**Journal of Diabetes Science and Technology** Volume 6, Issue 4, July 2012 © Diabetes Technology Society

# Increased Risk of Acute Hepatitis B among Adults with Diagnosed Diabetes Mellitus

Meredith L. Reilly, M.P.H.,<sup>1</sup> Sarah F. Schillie, M.D., M.P.H., M.B.A.,<sup>1</sup> Emily Smith, M.P.H.,<sup>1</sup> Tasha Poissant, M.P.H.,<sup>2</sup> Candace W. Vonderwahl, B.S.,<sup>3</sup> Kristin Gerard, M.P.H.,<sup>4</sup> Jennifer Baumgartner, M.P.H.,<sup>5</sup> Lynne Mercedes, B.A.<sup>6</sup> Kristin Sweet, M.P.H.,<sup>7</sup>
Daniel Muleta, M.D., M.P.H.,<sup>8</sup> Daniel J. Zaccaro, M.S.,<sup>9</sup> R. Monina Klevens, D.D.S., M.P.H.,<sup>1</sup> and Trudy V. Murphy, M.D.<sup>1</sup>

## Abstract

### Introduction:

The risk of acute hepatitis B among adults with diabetes mellitus is unknown. We investigated the association between diagnosed diabetes and acute hepatitis B.

### Methods:

Confirmed acute hepatitis B cases were reported in 2009–2010 to eight Emerging Infections Program (EIP) sites; diagnosed diabetes status was determined. Behavioral Risk Factor Surveillance System respondents residing in EIP sites comprised the comparison group. Odds ratios (ORs) comparing acute hepatitis B among adults with diagnosed diabetes versus without diagnosed diabetes were determined by multivariate logistic regression, adjusting for age, sex, and race/ethnicity, and stratified by the presence or absence of risk behaviors for hepatitis B virus (HBV) infection.

### **Results:**

During 2009–2010, EIP sites reported 865 eligible acute hepatitis B cases among persons aged  $\geq$ 23 years; 95 (11.0%) had diagnosed diabetes. Comparison group diabetes prevalence was 9.1%. Among adults without hepatitis B risk behaviors and with reported diabetes status, the OR for acute hepatitis B comparing adults with and without diabetes was 1.9 (95% confidence interval [CI] = 1.4, 2.6); ORs for adults ages 23–59 and  $\geq$ 60 years were 2.1 (95% CI = 1.6, 2.8) and 1.5 (95% = CI 0.9, 2.5), respectively.

### Conclusions:

Diabetes was independently associated with an increased risk for acute hepatitis B among adults without HBV risk behaviors.

J Diabetes Sci Technol 2012;6(4):858-866

Author Affiliations: <sup>1</sup>Division of Viral Hepatitis, Centers for Disease Control and Prevention, Atlanta, Georgia; <sup>2</sup>Oregon Health Authority, Portland, Oregon; <sup>3</sup>Colorado Department of Public Health and Environment, Denver, Colorado; <sup>4</sup>Connecticut Department of Public Health, Hartford, Connecticut; <sup>5</sup>New York City Department of Health and Mental Hygiene, Long Island City, New York; <sup>6</sup>Georgia Department of Public Health, Atlanta, Georgia; <sup>7</sup>Minnesota Department of Health, St. Paul, Minnesota; <sup>8</sup>Tennessee Department of Health, Nashville, Tennessee; and <sup>9</sup>RTI International, Research Triangle Park, North Carolina

Abbreviations: (ACIP) Advisory Committee on Immunization Practices, (anti-HBc) total antibody to hepatitis B core antigen, (BRFSS) Behavioral Risk Factor Surveillance System, (CDC) Centers for Disease Control and Prevention, (CI) confidence interval, (EIP) Emerging Infections Program, (HBsAg) hepatitis B surface antigen, (HBV) hepatitis B virus, (HepB) hepatitis b vaccine, (HIV) human immunodeficiency virus, (HIVRISK) human immunodeficiency virus infection risk, (IDU) injection drug use, (LTC) long-term care, (MSM) male sex with another male, (NHANES) National Health and Nutritional Examination Survey, (OR) odds ratio

Keywords: blood glucose monitoring, diabetes mellitus, hepatitis B, prevention

**Corresponding Author:** Sarah F. Schillie, MD, MPH, MBA, Division of Viral Hepatitis, Centers for Disease Control and Prevention 1600 Clifton Rd. NE, MS G-37, Atlanta, GA 30333; email address <u>sschillie@cdc.gov</u>

## Introduction

In 2010, an estimated 18.6 million U.S. adults aged ≥20 years were diagnosed with type 1 or type 2 diabetes mellitus,<sup>1</sup> and the annual incidence of diabetes diagnoses is expected to increase.<sup>2</sup> Persons with diabetes require comprehensive medical care to manage blood glucose and prevent diabetes complications such as cardiovascular disease, kidney disease, retinopathy, and neuropathy.<sup>3</sup> Regardless of treatment (insulin, oral medication, or nutrition), 86% of persons with diabetes self-monitor blood glucose levels at least once monthly.4,5 Assisted monitoring also takes place in various venues, including physician offices, hospitals, health fairs, schools, and assisted-living facilities.<sup>6</sup> Opportunities for transmission of blood-borne pathogens exist when patients are exposed to blood or body fluids from infected persons through contaminated equipment or surfaces (e.g., on blood glucose monitoring equipment, when insulin pens are used for more than one person, or during certain procedures).<sup>6–10</sup>

Hepatitis B virus (HBV) is a highly infectious bloodborne pathogen transmitted by percutaneous or mucosal exposure to blood or body fluids from an infected person; HBV remains stable on environmental surfaces for  $\geq$ 7 days.<sup>11,12</sup> Known behaviors that increase the risk for acquiring HBV infection include injection drug use (IDU), male sex with another male (MSM), and sex with multiple partners. Unvaccinated health care professionals and household or sexual contacts of an HBV-infected person are also at increased risk for HBV infection.<sup>13,14</sup> Approximately 5% of otherwise healthy adults with acute or asymptomatic HBV infection become chronically infected, which can lead to cirrhosis, hepatocellular carcinoma, and liver failure.<sup>15,16</sup>

Outbreaks of hepatitis B among persons with diabetes residing in long-term care (LTC) settings (e.g., nursing homes and assisted-living facilities) suggests there could be an increased risk for HBV infection in these settings.<sup>8,17-22</sup> However, the incidence and magnitude of risk for acute hepatitis B is unknown among the general population of adults with diabetes or after excluding persons whose HBV infection could reasonably be attributed to other recognized risk behaviors. For this analysis, we sought to determine the association between diabetes and acute hepatitis B among adults without known risk behaviors for acquiring HBV infection.

## Methods

### Study Population and Data Collection

For the period 2009-2010, we examined cases of acute hepatitis B reported from eight sites participating in the Emerging Infections Program (EIP), a network of health departments that conduct enhanced surveillance for emerging infectious diseases, including acute hepatitis B.<sup>14,23</sup> The residential population in the EIP sites [Connecticut, Colorado, Georgia, Minnesota, New York City, New York State (34 counties), Oregon, and Tennessee] constituted approximately 17% of the U.S. adult population during the study period. Three of the eight participating sites (Connecticut, Colorado, and New York City) had determined diabetes status for acute hepatitis B cases since 2009 or earlier; Oregon collected diabetes status for cases starting in early 2010. During 2010-2011, all participating sites retrospectively collected diabetes status for 2009–2010 cases with missing information; data from Tennessee included 2010 cases only.

Confirmed acute hepatitis B cases were eligible for analysis. The Council of State and Territorial Epidemiologists defines a confirmed case as having clinical indications (acute illness with a discrete onset of symptoms and either jaundice or elevated serum alanine aminotransferase levels) and a laboratory confirmation [immunoglobulin M antibody to hepatitis B core antigen positive or hepatitis B surface antigen (HBsAg) positive, with immunoglobulin M antibody to hepatitis A virus negative, if performed].<sup>14</sup>

Patient information collected in a standard case interview or medical record review by health department staff included demographics (e.g., age and race), HBV risk behaviors (e.g., IDU and MSM) carried out within six weeks to six months of symptom onset, other potential HBV exposures, and data on hospitalization and deaths attributed to acute hepatitis B. Diabetes status of cases was determined by self-reported history of a doctor's diabetes diagnosis (type 1 or type 2). If the case patient was unavailable for interview, diabetes status was provided by the physician or medical record review. If none of these sources were available, diabetes status was considered unknown. Cases with gestational or prediabetes or whose diabetes diagnosis occurred within the 6-month incubation period before onset of acute hepatitis B symptoms were classified as not having diabetes. De-identified data for acute hepatitis B cases were reported to the Centers for Disease Control and Prevention (CDC) as part of routine hepatitis B disease surveillance; because the activity was considered "disease control" rather than "human research," it was exempt from human subjects' research review.

The 2009 and 2010 Behavioral Risk Factor Surveillance System (BRFSS)<sup>24,25</sup> respondents residing in the eight sites comprised the comparison group. The BRFSS provides publicly accessible state-based, self-reported data on health conditions and risk behaviors among noninstitutionalized individuals. Respondent data were weighted to the overall population of each EIP site based on age, sex, and race/ethnicity. Diabetes status was determined by self-report using the following question: "Have you ever been told by a doctor that you have diabetes?" Respondents with gestational or prediabetes were classified as not having diabetes. HBV risk behavior was estimated using the BRFSS variable for human immunodeficiency virus (HIV) infection risk (HIVRISK), defined by history of IDU, treatment for a sexually transmitted infection, giving or receiving money or drugs in exchange for sex, or anal sex without a condom in the past year. The HIVRISK information was available for respondents aged <65 years.

### Analysis

Demographic information for analysis included age, sex, race, and ethnicity. We assumed that no subjects in the comparison group had acute hepatitis B; in 2009, the U.S. incidence of acute hepatitis B was 1.1 per 100,000 population.14 Cases and comparison subjects aged <23 years were excluded from analysis, as hepatitis B immunization laws targeting students 11-12 years of age took effect in 2000 in most EIP states. Thus, persons aged <23 years had high hepatitis B vaccination coverage.<sup>26</sup> We divided acute hepatitis B cases and comparison subjects into two age groups, 23–59 and ≥60 years, based on the increased likelihood of older adults receiving LTC<sup>27</sup> and having decreased responsiveness to hepatitis B vaccine (HepB).<sup>28</sup> Race and ethnicity were combined into one variable and categorized as non-Hispanic white, non-Hispanic black, Hispanic, Asian or Pacific Islander, and Other.

History of IDU, MSM, and sex with  $\ge 2$  partners were included to assess acute hepatitis B risk behavior. We created a combination variable, "Other HBV Risk Behaviors," defined by acute hepatitis B cases with a history of IDU, MSM, and/or multiple sex partners. For the comparison subjects, history of Other HBV Risk Behaviors was estimated using the BRFSS HIVRISK variable.

Characteristics of the acute hepatitis B cases and comparison subjects were examined, including age, sex, race/ethnicity, Other HBV Risk Behaviors, and diabetes status. Focusing on the acute hepatitis B cases, we compared demographics, LTC residence, hepatitis B risk behaviors, and health outcomes by diabetes status using chi-square tests or two-sided Fisher's exact tests with  $\alpha = .05$ .

Our initial analysis estimated the incidence of acute hepatitis B among persons with and without diabetes by summing acute hepatitis B cases according to diabetes status and dividing by totals in the comparison group. Poisson regression was used to determine 95% confidence intervals (CIs) for each incidence estimate.

To further investigate the association between diabetes and acute hepatitis B and to measure odds of acute hepatitis B among persons with diabetes compared with persons without diabetes, we developed models for estimation of odds ratios (ORs) and 95% CIs. Bivariate analysis assessed the relationship between acute hepatitis B and age, sex, race/ethnicity, Other HBV Risk Behaviors, and diabetes. We performed tests for interaction between diabetes and the other covariates and controlled for intraclass correlation within EIP sites. There was significant interaction between diabetes status and Other HBV Risk Behaviors (p = .02); therefore, analyses were stratified according to presence/absence of Other HBV Risk Behaviors. The main model excluded persons with unknown diabetes status and unknown or known history of Other HBV Risk Behaviors. Multivariate logistic regression analysis using weighted data controlled for age (grouped as 23–39, 40–49, 50–59, ≥60 years), sex, and race/ethnicity to determine adjusted ORs and 95% CIs comparing odds of acute hepatitis B among adults with diabetes with adults without diabetes and no Other HBV Risk Behaviors. Sensitivity analyses were performed assuming cases with unknown diabetes status had or did not have diabetes.

All statistical analyses were conducted using SAS software (version 9.2, SAS Institute Inc., Cary, NC).

## Results

A total of 865 confirmed acute hepatitis B cases were reported among adults aged  $\geq$ 23 years in the eight participating EIP sites during 2009–2010. The population of the comparison group was 64.2 million persons, derived from 90,941 unweighted 2009–2010 BRFSS respondents. The mean age was 44 years (range 23–88) and 49 years (range 23–99) for acute hepatitis B cases and comparison subjects, respectively. Diabetes prevalence among acute hepatitis B cases was 11.0%, compared with 9.1% for the comparison subjects. Males, non-Hispanic blacks, and Hispanics accounted for a higher proportion of acute hepatitis B cases than in comparison subjects (**Table 1**).

Among acute hepatitis B cases, adults with diabetes compared to adults without diabetes were older (mean age 52 years versus 43 years, p < .001), had less IDU (1.5% versus 10.8%, p = .009), and fewer reports of  $\ge 1$  HBV

risk behavior (19.5% versus 34.6%, p = .006). No significant differences were observed between adults with and without diabetes by race/ethnicity, LTC residence, hospitalizations due to HBV infection, or HBV-related deaths (**Table 2**).

The estimate of reported annual acute hepatitis B incidence among adults aged  $\geq$ 23 years with and without diabetes during 2009–2010 was 1.8 per 100,000 (95% CI = 1.5, 2.2) and 1.3 per 100,000 (95% CI = 1.2, 1.4), respectively. In bivariate analysis, covariates associated with acute hepatitis B were age (23–59 years versus  $\geq$ 60 years, OR 2.4, 95% CI = 2.0, 2.9), sex (male versus female, OR 2.0, 95% CI = 1.7, 2.3), race/ethnicity (all others versus non-Hispanic white, OR 2.4, 95% CI = 2.0, 2.7), Other HBV Risk Behaviors (OR 15.4, 95% CI = 12.9, 18.4), and diabetes (OR 1.3, 95% CI = 1.1, 1.7; **Table 3**).

Table 1.Characteristics of Acute Hepatitis B Cases and Behavioral Risk Factor Surveillance SystemComparison Group, 2009–2010

Comparison Group, 2009–2010							
Characteristic	Acute hepat N =	titis B cases 865	BRFSS comparison group <sup>a</sup> Unweighted $N = 90,941$				
	п	% <sup>b</sup>	Unweighted <i>n</i>	Weighted % <sup>b</sup>			
Age (years)							
23–59	756	87.4	50,866	74.4			
≥60	109	12.6	40,075	25.6			
Sex							
Male	561	64.9	33,997	48.0			
Female	303	35.0	56,944	52.0			
Race/ethnicity							
Non-Hispanic white	398	46.0	74,476	71.9			
Non-Hispanic black	220	25.4	6533	12.5			
Hispanic	81	9.4	5116	8.4			
Asian or Pacific Islander	35	4.1	1285	2.8			
Other	15	1.7	2502	3.3			
Other HBV Risk Behaviors <sup>c</sup>							
Yes	247	28.6	1259	2.4			
No	503	58.2	56,723	74.8			
Diagnosed diabetes							
Yes	95	11.0	10,076	9.1			
No	707	81.7	80,766	90.8			

<sup>a</sup> Assumed not to have hepatitis B.

<sup>b</sup> Figures may not add to 100% due to missing data.

<sup>c</sup> In acute hepatitis B cases, at least one of the following occurred 6 weeks to 6 months prior to onset of acute hepatitis B symptoms: injection drug use (IDU), male sex with another male (MSM), or sex with multiple partners. For BRFSS respondents, at least one of the following occurred in the past year: IDU, treatment for a sexually transmitted infection, giving or receiving money or drugs in exchange for sex, or anal sex without a condom.

### Table 2.

Demographics, HBV Risk Behaviors,<sup>a</sup> and Health Outcomes for 865 Acute Hepatitis B Cases by Diagnosed Diabetes Status, 2009–2010

Characteristic	Diagnosed diabetes mellitus		No diagnosed diabetes mellitus		Unknown diagnosis of diabetes mellitus		P value <sup>b</sup>
	n	% <sup>c</sup>	n	%	n	%	
Ν	95	11.0	707	81.7	63	7.3	—
Age (years)							
23–59 <sup>d</sup>	68	71.6	633	89.5	55	87.3	<0.001
≥60	27	28.4	74	10.5	8	12.7	
Sex						^	
Male	59	62.1	457	64.7	45	71.4	0.616
Female	36	37.9	249	35.3	18	28.6	
Race/ethnicity						^	
Non-Hispanic white	38	43.2	329	54.1	31	58.5	
Non-Hispanic black	34	38.6	176	28.9	10	18.9	]
Hispanic	10	11.4	64	10.5	7	13.2	0.055 <sup>e</sup>
Asian or Pacific Islander	4	4.5	28	4.6	3	5.7	
Other	2	2.3	11	1.8	2	3.8	
Long-term care residence							
Yes	2	3.0	7	1.3	2	5.9	0.1669 <sup>f</sup>
No	64	97.0	531	98.7	32	94.1	
Injection drug use							
Yes	1	1.5	60	10.8	5	14.3	0.009 <sup>f</sup>
No	68	98.5	495	89.2	30	85.7	
Male sex with another male							
Yes	6	8.2	62	11.6	6	14.0	0.392
No	67	91.8	473	88.4	37	86.0	-
Multiple sex partners							
Yes	11	16.4	110	22.4	8	21.6	0.265
No	56	83.6	381	77.6	29	78.4	
Other HBV Risk Behaviors <sup>g</sup>							
Yes	16	19.5	215	34.6	16	34.8	0.006
No	66	80.5	407	65.4	30	65.2	
Hospitalization due to acute hepatitis B							
Yes	42	52.5	287	45.4	13	31.0	0.231
No	38	47.5	345	54.6	29	69.0	
Death due to acute hepatitis B							
Yes	4	4.6	12	2.0	3	5.4	0.127 <sup>f</sup>
No	83	95.4	599	98.0	52	94.6	

<sup>a</sup> Six weeks to 6 months prior to onset of acute hepatitis B symptoms.

<sup>b</sup> Diabetes versus no diabetes, chi-square test unless otherwise indicated.

<sup>c</sup> Proportion of cases with characteristic out of total cases with available information.

<sup>d</sup> Age breakout for ages 23-59 years by diagnosed diabetes status. Diagnosed diabetes mellitus (n = 95): 23-39 years, 15.8%;

40-49 years, 28.4%; 50-59 years, 27.4%. No diagnosed diabetes mellitus (n = 707): 23-39 years, 42.4%; 40-49 years, 31.1%;

50-59 years, 16.0%. Unknown diagnosis of diabetes mellitus (n = 63): 23-39 years, 39.7%; 40-49 years, 31.7%; 50-59 years, 15.9%. <sup>e</sup> Non-Hispanic white versus all others.

<sup>f</sup> Fisher's exact test.

<sup>g</sup> At least one of the following occurred 6 weeks to 6 months prior to onset of acute hepatitis B symptoms: Injection drug use, male sex with another male, or sex with multiple partners.

### Table 3.

Bivariate Analysis of Covariates Associated with Acute Hepatitis B among Adults Aged ≥23 Years, 2009–2010

Characteristic	OR (95% CI)
Age <sup>a</sup>	2.4 (2.0, 2.9)
Sex <sup>b</sup>	2.0 (1.7, 2.3)
Race/ethnicity <sup>c</sup>	2.4 (2.0, 2.7)
Other HBV Risk Behaviors	15.4 (12.9, 18.4) <sup>d</sup>
Diagnosed diabetes	1.3 (1.1, 1.7)
<sup>a</sup> 23–59 years versus ≥60 years. <sup>b</sup> Male versus female	

<sup>c</sup> All others versus non-Hispanic white.

<sup>d</sup> Estimate may not be reliable, definition of Other HBV Risk

Behaviors varied for cases and comparison subjects.

The final main model included cases and comparison subjects with known diabetes status and no Other HBV Risk Behaviors. This subset of the data consisted of 414 cases of acute hepatitis B and 56,158 weighted comparison subjects. Controlling for age, sex, and race/ ethnicity, adults with diabetes and no Other HBV Risk Behaviors had 1.9 (95% CI = 1.4, 2.6) times the odds of acute hepatitis B compared with adults without diabetes and no Other HBV Risk Behaviors. Sensitivity analysis resulted in an OR of 1.8 (95% CI = 1.3, 2.4) for adults with diabetes versus no diabetes when records with unknown diabetes status were categorized as not having diabetes and an OR of 2.8 (95% CI = 2.1, 3.7) when cases with unknown status were categorized as having diabetes. The adjusted ORs for adults with diabetes and no Other HBV Risk Behaviors aged 23-59 years and  $\geq 60$  years were 2.1 (95% CI = 1.6, 2.8) and 1.5 (95% CI = 0.9, 2.5), respectively (Table 4).

## Discussion

Of adults without certain well-established risk factors for HBV infection, our results suggest adults with diagnosed diabetes overall and adults with diabetes ages 23–59 years have approximately twice the risk for acute hepatitis B than adults without diabetes. The increased risk persisted in sensitivity analyses that examined the effect of cases with unknown diabetes status. Adults with diabetes aged  $\geq 60$  years may also have increased risk for acute hepatitis B, although the results were not statistically significant. A major strength of the analysis is its large sample size (approximately 17% of the U.S. adult population), enabling determination of the odds of acute hepatitis B while controlling for demographic characteristics among persons with diabetes who did not report Other HBV Risk Behaviors.

Age, race/ethnicity, and Other HBV Risk Behaviors were covariates with potential to influence the interpretation of the results. Diabetes and hepatitis B disproportionately affect different age, race, and ethnic groups. In 2005 to 2008, older adults (≥65 years) had the highest diabetes prevalence;<sup>1</sup> in contrast, 2009 national surveillance data showed the highest incidence of acute hepatitis B among adults aged 30-59 years.14 In 2007-2009, the National Health Interview Survey reported that diagnosed diabetes was 18% higher among Asian Americans, 66% higher among Hispanics, and 77% higher among non-Hispanic blacks compared with non-Hispanic whites.<sup>1</sup> Results from the 1996–2006 National Health and Nutritional Examination Survey (NHANES) showed a higher seroprevalence of past or present HBV infection [total antibody to hepatitis B core antigen (anti-HBc)] among non-Hispanic blacks compared with non-Hispanic whites (12.2% versus 2.8%, p = .001).<sup>29</sup> In our study, acute hepatitis B cases

Table 4.

Main Model and Sensitivity Analyses Results: Adjusted Odds Ratios of Acute Hepatitis B by Age Group, Diagnosed Diabetes versus No Diagnosed Diabetes<sup>a</sup>

Age group (years)	Main model, unknown diagnosis of diabetes mellitus <sup>b</sup> → excluded	Sensitivity model, unknown diagnosis of diabetes mellitus → no diagnosed diabetes mellitus	Sensitivity model, unknown diagnosis of diabetes mellitus → diagnosed diabetes mellitus	
	OR (95% CI)	OR (95% CI)	OR (95% CI)	
23–59	2.1 (1.6, 2.8) <sup>c</sup>	1.9 (1.4, 2.7)	3.3 (2.4,4.4)	
≥60 <sup>d</sup>	1.5 (0.9, 2.5) <sup>c</sup>	1.4 (0.8, 2.5)	1.8 (1.0, 3.2)	
All	1.9 (1.4, 2.6)	1.8 (1.3, 2.4)	2.8 (2.1, 3.7)	

<sup>a</sup> Models controlled for sex, age, and race/ethnicity and excluded persons with Other HBV Risk Behaviors.

<sup>b</sup> Unknown diagnosis of diabetes mellitus = cases with missing diagnosed diabetes status.

<sup>c</sup> Controlled for intraclass correlation.

<sup>d</sup> Models analyzing adults aged  $\geq$ 60 years did not adjust for age.

without diagnosed diabetes reported IDU and Other HBV Risk Behaviors more frequently than those with diagnosed diabetes. Of 1,715 acute hepatitis B case reports with available risk information captured by national CDC surveillance in 2009, 39.9% indicated at least one risk behavior/exposure for HBV, including IDU, MSM, and sex with  $\geq$ 2 partners.<sup>14</sup> Adjusting for age and race/ethnicity and limiting the analysis to cases and comparison subjects with no Other HBV Risk Behaviors strengthened the results.

Although this study is the first to evaluate the risk for acute hepatitis B among adults with diabetes in the United States, seroprevalence data support our findings. In 1999–2010, NHANES, a nationally representative survey that excludes institutionalized adults, found a 60% (p < .001) higher seroprevalence of anti-HBc among adults with diabetes than adults without diabetes.<sup>30</sup>

In Turkey, Gulcan and colleagues<sup>31</sup> compared 630 persons with diabetes and 314 persons without diabetes attending an internal medicine clinic and found HBV infections were increased but not significantly more common among persons with diabetes compared with persons without diabetes (5.1% versus 3.8%); however, investigators noted significant correlations between HBsAg-positive serology (indicative of chronic hepatitis B) and history of hospital admission, long duration of diabetes, and use of insulin. Halota and associates<sup>32</sup> identified anti-HBc seropositivity among 123 (39.0%) of 315 persons with diabetes in Poland. The percentage of study participants with anti-HBc increased with age and duration of diabetes. In Italy, Sangiorgio and coauthors<sup>33</sup> identified a higher percentage of HBsAg-positive persons with diabetes compared to a control group of blood donors (7.1% versus 1.6%, p < .001), and in another Italian study, a higher seroprevalence of anti-HBc was observed among persons with diabetes compared with blood donors.34

Outbreaks of HBV infections in institutional settings were first reported to CDC in 1990.<sup>6</sup> During 1996–2011, 30 LTC facility HBV outbreaks were reported to CDC, 27 of which predominantly affected persons with diabetes.<sup>35</sup> The outbreaks were attributed to lapses in infection control, mainly during assisted blood glucose monitoring; dental procedures and podiatric care also could have played a role in HBV transmission.<sup>8,10,17–22</sup> Although most cases in these outbreaks were associated with procedures performed in congregate living settings, the potential for transmission of HBV is present whenever equipment or surfaces are contaminated with blood or body fluids from an HBV-infected person. Persons with diabetes who monitor blood glucose have regular breaks in the skin and may be particularly susceptible to HBV infection because of stability of the virus on environmental surfaces. Across the health care system and in nontraditional settings where persons with diabetes receive care, reinforcing infection control practice may facilitate the prevention of blood-borne pathogen transmission.<sup>36,37</sup>

Given the history of HBV outbreaks among older adults in institutional settings (i.e., LTC), we expected but did not find an increased risk for acute hepatitis B among adults aged  $\geq 60$  years with diabetes. The lower effect size among older adults with diabetes likely resulted from greater under-recognition and underdiagnosis of acute hepatitis B among older adults compared to younger adults. A high proportion of acute hepatitis B cases among older adults evaluated in LTC outbreaks had atypical symptoms or were asymptomatic and were recognized only after serologic testing; such cases would not have been reported to the EIP sites or eligible for analysis.<sup>21,38</sup>

Hepatitis B is vaccine-preventable. As part of a comprehensive strategy to eliminate HBV transmission in the United States, the Advisory Committee on Immunization Practices (ACIP) recommends routine hepatitis B vaccination for all children, adults at increased risk for HBV infection, and anyone seeking protection from HBV infection.<sup>13,39</sup> In October 2011, the ACIP recommended hepatitis B vaccination for unvaccinated adults aged 19–59 years with diabetes and at the discretion of the treating clinician for adults aged  $\geq 60$  years with diabetes.<sup>40</sup> The HepB vaccine is safe and effective.<sup>41</sup> Young adults with diabetes achieve protection at rates similar to persons without diabetes. The immune response wanes with increasing age and comorbidities.<sup>27,42,43</sup>

This study has several limitations. A cohort study of persons with diabetes would have provided the best measure of the risk for acute hepatitis B. In the absence of such a study, we used two sources of data from the same population that provided information from a large segment of the United States and had sufficient detail to estimate the risk for acute hepatitis B, controlling for important potential confounders. However, the definition of Other HBV Risk Behaviors differed between comparison subjects and acute hepatitis B cases, which could have affected the reliability of the estimates. Compared to adults without diabetes, adults with diabetes might have had increased health care utilization, which may lead to increased testing and, thus, greater likelihood of acute hepatitis B diagnosis. Unlike EIP case surveillance,

the BRFSS was limited to noninstitutionalized adults. Among acute hepatitis B cases, 11 (1.3%) reported a history of LTC, and the proportion of acute hepatitis B cases in LTC did not differ by diabetes status. Therefore, lack of exclusion of cases in LTC likely would not have affected the results. We assumed none of the sampled BRFSS respondents had acute hepatitis B, and the analysis did not account for vaccination because vaccination histories are not available for 2009-2010 BRFSS records. The direction of any resulting bias would have depended on variation in acute hepatitis B incidence and vaccination coverage by diabetes status among comparison subjects. Other data were limited or unavailable for variables including health-care-related occupation, history of hemodialysis or dental care, HepB vaccine, and the frequency of blood glucose monitoring or insulin use.

## Conclusions

Our findings suggest an increased risk for acute hepatitis B among adults with diagnosed diabetes. Hepatitis B vaccination and continued infection control practice related to diabetes care and monitoring may reduce transmission of blood-borne pathogens and prevent morbidity and mortality associated with HBV infection.

#### Funding:

Funding was provided by the Centers for Disease Control and Prevention.

#### Acknowledgments:

The authors thank Paul Cieslak for providing input to the study concept; Faduma Ahmed, Brittney Baack, Katherine Bornschlegel, Donna Cordova, Steven Fiala, Elena Rizzo, Timothy Wen, Kara Woodlief, and the Central and Regional Health Office staff of the Tennessee Department of Health Central and Regional Health Office staff for contributing to data collection; and Nita Patel for analytical assistance. The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or any other of the authors' affiliations. This study was presented, in part, in poster form at the 49th Annual Meeting of the Infectious Diseases Society of America, October 22, 2011, Boston, MA.

#### **References:**

- 1. Centers for Disease Control and Prevention (CDC). National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2011.
- 2. Boyle JP, Thompson TJ, Gregg EW, Barker LE, Williamson DF. Projection of the year 2050 burden of diabetes in the US adult population: dynamic modeling of incidence, mortality, and prediabetes prevalence. Popul Health Metr. 2010;8:29.

- 3. American Diabetes Association. Standards of medical care in diabetes--2011. Diabetes Care. 2011;34 Suppl 1:S11–61.
- 4. Centers for Disease Control and Prevention. Diabetes data and trends. <u>www.cdc.gov/diabetes/statistics</u>. Accessed November 8, 2011.
- Burrows NR. Update: national diabetes statistics. Presented at: Meeting of the Advisory Committee on Immunization Practices (ACIP), Atlanta, GA, February 24, 2011. <u>http://www.cdc.gov/vaccines/ recs/acip/</u>.
- 6. Klonoff DC. Improving the safety of blood glucose monitoring. J Diabetes Sci Technol. 2011;5(6):1307–11.
- 7. Louie RF, Lau MJ, Lee JH, Tang Z, Kost GJ. Multicenter study of the prevalence of blood contamination on point-of-care glucose meters and recommendations for controlling contamination. Point Care. 2005;4(4):158–63.
- 8. Thompson ND, Barry V, Alelis K, Cui D, Perz JF. Evaluation of the potential for bloodborne pathogen transmission associated with diabetes care practices in nursing homes and assisted living facilities, Pinellas County. J Am Geriatr Soc. 2010;58(5):914–8.
- 9. Schaefer MK, Jhung M, Dahl M, Schillie S, Simpson C, Llata E, Link-Gelles R, Sinkowitz-Cochran R, Patel P, Bolyard E, Sehulster L, Srinivasan A, Perz JF. Infection control assessment of ambulatory surgical centers. JAMA. 2010;303(22):2273–9.
- Wise ME, Marquez P, Sharapov U, Hathaway S, Katz K, Tolan S, Beaton A, Drobeniuc J, Khudyakov Y, Hu DJ, Perz J, Thompson ND, Bancroft E. Outbreak of acute hepatitis B virus infections associated with podiatric care at a psychiatric long-term care facility. Am J Infect Control. 2012;40(1):16–21.
- Bond WW, Favero MS, Petersen NJ, Gravelle CR, Ebert JW, Maynard JE. Survival of hepatitis B virus after drying and storage for one week. Lancet. 1981;1(8219):550–1.
- Favero MS, Bond WW, Petersen NJ, Berquist KR, Maynard JE. Detection methods for study of the stability of hepatitis B antigen on surfaces. J Infect Dis. 1974;129(2):210–2.
- 13. Mast EE, Weinbaum CM, Fiore AE, Alter MJ, Bell BP, Finelli L, Rodewald LE, Douglas JM Jr, Janssen RS, Ward JW; Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention (CDC). A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: immunization of adults. MMWR Recomm Rep. 2006;55(RR-16):1–33.
- Centers for Disease Control and Prevention. Viral hepatitis surveillance - United States, 2009. <u>www.cdc.gov/hepatitis/Statistics/</u> <u>2009Surveillance/index.htm</u>. Accessed September 22, 2011.
- 15. Hyams KC. Risks of chronicity following acute hepatitis B virus infection: a review. Clin Infect Dis. 1995;20(4):992–1000.
- Weinbaum CM, Williams I, Mast EE, Wang SA, Finelli L, Wasley A, Neitzel SM, Ward JW; Centers for Disease Control and Prevention (CDC). Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. MMWR Recomm Rep. 2008;57(RR-8):1–20.
- 17. Thompson ND, Schaefer MK. "Never events": hepatitis B outbreaks and patient notifications resulting from unsafe practices during assisted monitoring of blood glucose, 2009-2010. J Diabetes Sci Technol. 2011;5(6):1396–402.
- Centers for Disease Control and Prevention (CDC). Notes from the field: deaths from acute hepatitis B virus infection associated with assisted blood glucose monitoring in an assisted-living facility-North Carolina, August-October 2010. MMWR Morb Mortal Wkly Rep. 2011;60(6):182.
- Counard CA, Perz JF, Linchangco PC, Christiansen D, Ganova-Raeva L, Xia G, Jones S, Vernon MO. Acute hepatitis B outbreaks related to fingerstick blood glucose monitoring in two assisted living facilities. J Am Geriatr Soc. 2010;58(2):306–11.

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- Thompson ND, Perz JF. Eliminating the blood: ongoing outbreaks of hepatitis B virus infection and the need for innovative glucose monitoring technologies. J Diabetes Sci Tehnol. 2009;3(2):283–8.
- Centers for Disease Control and Prevention (CDC). Transmission of hepatitis B virus among persons undergoing blood glucose monitoring in long-term-care facilities--Mississippi, North Carolina, and Los Angeles County, California, 2003-2004. MMWR Morb Mortal Wkly Rep. 2005;54(9):220–3.
- 22. Schaffzin JK, Southwick KL, Clement EJ, Konings F, Ganova-Raeva L, Xia G, Khudyakov Y, Johnson GS. Transmission of hepatitis B virus associated with assisted monitoring of blood glucose at an assisted living facility in New York State. Am J Infect Control. 2012. Epub ahead of print.
- Centers for Disease Control and Prevention. Emerging infections programs. <u>www.cdc.gov/ncezid/dpei/eip/index.html</u>. Accessed October 28, 2011.
- Centers for Disease Control and Prevention. Behavioral Risk Factor Surveillance System survey data, 2009. <u>http://www.cdc.gov/brfss/</u> <u>technical\_infodata/surveydata/2009.htm</u>. Accessed August 23, 2011.
- Centers for Disease Control and Prevention. Behavioral Risk Factor Surveillance System survey data, 2010. <u>http://www.cdc.gov/brfss/</u> <u>technical\_infodata/surveydata/2010.htm</u>. Accessed August 23, 2011.
- Immunization Action Coalition. Hepatitis B prevention mandates for daycare and K-12. <u>www.immunize.org/laws/hepb.asp</u>. Accessed November 7, 2011.
- Zhang X, Decker FH, Luo H, Geiss LS, Pearson WS, Saaddine JB, Gregg EW, Albright A. Trends in the prevalence and comorbidities of diabetes mellitus in nursing home residents in the United States: 1995-2004. J Am Geriatr Soc. 2010;58(4):724–30.
- Averhoff F, Mahoney F, Coleman P, Schatz G, Hurwitz E, Margolis H. Immunogenicity of hepatitis B vaccines. Implications for persons at occupational risk of hepatitis B virus infection. Am J Prev Med. 1998;15(1):1–8.
- 29. Wasley A, Kruszon-Moran D, Kuhnert W, Simard EP, Finelli L, McQuillan G, Bell B. The prevalence of hepatitis B virus infection in the United States in the era of vaccination. J Infect Dis. 2010;202(2):192–201.
- 30. Schillie SF, Xing J, Murphy TV, Hu DJ. Prevalence of hepatitis B virus infection among persons with diagnosed diabetes mellitus in the United States, 1999-2010. J Viral Hepat. 2012. Epub ahead of print.
- Gulcan A, Gulcan E, Toker A, Bulut I, Akcan Y. Evaluation of risk factors and seroprevalence of hepatitis B and C in diabetic patients in Kutahya, Turkey. J Investig Med. 2008;56(6):858–63.
- Halota W, Muszynska M, Pawlowska M. Hepatitis B virus serologic markers and anti-hepatitis B vaccination in patients with diabetes. Med Sci Monit. 2002;8(7):CR516–9.
- 33. Sangiorgio L, Attardo T, Gangemi R, Rubino C, Barone M, Lunetta M. Increased frequency of HCV and hepatitis B infection in type 2 diabetic patients. Diabetes Res Clin Pract. 2000;48(2):147–51.
- 34. Savagnone E, Caruso V, Mondello P, Patti S, Spicola L, Spano C. Hepatitis B virus in diabetic patients. Acta Diabetol Lat. 1980;17(3-4):207–11.
- 35. Centers for Disease Control and Prevention. Outbreaks related to healthcare: healthcare-associated hepatitis B and C outbreaks reported to CDC in 2008-2011. <u>www.cdc.gov/hepatitis/outbreaks</u>. Accessed March 29, 2012.
- 36. Centers for Disease Control and Prevention. Guide to infection prevention for outpatient settings: minimum expectations for safe care. <u>www.cdc.gov/HAI/prevent/prevention.html</u>. Accessed December 12, 2011.
- 37. Perz JF, Grytdal S, Beck S, Fireteanu AM, Poissant T, Rizzo E, Bornschlegel K, Thomas A, Balter S, Miller J, Klevens M, Finelli L. Case-control study of hepatitis B and hepatitis C in older adults: Do healthcare exposures contribute to burden of new infections? Hepatology. 2012. Epub ahead of print.

- Kondo Y, Tsukada K, Takeuchi T, Mitsui T, Iwano K, Masuko K, Itoh T, Tokita H, Okamoto H, Tsuda F. High carrier rate after hepatitis B virus infection in the elderly. Hepatology. 1993;18(4):768–74.
- 39. Mast EE, Margolis HS, Fiore AE, Brink EW, Goldstein ST, Wang SA, Moyer LA, Bell BP, Alter MJ; Advisory Committee on Immunization Practices (ACIP). A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) part 1: immunization of infants, children, and adolescents. MMWR Recomm Rep. 2005;54(RR-16):1–31.
- 40. Centers for Disease Control and Prevention (CDC). Use of hepatitis B vaccination for adults with diabetes mellitus: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep. 2011;60(50):1709–11.
- 41. Institute of Medicine. Adverse effects of vaccines: evidence and causality. Washington DC: The National Academies Press; 2012.
- 42. Douvin C, Simon D, Charles MA, Deforges L, Bierling P, Lehner V, Budkowska A, Dhumeaux D. Hepatitis B vaccination in diabetic patients. Randomized trial comparing recombinant vaccines containing and not containing pre-S2 antigen. Diabetes Care. 1997;20(2):148–51.
- 43. Bouter KP, Diepersloot RJ, Wismans PJ, Gmelig Meyling FH, Hoekstra JB, Heijtink RA, van Hattum J. Humoral immune response to a yeast-derived hepatitis B vaccine in patients with type 1 diabetes mellitus. Diabet Med. 1992;9(1):66–9.