination staff trained in HepB-BD	37	25	(68)
SBAs trained in HepB-BD	31	24	(77)
Report incorrect contraindications	37	33	(89)
Inappropriately discard second dose	35	11	(31)
Out of vaccine stock during assessment period	35	13	(37)
No stock on day of assessment	37	18	(49)
If facility delivers births, vaccine available 24 hrs/day	31	18	(58)
Administers HepB-BD in delivery room	31	16	(52)
Home births and postnatal care			
Staff members attend home births	37	17	(46)
Include HepB-BD vaccination at home births	17	7	(41)
Conduct postnatal home visits	37	23	(62)
Include HepB-BD at postnatal home visits	23	15	(65)

Abbreviation: SBA = skilled birth attendant.
* Includes seven central or provincial hospitals, nine district hospitals, one district health office, and 20 health centers.

services reported providing newborns with HepB-BD, for a total of 35 (95%) facilities reporting provision of HepB-BD.

Vaccination practices varied (Table). Of the 35 sites administering HepB-BD, 10 (29%) relied on untrained staff members. Interviewees from 33 (89%) of 37 sites listed erroneous contraindications for hepatitis B vaccination at their facilities, including prematurity, low birth weight, jaundice, and having a mother with HIV infection (the only contraindication to hepatitis B vaccine is severe allergic reaction, such as anaphylaxis, following a previous dose or component of the vaccine). Of the 35 sites routinely administering HepB-BD, 13 (37%) reported not having vaccine in stock at some time during the 3-month study period, and 11 (32%) reported improperly discarding the second dose of the 2-dose HepB-BD vials. Eighteen (49%) of 37 facilities had no vaccine in stock on the day of the visit. Thirteen (42%) of 31 facilities providing delivery services did not provide vaccine at all times of day.

Home-Based Births and Postnatal Visits

Of the 37 facilities visited, 17 (46%) reported assisting with home births, and 23 (62%) reported conducting postnatal home visits (Table). Seven (41%) of the 17 facilities providing home birth services also provide HepB-BD at the time of birth. Of the 23 facilities providing postnatal home visits, 15 (65%) provided HepB-BD as part of the visit. However, the facilities providing outreach services reported only 48 birth and 81 postnatal visits conducted during the 3-month period.

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Editorial Note

Median HepB-BD coverage among infants born in health facilities was only 74% in this assessment of 37 health facilities in Laos. This assessment identified low HepB-BD vaccination coverage rates and multiple challenges in HepB-BD implementation in health facilities in Laos, including vaccine stock outages, a lack of trained staff members to vaccinate newborns, and among staff members surveyed, common misperceptions about contraindications, all resulting in missed opportunities for vaccination. Additional challenges, given the large proportion

of home births in Laos, include limited outreach birthing and postnatal services provided by the health facilities, which contribute to low HepB-BD coverage. These challenges also have been reported in other countries (*9*).

The results of this assessment highlight multiple opportunities for increasing HepB-BD coverage using existing health services: 1) focusing initial efforts on increasing coverage among newborns in health-care facilities, who are easier to access than those born at home; 2) ensuring vaccine stock availability so that HepB-BD prevention opportunities are not missed; and 3) integrating HepB-BD vaccination into ongoing home birthing and postnatal home visit services.

Vaccination coverage in Laos might be improved by designating a staff member responsible for implementing HepB-BD vaccination at each facility and ensuring that birthing professionals are provided with training. Such training could include emphasizing the importance of early vaccination in preventing mother-to-child HBV infection during birth (*2*). Training also could stress that there are no contraindications to HepB-BD except for known allergic reaction to the vaccine, which cannot be predicted at birth (*3*). All facilities should aim to administer HepB-BD within 24 hours of birth and, if this is not feasible, vaccine should be administered as soon as practical (*2*). Lack of vaccine onsite is another major barrier to vaccinating newborns in Laos. Understanding and correcting causes of vaccine stock outages are critical for increasing HepB-BD coverage.

Despite the small proportion of deliveries that occur in health facilities in Laos, implementing HepB-BD vaccination in health facilities is an efficient and practical approach to preventing perinatal HBV transmission (*9*). Making incentives to health-care workers contingent on provision of HepB-BD might be a feasible strategy to improve coverage in facilities (*9*). As more births occur in health-care settings, facility-based implementation of HepB-BD will become increasingly important.

Opportunities for increasing coverage to newborns born at home include integrating HepB-BD into existing maternal and newborn outreach activities. Policies supporting this activity are in place in Laos, including inclusion of HepB-BD vaccination in the recommended neonatal care package. However, outreach services remain limited because they are costly, underfunded, and highly dependent on external funding. As demonstrated in this assessment by the minimal number of home visits, outreach by a skilled provider is currently available to only a small proportion of new mothers. However, integrating HepB-BD vaccination with existing outreach activities is feasible by raising awareness, training staff members, ensuring the supply of vaccine, and taking advantage of the proven heat stability of hepatitis B vaccines, which allows for their use where refrigeration is not available (*10*).

What is already known on this topic?

Hepatitis B virus (HBV) infection is highly endemic in Laos, which has adopted vaccination strategies to reduce infection rates in children. A hepatitis B vaccine birth dose (HepB-BD), as part of a 3-dose schedule, is effective in preventing perinatal hepatitis B transmission. However, vaccination coverage with HepB-BD in Laos was estimated at only 34% in 2011.

What is added by this report?

In a survey of 37 health facilities conducted during December 2011–February 2012 in five of the 24 provinces in Laos, the median HepB-BD vaccination coverage among infants born in health-care facilities was 74%. Hepatitis B vaccine was out of stock at 49% of facilities at the time they were visited. Missed opportunities to vaccinate because of misunderstanding of vaccine contraindications and low rates of medical attendance at home births also were observed.

What are the implications for public health practice?

To reduce the prevalence of chronic hepatitis B infection in Laos, efforts could be directed at preventing missed opportunities for administration of HepB-BD by eliminating stock outages and dispelling misunderstandings about the vaccine among health facility staff members who attend to births. In addition, significantly improving overall birth dose coverage in the country will require ensuring inclusion of HepB-BD in home birthing and postnatal services, an increase in the proportion of home births that are medically attended, and an increase in postnatal home visits by medical staff members.

The findings in this report are subject to at least three limitations. First, the assessment covered only 37 health facilities in five of the 24 provinces in Laos and cannot represent the country as a whole. Second, facility-based birth dose coverage likely is overestimated because newborns born outside of the facilities who later received HepB-BD at the facilities could not be distinguished in most instances from those born in the facility who received HepB-BD. Finally, responses on the questionnaire could not be independently verified.

Laos has shown a strong commitment toward the Western Pacific Region goal of reducing chronic HBV infection prevalence in children aged ≥5 years to <1%. Such a reduction in HBV prevalence will require prevention of both perinatal and early childhood infections. Activities identified in this assessment can provide direction to help further strengthen efforts to prevent HBV infection in Laos.

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Human Papillomavirus Vaccination Coverage Among Adolescent Girls, 2007–2012, and Postlicensure Vaccine Safety Monitoring, 2006–2013 — United States

Since mid-2006, the Advisory Committee on Immunization Practices (ACIP) has recommended routine vaccination of adolescent girls at ages 11 or 12 years with 3 doses of human papillomavirus (HPV) vaccine (*1*). Two HPV vaccines are currently available in the United States. Both the quadrivalent (HPV4) and bivalent (HPV2) vaccines protect against HPV types 16 and 18, which cause 70% of cervical cancers and the majority of other HPV-associated cancers; HPV4 also protects against HPV types 6 and 11, which cause 90% of genital warts.* This report summarizes national HPV vaccination coverage levels among adolescent girls aged 13–17 years† from the 2007–2012 National Immunization Survey-Teen (NIS-Teen) and national postlicensure vaccine safety monitoring. Although vaccination coverage with ≥1 dose of any HPV vaccine increased from 25.1% in 2007 to 53.0% in 2011, coverage in 2012 (53.8%) was similar to 2011. If HPV vaccine had been administered during health-care visits when another vaccine was administered, vaccination coverage for ≥1 dose could have reached 92.6%. Safety monitoring data continue to indicate that HPV4 is safe. Despite availability of safe and effective vaccines and ample opportunities for vaccine delivery in the health-care setting, HPV vaccination coverage among adolescent girls failed to increase from 2011 to 2012.

Vaccination Coverage

Since 2006, NIS-Teen has collected vaccination information for adolescents aged 13–17 years in the 50 states, the District of Columbia, and selected areas,§ using a random-digit–dialed sample of landline and (starting in 2011) cellular telephone numbers.¶ After a teen's parent/guardian grants permission to contact their teen's vaccination provider(s), a questionnaire is mailed to each provider to obtain a vaccination history from medical records. In 2012, the Council of American Survey Research Organizations (CASRO) landline response rate was 55.1%. A total of 14,133 adolescents with vaccination provider–reported vaccination records were included, representing 62% of all adolescents from the landline sample with completed household interviews. The cellular telephone sample CASRO response rate was 23.6%. A total of 5,066 adolescents with vaccination provider–reported vaccination records were included, representing 56.4% of all adolescents from the cellular telephone sample with completed household interviews.** Analysis for this report was limited to girls with provider-reported vaccination histories.†† HPV vaccination coverage represents receipt of any HPV vaccine and does not distinguish between HPV2 or HPV4. NIS-Teen methodology, including weighting procedures, has been described previously.§§ Differences in vaccination coverage were evaluated using t-tests and were considered statistically significant if $p \leq 0.05$.

Vaccination coverage was assessed for each dose of the HPV vaccination series: ≥1 dose represents initiation of the series, ≥2 doses represents progress with girls returning for additional doses, and ≥3 doses represents completion of the series. Coverage for ≥1, ≥2, and ≥3 HPV doses significantly increased annually during 2007–2011, but 2011 and 2012 coverage levels were similar (Table 1).

A missed opportunity was defined as a health-care encounter occurring on or after a girl's 11th birthday and on or after March 23, 2007 (the publication date of ACIP's HPV4 recommendation), during which a girl received at least one vaccine but did not receive HPV vaccine. The percentage of unvaccinated girls with at least one missed opportunity for

* Quadrivalent HPV vaccine was licensed in 2006 (information available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5602a1.htm) and the bivalent HPV vaccine was licensed in 2009 (information available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5920a4.htm?s_cid=mm5920a4_e).

† For each survey year, eligible participants were born during the following periods: 2007, October 1989–February 1995; 2008, January 1990–February 1996; 2009, January 1991–February 1997; 2010, January 1992–February 1998; 2011, January 1993–February 1999; and 2012, January 1994–February 2000.

§ Six areas that received federal Section 317 immunization grants were sampled separately: District of Columbia; Chicago, Illinois; New York, New York; Philadelphia County, Pennsylvania; Bexar County, Texas; and Houston, Texas.

¶ All identified cellular telephone households from the cellular telephone sampling frame were eligible for interview; sampling weights have been adjusted from dual-frame sampling, nonresponse, noncoverage, and overlapping samples of mixed telephone users (i.e., those having both a landline and a cellular telephone). A description of NIS-Teen dual-frame survey methodology and its effect on reported vaccination estimates is available at http://www.cdc.gov/vaccines/stats-surv/nis/dual-frame-sampling-08282012.htm.

** The CASRO response rate is the product of three other rates: 1) the resolution rate, which is the proportion of telephone numbers that can be identified as either for a business or residence; 2) the screening rate, which is the proportion of qualified households that complete the screening process; and 3) the cooperation rate, which is the proportion of contracted eligible households for which a completed interview is obtained. CASRO response rates for survey years 2007–2011 are available at ftp://ftp.cdc.gov/pub/health_statistics/nchs/dataset_documentation/nis/nisteenpuf11_dug.pdf.

†† The number of adolescent girls with provider-reported vaccination histories for each survey year are as follows: 2007, n = 1,440; 2008, n = 8,607; 2009, n = 9,621; 2010, n = 9,220; 2011, n = 11,236; 2012, n = 9,058.

§§ Information available at ftp://ftp.cdc.gov/pub/health_statistics/nchs/dataset_documentation/nis/nisteenpuf10_codebook.pdf.

TABLE 1. Estimated human papillomavirus (HPV) vaccine coverage among adolescent girls aged 13–17 years, by number of doses — National Immunization Survey–Teen, United States, 2007–2012

	Survey year*											
	2007		2008		2009		2010		2011		2012	
Characteristic	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)
≥1 dose HPV vaccine†	25.1	(22.3–28.1)	37.2	(35.2–39.3)§	44.3	(42.4–46.1)§	48.7	(46.9–50.5)§	53.0	(51.4–54.7)§	53.8	(52.0–55.7)
≥2 doses HPV vaccine	16.9	(14.6–19.6)	28.3	(26.4–30.3)§	35.8	(34.1–37.6)§	40.7	(38.9–42.5)§	43.9	(42.3–45.6)§	43.4	(41.5–45.2)
≥3 doses HPV vaccine	5.9	(4.4–7.8)	17.9	(16.3–19.6)§	26.7	(25.2–28.3)§	32.0	(30.3–33.6)§	34.8	(33.2–36.4)§	33.4	(31.7–35.2)
Unvaccinated girls with ≥1 missed opportunity for HPV vaccine¶	20.8	(17.6–24.3)	30.8	(28.5–33.2)§	52.5	(50.1–55.0)§	67.9	(65.5–70.2)§	77.7	(75.7–79.6)§	84.0	(82.1–85.8)§
Potential coverage with ≥1 dose of HPV vaccine if no missed opportunity	40.6	(37.3–44.0)	56.5	(54.4–58.6)§	73.5	(71.9–75.1)§	83.5	(82.2–84.8)§	89.5	(88.5–90.5)§	92.6	(91.7–93.5)§

Abbreviation: CI = confidence interval.

* The number of adolescent girls with provider-reported vaccination histories for each survey year are as follows: 2007, n = 1,440; 2008, n = 8,607; 2009, n = 9,621; 2010, n = 9,220; 2011, n = 11,236; and 2012, n = 9,058.

† HPV, either quadrivalent or bivalent.

§ Statistically significant difference ($p \leq 0.05$) compared with the previous year's estimate.

¶ Missed opportunity defined as a health-care encounter occurring on or after a girl's 11th birthday and on or after March 23, 2007 (the publication date of the Advisory Committee on Immunization Practices' HPV4 recommendation), during which a girl received at least one vaccine but did not receive HPV vaccine.

HPV vaccination increased from 20.8% in 2007 to 84.0% in 2012 (Table 1). In 2012, if all missed opportunities for HPV vaccination had been eliminated, coverage with ≥1 dose of HPV vaccine could have reached 92.6% (Table 1).

The 2012 NIS-Teen asked parents who did not intend to vaccinate their daughters in the next 12 months (23% of respondents) the main reason why their daughters would remain unvaccinated. The top five responses were as follows: vaccine not needed (19.1%), vaccine not recommended (14.2%), vaccine safety concerns (13.1%), lack of knowledge about the vaccine or the disease (12.6%), and daughter is not sexually active (10.1%).

Vaccine Safety

In the United States, postlicensure vaccine safety monitoring and evaluation are conducted independently by federal agencies and vaccine manufacturers. From June 2006 through March 2013, approximately 56 million doses of HPV4 were distributed in the United States, and from October 2009 through May 2013, a total of 611,000 doses of HPV2 were distributed. Because HPV4 accounts for 99% of the doses distributed in the United States, analysis of vaccine safety data was limited to HPV4. During June 2006–March 2013, the Vaccine Adverse Event Reporting System (VAERS)¶¶ received a total of 21,194 adverse event reports occurring in females after receipt of HPV4; 92.1% were classified as nonserious. Reporting peaked in 2008 and decreased each year thereafter; the proportion of reports to VAERS that were classified as serious reports*** peaked in 2009 at 12.8% and decreased thereafter to 7.4% in 2013 (Figure). Among nonserious adverse events, the most commonly reported generalized symptoms were syncope (fainting), dizziness, nausea, headache, fever, and urticaria (hives); the most commonly reported local symptoms were injection-site pain, redness, and swelling. Among the 7.9% of HPV4-related VAERS reports classified as serious, headache, nausea, vomiting, fatigue, dizziness, syncope, and generalized weakness were the most frequently reported symptoms. Overall reporting of adverse events to VAERS is consistent with prelicensure clinical trial data and, during the last 7 years, reporting patterns have remained consistent with the 2009 published summary of the first 2.5 years of postlicensure reporting to VAERS (*2*).

Three population-based published studies of HPV4 vaccine safety, including one from CDC's Vaccine Safety Datalink,††† have been conducted in the United States (Table 2). Although one postlicensure observational study found an increased risk for syncope, no serious safety concerns have been identified in these large postlicensure observational studies.

¶¶ Additional information available at http://www.cdc.gov/vaccinesafety/activities/vaers.html.

*** In VAERS, reports are classified as serious if the submitter reports one or more of the following: hospitalization, prolongation of an existing hospitalization, permanent disability, life-threatening illness, or death.

††† Additional information available at http://www.cdc.gov/vaccinesafety/activities/vsd.html.

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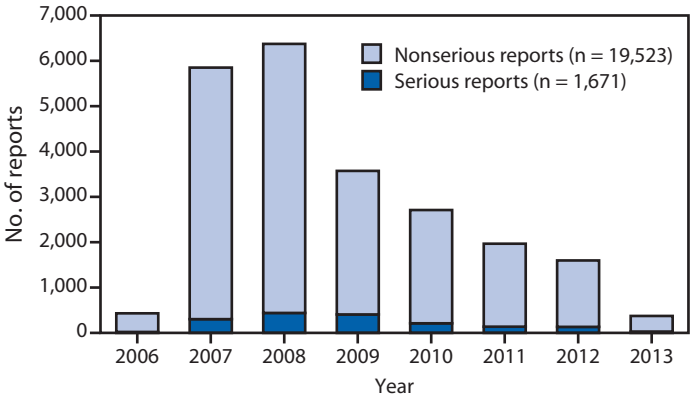
FIGURE. Number of serious and nonserious reports of adverse events after administration of quadrivalent human papillomavirus (HPV4) vaccine in females, by year — Vaccine Adverse Event Reporting System, United States, June 2006–March 2013*



* Total number of reports (serious and nonserious) = 21,194. In the Vaccine Adverse Event Reporting System, reports are classified as serious if the submitter reports one or more of the following: hospitalization, prolongation of an existing hospitalization, permanent disability, life-threatening illness, or death.

Editorial Note

Although HPV vaccination coverage has lagged behind that of other vaccines recommended for adolescents (*3*), coverage among adolescent girls increased each year during 2007–2011; 2012 is the first year with no observed increase. In 2012, only 53.8% of girls had received ≥1 dose of HPV vaccine, and only 33.4% had received all 3 doses of the series. Despite the availability of safe and effective HPV vaccines, approximately one quarter of surveyed parents did not intend to vaccinate their daughters in the next 12 months. Missed vaccination opportunities remain high. Every health-care visit, whether for back-to-school evaluations or acute problems, should be used to assess teenagers' immunization status and provide recommended vaccines if indicated.

Approximately 79 million persons in the United States are infected with HPV, and approximately 14 million will become newly infected each year (*4*). Some HPV types can cause cervical, vaginal, and vulvar cancer among women; penile cancer among men; and anal and some oropharyngeal cancers among both men and women (*4*). Other HPV types can cause genital warts among both sexes (*4*). Each year in the United States,

TABLE 2. Published population-based, postlicensure observational safety studies of HPV4 vaccine in U.S. females aged 9–26 years

Organization	System or review	No. of doses evaluated	Description	Methods	Findings
CDC	Vaccine Safety Datalink*	600,559	Large database used for active surveillance and research; safety assessment of seven prespecified health outcomes among female HPV4 vaccine recipients at seven managed-care organizations†	Cohort design with weekly sequential analyses of electronic medical data§	No statistically significant increase in risk for the outcomes monitored
Merck	Postmarketing commitment to FDA¶	346,972	General study assessment of HPV4 vaccine after routine administration at two large managed-care organizations	Self-controlled risk interval design, supplemented with medical record review	HPV4 vaccine associated with syncope on the day of vaccination and skin infections** in the 2 weeks after vaccination; no other vaccine safety signals detected
Merck	Postmarketing commitment FDA††	346,972	Assessment of 16 prespecified autoimmune conditions after routine use of HPV4 vaccine at two large managed-care organizations	Retrospective cohort using electronic medical data, supplemented with medical record review§§	No confirmed safety signals for the outcomes monitored

Abbreviations: HPV4 = quadrivalent human papillomavirus; FDA = Food and Drug Administration.

* Gee J, Naleway A, Shui I, et al. Monitoring the safety of quadrivalent human papillomavirus vaccine: findings from the Vaccine Safety Datalink. Vaccine 2011;29:8270–84.

† Prespecified outcomes included Guillain-Barré syndrome, stroke, appendicitis, seizures, allergic reactions, anaphylaxis, syncope, and venous thromboembolism

§ Comparison groups included historic background rates for Guillain-Barré syndrome, stroke, appendicitis, venous thromboembolism, and anaphylaxis; concurrent preventive health visits for seizures; or adolescent vaccination visits for syncope and allergic reactions.

¶ Klein NP, Hansen J, Chao C, et al. Safety of quadrivalent human papillomavirus vaccine administered routinely to females. Arch Pediatr Adolesc Med 2012; 166:1140–8.

** Medical record review suggested some cases might have been local injection site reactions.

†† Chao C, Klein NP, Velicer CM, et al. Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine. J Intern Med 2012;271:193–203.

§§ Comparison group included background incidence rates.

What is already known on this topic?

Since mid-2006, a licensed human papillomavirus (HPV) vaccine has been available and recommended by the Advisory Committee on Immunization Practices for routine vaccination of girls at ages 11 or 12 years. Based on results of the 2011 National Immunization Survey-Teen, only 53.0% of girls aged 13–17 years received ≥1 dose of HPV vaccine, and only 34.8% received all 3 doses of the HPV vaccine series.

What is added by this report?

Vaccination coverage of adolescent girls remained unchanged in 2012; only 53.8% of girls received ≥1 dose of HPV vaccine, and only 33.4% received all 3 doses of the series. Among unvaccinated girls, 84% had a health-care encounter in which they received a vaccine but not HPV vaccine. National safety monitoring data continue to indicate that the quadrivalent HPV vaccine is safe.

What are the implications for public health practice?

Despite the availability of safe and effective vaccines, many girls remain unprotected against HPV infections. If HPV vaccine was administered at health-care encounters when other recommended vaccines were administered, vaccination coverage could be as high as 92.6%. Improving practice patterns so that health-care providers and their staff members use every opportunity to offer HPV vaccines and are well-equipped to address questions from parents is necessary to reduce HPV-attributable cancers further.

an estimated 26,200 new cancers attributable to HPV occur: 17,400 among females (of which 10,300 are cervical cancer) and 8,800 among males (of which 6,700 are oropharyngeal cancers).[§§§]

Because cancers attributable to HPV occur years after infection, decades might be required before the impact of vaccination on reducing cancers is well-documented. However, shorter-term, vaccine-preventable outcomes are being monitored (including HPV prevalence, genital warts, and cervical precancers). Recent data from the National Health and Nutrition Examination Survey show a greater than 50% decrease in HPV infections caused by types targeted by HPV4 vaccine among females aged 14–19 years within the first 4 years of the HPV vaccination program (*5*). Administrative claims data from privately insured patients show declining genital warts incidence among patients aged 15–19 years, from 2.9 per 1,000 person-years in 2006 to 1.8 in 2010 (*6*). Substantial reductions in genital warts have occurred in other countries where vaccination programs achieved high coverage in target and catch-up age groups (*7,8*). In Australia, where the national vaccination program targeted females, rates of genital warts also decreased among males (*7*).

§§§ Additional information available at http://www.cdc.gov/cancer/hpv/statistics/cases.htm.

In addition to prelicensure HPV4 clinical trials that demonstrated safety and efficacy among thousands of patients, nearly 7 years of postlicensure vaccine safety monitoring provide further evidence of the safety of HPV4. Syncope can occur among adolescents who receive vaccines, including HPV4. To decrease the risk for falls and other injuries that might follow syncope, ACIP recommends that clinicians consider observing patients for 15 minutes after vaccination.

This report highlights three areas that need to be addressed to improve HPV vaccination coverage. The first area is education of parents. Three of the five main reasons parents reported for not intending to vaccinate their daughters (i.e., vaccine not needed, lack of knowledge, and daughter not sexually active) indicate gaps in understanding, including why vaccination is recommended by age 13 years. Parents also reported vaccine safety concerns as a main reason for not vaccinating. Updated educational materials that address these issues are available from CDC at http://www.cdc.gov/vaccines/who/teens/index.html.

Second, health-care providers must increase the consistency and strength of HPV vaccination recommendations. Studies have documented that, especially when counseling younger adolescents or their parents, providers give weaker recommendations for HPV vaccination compared with other vaccinations recommended for adolescents (*9*). Because provider counseling and recommendations greatly influence parental acceptance of vaccines, CDC has recently developed a tip sheet (available at http://www.cdc.gov/vaccines/who/teens/for-hcp-tipsheet-hpv.html) to help providers respond to parents' questions and communicate strong, clear HPV vaccination recommendations.

Finally, missed vaccination opportunities need to be reduced. Although providers cite infrequent preventive health-care visits among the adolescent population as a vaccination barrier (*10*), these data demonstrate that health-care access is not the main impediment. The increase in missed opportunities observed during 2007–2012 is attributable to higher and steadily increasing coverage for other vaccines recommended for adolescents (*3*). The 2012 NIS-Teen shows that 84% of unvaccinated girls had a health-care encounter where another vaccine was administered. Had the 3-dose HPV series been initiated at these visits, coverage for ≥1 dose could be as high as 92.6%.

High HPV vaccination coverage with existing infrastructure and health-care utilization is possible in the United States. Taking advantage of every health-care encounter, including acute-care visits, to assess every adolescent's vaccination status can help minimize missed opportunities. Potential strategies include using vaccination prompts available through electronic health records or checking local and state immunization information systems to assess vaccination needs at every encounter. Series completion also can be promoted through scheduling

appointments for second and third doses before patients leave providers' offices after receipt of their first HPV vaccine doses and with automated reminder-recall systems.

The findings in this report are subject to at least four limitations. First, the cellular telephone household response rate was only 23.6%, and the landline household response rate was only 56.1%. Nonresponse and noncoverage bias (from exclusion of households without telephones) might remain after weighting adjustments. Second, underestimates of vaccination coverage might have resulted from the exclusive use of provider-verified vaccination histories because the completeness of the records is unknown. Third, frequency of missed opportunities might be underestimated because health-care encounters in which a vaccination was not administered could not be included. Finally, VAERS is a passive reporting system that accepts reports from anyone, including health-care providers, patients, or family members. VAERS cannot determine cause-and-effect; a report of an adverse event to VAERS does not mean that a vaccine caused the event. Underreporting might occur and serious medical events are more likely to be reported than minor ones.

Additional information on VAERS is available at http://vaers.hhs.gov/data/index. The Vaccine Safety Datalink (VSD) is a population-based monitoring system that evaluates adverse events in those vaccinated with HPV vaccine compared with a control group and can estimate risk. Safety concerns raised through VAERS are evaluated more thoroughly using VSD. Data from VSD and from other published population-based studies provide more specific evidence about vaccine safety.

By increasing 3-dose HPV vaccination coverage to 80%, an estimated additional 53,000 cases of cervical cancer could be prevented over the lifetimes of those aged ≤12 years.¶¶¶ For every year that increases in coverage are delayed, another 4,400 women will go on to develop cervical cancer. Improving practice patterns and clinical skills so that health-care providers are well-equipped to address questions from parents and are committed to using every opportunity to strongly recommend HPV vaccination is necessary to achieve potential reductions in HPV-attributable cancers.

¶¶¶ Estimates obtained from an adaptation of the model presented in the following report: Chesson HW, Ekwueme DU, Saraiya M, Dunne EF, Markowitz LE. The cost-effectiveness of male HPV vaccination in the United States. Vaccine 2011;29:8443–50.

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