Hepatitis B Virus Mutant Infections in Hemodialysis Patients: A Case Series

Ibironke Apata, Emory University
Duc B. Nguyen, Centers for Disease Control and Prevention
Yury Khudyakov, Centers for Disease Control and Prevention
Tonya Mixson-Hayden, Centers for Disease Control and Prevention
Jon Rosenberg, Healthcare-Associated Infections Program
Matt Zahn, Orange County Public Health Laboratory
Jane Greenko, New York State Department of Health
Ernest Clement, New York State Department of Health
Allison E. Portney, New Jersey Department of Health and Senior Services
Prathit A. Kulkarni, Centers for Disease Control and Prevention

Only first 10 authors above; see publication for full author list.

Journal Title: Kidney Medicine
Volume: Volume 1, Number 6
Publisher: Elsevier | 2019-11-01, Pages 347-353
Type of Work: Article | Final Publisher PDF
Publisher DOI: 10.1016/j.xkme.2019.07.011
Permanent URL: https://pid.emory.edu/ark:/25593/vp8kd

Final published version: http://dx.doi.org/10.1016/j.xkme.2019.07.011

Copyright information:
© 2019 Published by Elsevier Inc. on behalf of the National Kidney Foundation, Inc.
This is an Open Access work distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (https://creativecommons.org/licenses/by-nc-nd/4.0/).

Accessed July 7, 2022 6:24 PM EDT
Hepatitis B virus (HBV) transmission events in hemodialysis settings in the 1990s\(^1,2\) led the Centers for Disease Control and Prevention (CDC) to develop hemodialysis-specific HBV control guidelines that include recommendations for: (1) performing dialysis in an HBV isolation (separate) room and having dedicated staff and equipment for treatment of patients who test positive for hepatitis B surface antigen (HBsAg; ie, HBV isolation precautions), (2) monthly screening for HBsAg in HBV-susceptible patients (based on low or absent antibody to hepatitis B surface antigen [anti-HBs]) to rapidly identify newly infected patients, and (3) hepatitis B vaccination for all HBV-susceptible hemodialysis patients.\(^3\) To our knowledge, since the implementation of these guidelines, only a single hemodialysis-related HBV transmission has been reported in the United States.\(^4\)

The primary laboratory assessment for active HBV infection is HBsAg testing.\(^5\) HBsAg seroconversion among hemodialysis patients, defined as seroconversion in a patient testing HBsAg negative and subsequently testing HBsAg positive, warrants an assessment to determine the cause of seroconversion and if there have been other seroconversions in the respective dialysis clinic.\(^6\) HBV seroconversion can occur secondary to a new HBV infection or HBV reactivation (ie, an abrupt increase in HBV replication in a patient with inactive or resolved hepatitis B occurring spontaneously or due to immunosuppression).\(^7\)

False-negative HBsAg results have been known to occur rarely despite high levels of circulating HBV DNA when there are mutations in the S-gene of the HBV genome.\(^8-15\) These mutations have the potential to alter the antigenicity of HBsAg by modification of the primary, secondary, or tertiary structure; may disrupt binding of antibodies against the HBsAg; and may be transmitted de novo or arise after reactivation of occult infection.\(^5,16\) These conformational changes can allow the virus to escape the neutralizing anti-HBs antibodies induced by vaccination\(^10,17\) and can result in undetectable HBsAg by some diagnostic assays that have not yet incorporated these mutants.\(^10-14\) False-negative HBsAg test results can lead to a delay in diagnosis and implementation of essential infection control measures in hemodialysis settings.

In this case series, we describe the identification, public health investigation, and follow-up measures for 4 cases of mutant HBV infection among hemodialysis patients in 2014 to 2016. In each case, likely false-negative HBsAg
METHODS

Case Definition

A case patient was defined as a hemodialysis patient with suspected mutant HBV infection because of either: (1) a negative HBsAg result and concomitant high levels of HBV DNA, or (2) a newly detected positive HBsAg result with inconsistent HBsAg results on different HBsAg testing platforms. Patients with HBV DNA sequences demonstrating S-gene mutations were considered confirmed case-patients.

Epidemiologic Investigation

Following identification of possible HBsAg seroconversion, each hemodialysis clinic notified their local or state public health departments, which subsequently conducted public health investigations to: (1) conduct further testing of case patients’ samples for HBV markers, including sequencing of HBV DNA; (2) identify other HBV-infected patients in the clinic through screening HBsAg-negative patients with tests that could detect mutants; and (3) identify other HBV-infected patients in the clinic. The investigations involved conducting patient interviews, reviewing patient medical records, and collecting historical laboratory data, particularly results of HBV serologic tests. Recommendations for follow-up testing of potentially exposed HBV-susceptible patients included the following options: (1) complete HBV serologic panel including total antibodies to hepatitis B core antigen (total anti-HBc) with reflex to HBV DNA testing if total anti-HBc was positive, (2) HBV DNA quantitation, or (3) HBsAg performed on a platform with demonstrated ability to detect various HBsAg mutants for the case patient in question.

All data collection was conducted during the routine course of public health investigation; thus, institutional review board approval and informed consent was not required.

HBV Whole-Genome Amplification, Sequencing, and Analyses

HBV whole-genome amplification and sequencing were performed at CDC’s Division of Viral Hepatitis laboratory. HBV whole-genome sequences were amplified using 2 rounds of polymerase chain reaction and sequenced, as previously described. The detection sensitivity of this approach is 5×10^3 IU/mL, using the third World Health Organization International standard for HBV DNA. HBV genotyping was performed by nucleotide sequencing of the full-length HBV genome. For analysis of mutations, sequences were aligned with genotype-matched GenBank reference sequences.

RESULTS

Case 1

Clinical and Laboratory History

The case patient was a man in his 80s with a medical history significant for end-stage renal disease (ESRD), diabetes mellitus, and lymphoma (status post chemotherapy in 2009). At hemodialysis initiation in 2008, he was considered HBV-susceptible (anti-HBs and HBsAg negative) but failed to respond to a full HBV vaccination series. In 2009, HBV testing confirmed he was HBV-susceptible (Table 1).

In January 2012, the case patient was anti-HBs positive and HBsAg negative and considered HBV immune. In 2014, he tested negative for anti-HBs and positive for HBsAg (test platform unknown); HBV isolation precautions were implemented. Further HBV testing revealed that he had chronic HBV infection (negative immunoglobulin M [IgM] anti-HBc, positive total anti-HBc, positive hepatitis B e antigen, positive HBsAg, and high HBV DNA levels of 593,045,000 copies/mL [UltraQuant] and 101,898,000 IU/mL [AmpliPrep/cobas-Roche]. Given the unusual serologic picture of HBsAg seroconversion several months after the initial laboratory evidence of exposure to HBV infection (newly anti-HBs positive in January 2012) paired with high HBV DNA levels, infection with an HBV mutant strain was suspected. Sequencing of HBV DNA revealed a genotype H infection with an sP127L mutation in the “a” determinant region.

Public Health Investigations and Outcomes

Screening of potentially exposed hemodialysis patients in 2014 did not reveal new HBV infections. The source of HBV infection was not discovered. The case patient died in 2014 from complications of ESRD and nonalcoholic-related cirrhosis. It is unknown whether his death was related to HBV infection.

Case 2

Clinical and Laboratory History

The case patient was a man in his 60s with ESRD receiving hemodialysis since 2011 and with insulin-dependent diabetes. HBV serologic test results in October 2013 were consistent with a past HBV infection that had cleared (total [IgM and IgG] anti-HBc positive and HBsAg negative; Table 1). In October 2014, the patient was admitted to a long-term acute care facility, where routine HBV serologic testing again suggested a past resolved infection. However, HBV serologic testing performed the following month revealed a positive HBsAg result (test platform unknown), suggesting an active HBV infection. Further laboratory testing results included negative IgM anti-HBc, equivocal anti-HBs, and liver function test results within the reference range. At this point, HBV isolation precautions were initiated.

Given the unusual serologic picture of HBsAg seroconversion after evidence of a resolved HBV infection,
clinicians suspected possible infection with a mutant HBV strain and/or reactivation of previous HBV infection. Sequencing of HBV DNA revealed HBV genotype C2 and mutations sG145K and sF134S in the “a” determinant region. HBsAg testing revealed that HBsAg was positive on the Abbott ARCHITECT platform and negative on the VITROS platform. Testing of a reserved specimen collected in November 2014 showed HBV DNA levels of 33,200 IU/mL.

**Public Health Investigations and Outcomes**

Screening of potentially exposed hemodialysis patients in 2014 did not reveal new HBV infections. The source of HBV infection for the case patient was not discovered. The case patient died in 2014 of myocardial infarction.

**Case 3**

**Clinical and Laboratory History**

The case patient was a man in his early 50s with a medical history of ESRD receiving hemodialysis and human immunodeficiency virus and hepatitis C virus coinfections. At hemodialysis initiation at hospital A’s outpatient clinic in 2012, his HBV serologic test results suggested a possible past resolved HBV infection with positive total anti-HBc, positive anti-HBs, and negative HBsAg (Table 1). In December 2013, the patient lost HBV immunity and became anti-HBs negative while remaining HBsAg negative.

Repeat HBV testing for inpatient dialysis during an August 2015 hospitalization showed a weakly-reactive HBsAg result on Siemens Advia Centaur XP platform (using the Siemens HBs assay). However, subsequent HBsAg testing on VITROS platform was negative, while HBV DNA levels were 3,945,459 IU/mL. From this point onward, HBV isolation precautions were initiated for this patient.

HBsAg mutation was suspected as a possible explanation for the negative HBsAg result with concurrent high HBV DNA levels. Testing at CDC revealed positive HBsAg with Abbott ARCHITECT platform and negative HBsAg with VITROS platform, suggesting that it was a presumed HBsAg mutant strain, although attempts to sequence HBV DNA were unsuccessful due to low HBV DNA levels (500 copies/mL) at that time.

**Public Health Investigations and Outcomes**

The investigation launched in September 2015 revealed that the case patient received dialysis at 2 out-of-state hemodialysis clinics A and B in June 2015. At out-of-state hemodialysis clinic A, he was dialyzed in an HBV isolation room because of serologic test results demonstrating potential HBV infectivity (hepatitis B e antigen positive and HBsAg negative). However, he was not dialyzed in an HBV isolation room at out-of-state hemodialysis clinic B because he tested negative for HBsAg (on Siemens HBs assay, not the newer HBsII assay).

Screening of potentially exposed hemodialysis patients did not reveal new HBV infections. The case patient was treated for HBV infection and his last HBV DNA levels were very low. He continues to receive hemodialysis with HBV isolation precautions in place.

**Case 4**

**Clinical and Laboratory History**

The case patient was a man in his 70s whose medical history was notable for an orthotopic heart transplant in the 1990s and chronic kidney disease from tacrolimus toxicity. In November 2015, he initiated hemodialysis at a hospital due to acute kidney injury. HBV serologic testing results at hemodialysis initiation suggested a past HBV infection that had cleared (negative HBsAg [on VITROS ECI platform], anti-HBs levels of 169 mIU/mL, and positive total anti-HBc; Table 1).

In December 2015, the case patient was admitted to an outpatient hemodialysis clinic. A few days later, he was dialyzed in an HBV isolation room because admission laboratory testing at this clinic demonstrated an HBV infection (positive HBsAg on Siemens Advia Centaur platform HBsII assay), anti-HBs level of 121 mIU/mL, and positive total anti-HBc. HBV DNA testing revealed a level of 3,458,880 IU/mL. In February 2016, testing performed at CDC revealed HBV DNA levels of 1,560,000 IU/mL, positive HBsAg using the Abbott ARCHITECT platform, and negative HBsAg on the VITROS ECI platform. HBV DNA sequencing revealed HBV genotype D4 with a mutation sT143L in the “a” determinant region.

**Public Health Investigations and Outcomes**

During January to April 2016, the patient received hemodialysis at 3 different hospitals’ inpatient dialysis units, without application of HBV isolation precautions, due to false-negative HBsAg results. Screening of potentially exposed hemodialysis patients did not reveal new HBV infections and the source of the case patient’s HBV infection was not found. In February 2016, the case patient was started on tenofovir for treatment of hepatitis B. He died several months later from complications of other underlying illnesses.

**DISCUSSION**

Four cases of mutant HBV infections in US hemodialysis patients are presented in this report; in 3 cases, the mutations were confirmed using molecular sequencing. These cases demonstrate the varying ability of different HBsAg assays to detect mutant HBV strains, as has been previously described,11-15,19 and highlight the potential public health risk to hemodialysis patients.13,15 In some instances, patients who had had active HBV infection diagnosed had subsequent false-negative HBsAg test results (eg, at a different health care facility), which led to
Table 1. Demographic and Clinical Characteristics of 4 HBV Infection Cases (3 laboratory confirmed; 1 suspected) With HBsAg Mutation Detected in the US Hemodialysis Setting 2014-2016

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>State where case was identified</td>
<td>California</td>
<td>California</td>
<td>New York</td>
</tr>
<tr>
<td>Age (rounded by decade), y</td>
<td>80</td>
<td>60</td>
<td>50</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td><strong>Medical History</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td>ESRD; diabetes mellitus; lymphoma (s/p chemotherapy in 2009); coronary artery disease</td>
<td>ESRD; HBV infection (cleared); diabetes mellitus</td>
<td>ESRD; HBV infection (cleared); HIV; chronic HCV infection</td>
</tr>
<tr>
<td>Year of HD initiation</td>
<td>2008</td>
<td>2011</td>
<td>2012</td>
</tr>
</tbody>
</table>

| **Laboratory Data** | | | |
| HBV serology | | | |
| First known negative HBsAg | 7/2010 | 5/2014 | 6/2012 | 11/2015 |
| Last known negative HBsAg | 7/2012 | 10/2014 | 7/2015 | 11/2015 |
| First known positive HBsAg | 1/2014 | 11/2014 | 8/2015 | 12/2015 |
| First known negative anti-HBs | 12/2010 | 7/2014 | 12/2013 | Unknown |
| Last known negative anti-HBs | 7/2011 | 7/2014 | 8/2015 | Unknown |
| First known positive anti-HBs (before HBsAg seroconversion) | 1/2012 (negative in 1/2014) | 8/2014 | 10/2013 | 11/2015 |
| HBV DNA level (date) | 593,045,000 copies/mL (2/2014) | 33,200 IU/mL (11/2014) | 3,945,000 copies/mL (8/2015) | 3,900,000 copies/mL (2/2016) |
| Highest known ALT/AST (date) | 19/54 (May 2013) | Unknown | 241/148 (March 2013) | 18/51 (12/2015) |
| HBsAg testing by platform (dates) | | | |
| Other HBV testing | | | |
| HBV genotype | H | C2 | Not tested | D4 |
| HBV molecular sequencing results | S gene mutation at P127L | S gene mutations at G145K and F134S | Not tested | S gene mutation at T143L |

| **Public Health Investigation** | | | |
| Last HBV vaccination series | 2010 | No reported history of vaccination | 8/2015 | No reported history of vaccination |
| Potential exposures | Travel history (dates) | | | |

(Continued)
Table 1 (Cont’d). Demographic and Clinical Characteristics of 4 HBV Infection Cases (3 laboratory confirmed; 1 suspected) With HBSAg Mutation Detected in the US Hemodialysis Setting 2014-2016

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Died 2014, cause:</td>
<td>Died 2014, cause:</td>
<td>Alive</td>
<td>Died 2016, cause:</td>
</tr>
<tr>
<td>complications of HD</td>
<td>complications of HD</td>
<td></td>
<td>complications of multiple</td>
</tr>
<tr>
<td>and myocardial infarction</td>
<td>and myocardial infarction</td>
<td></td>
<td>underlying illnesses</td>
</tr>
</tbody>
</table>

**Clinical events and procedures (dates)**
- Hospitalization (2013): multiple invasive procedures including HD, surgery
- Hospitalization (2015): multiple invasive procedures including surgery and HD

**Patient Outcome**

<table>
<thead>
<tr>
<th>Clinical outcome</th>
<th>Died 2014, cause:</th>
<th>Died 2014, cause:</th>
<th>Alive</th>
<th>Died 2016, cause:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died 2014, cause:</td>
<td>complications of HD</td>
<td></td>
<td></td>
<td>complications of multiple</td>
</tr>
<tr>
<td>and myocardial infarction</td>
<td>and myocardial infarction</td>
<td></td>
<td>underlying illnesses</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** ALT, alanine aminotransferase; AST, aspartate aminotransferase; CKD, chronic kidney disease; ESRD, end-stage renal disease; HBc, hepatitis B core antibody; HBs; hepatitis B surface antibody; HBSAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HD, hemodialysis; HIV, human immunodeficiency virus.

*Age rounded to the nearest decade for deidentification purposes.*

The prevalence of mutant HBV strains among hemodialysis patients has not been established. These infections might be rare in the hemodialysis population. However, there is a risk that these infections are undetected.

Considerations for monitoring of HBV-susceptible dialysis patients are summarized in Figure 1. Clinicians should be aware that in some instances it is possible for a patient to have HBV infection in the absence of detectable HBSAg. To date, there does not seem to be a consistent clinical picture that should prompt suspicion of this condition. However, the possibility of a false-negative HBsAg test result should be considered when laboratory test results are inconsistent with each other or with the clinical picture. In such circumstances, quantitative HBV DNA testing should be performed to evaluate for possible active HBV infection. HBSAg assays that use monoclonal antibodies to capture HBsAg may produce false-negative results in the presence of altered HBsAg due to conformational changes induced by various S-gene mutations.

In hemodialysis settings, routine use of HBSAg assays that use a pool of well-characterized polyclonal antibodies to detect the most commonly occurring S-gene mutants should be considered. At the time of drafting this report and to our knowledge, such tests (HBSag assays) performed on major automated platforms currently available in the United States included the Abbott ARCHITECT instrument, the ETI-MAK-2 PLUS, and the Siemens Advia Centaur XP or XPT instrument using the newer HBSII assay first available in the United States in 2015. The Siemens Advia Centaur XP or XPT using older HBS assays (before 2015) remain available and may not detect HBSAg mutations. Of note, while the ETI-MAK-2 PLUS enzyme-linked immunosorbent assay detected a strain with sG145R mutation in 2017, it failed to detect a strain with multiple mutations in a 2010 investigation. It is important that dialysis providers report HBV seroconversions and suspected mutant HBV infections to the appropriate public health authority.

In all 4 cases presented in this report, mutant HBV infection could have arisen with reactivation of an occult HBV infection or been acquired de novo. Residual HBV DNA remains integrated in host hepatocytes after acute infection even when there is serologic evidence of previously resolved (ie, cleared) or inactive chronic infection. Rarely, severe immunosuppression can promote renewed HBV replication, or reactivation, among persons with inactive chronic infection. Moderate immunosuppression can promote renewed HBV replication, or reactivation, among persons with inactive chronic infection. Rarely, severe immunosuppression can promote reverse seroconversion ( reappearance of HBSAg and circulating HBV DNA) and reactivation among persons with previously resolved infection. Patient 1 had HBV genotype H, which is prevalent in some countries outside the United States, including Mexico, and is known to frequently cause occult HBV infection with low-level viremia. Patients 2 and 3 had serologic evidence of previous HBV infection (total anti-HBc positive) before initiation of hemodialysis; therefore, their HBSAg seroconversions could have been the result of reactivation of
Figure 1. Considerations for hepatitis B monitoring of hepatitis B virus (HBV)-susceptible hemodialysis (HD) patients. * Dialysis providers should ensure that routine hepatitis B surface antigen (HBsAg) testing is performed with assays that can detect the commonly occurring HBsAg mutants. At the time of drafting this report and to our knowledge, such tests on major automated platforms currently available in the United States included those performed on the Abbot ARCHITECT instrument, the ETI-MAK-2 PLUS, and the Siemens Advia Centaur XP or XPT instrument using the newer HBsII assay first available in the United States in 2015 (the older HBs assay remains available), and the ETI-MAK-2 PLUS. It is important that dialysis providers report HBV seroconversions and suspected mutant HBV infections to the appropriate public health authority. † Hepatitis B susceptible is defined as patients negative for total antibodies to hepatitis B core antigen (total anti-HBc), hepatitis B surface antibody (anti-HBs), and HBsAg. HBsAg testing may also be warranted for patients with past resolved hepatitis B (total anti-HBc positive, HBsAg negative) with immunosuppression. ‡ The possibility of a false-negative HBsAg test result should be considered when laboratory test results are inconsistent with each other or with the clinical picture. In such circumstances, quantitative HBV DNA testing should be performed to evaluate for possible active HBV infection. Mutant HBV infections should be suspected in patients who test HBsAg negative and concurrently test positive for HBV DNA at high levels. Follow-up testing of HD patients potentially exposed to mutant HBV strains should include tests that can reliably identify the infection; these tests may include quantitative HBV DNA, total anti-HBc with follow-up HBV DNA if positive, or use of a HBsAg assay known to detect mutant HBV strains.

resolved HBV infection with mutant HBV strains rather than new infection. Patient 4 likely had active infection at the time of hemodialysis initiation with a false-negative initial HBsAg result.

To our knowledge, there has been no documented hemodialysis-related transmission of a mutant strain of HBV. In these 4 cases and a recent single case report from Nebraska, no HBV transmission was identified. Although the exact number of potentially exposed patients screened in the 4 investigations was not available retrospectively, we estimate from dialysis center patient census data that more than 600 may have been potentially exposed. Although cases of mutant HBV infection among hemodialysis patients may be uncommon, their management and investigation can incur substantial costs and burden to public health and clinical providers. Loss of information during patient transfers between health care settings further complicates the issue. Strict adherence to recommended infection control practices for all patients, including applying HBV isolation precautions when dialyzing patients with HBV infection, is integral to preventing the transmission of mutant HBV infections. Currently there is insufficient evidence to recommend isolating patients with mutant HBV infection from patients with wild-type HBV infection.

Public health providers should recommend follow-up testing of hemodialysis patients potentially exposed to mutant HBV strains with tests that can reliably identify the infection; these tests may include quantitative HBV DNA, total anti-HBc with follow-up HBV DNA if positive, or use of a HBsAg assay known to detect mutant HBV strains. Until more is known about the risk for HBV mutant infection in individuals with evidence of natural or vaccine-induced immunity, patients with anti-HBs should be included in the group that undergoes testing following exposure. In addition, dialysis providers should ensure that routine HBsAg testing is performed with assays that can detect the commonly occurring HBsAg mutants.

ARTICLE INFORMATION

Authors’ Full Names and Academic Degrees: Ibironke W. Apata, MD, Duc B. Nguyen, MD, Yury Khudyakov, PhD, Tonya Mixson-Hayden, PhD, Jon Rosenberg, MD, Matt Zahn, MD, Jane Greenko, MPH, Ernest Clement, MSN, Allison E. Portney, MPH, Prathit A. Kulkarni, MD, Maura Comer, MPH, Eleanor Adams, MD, Saleem Kamili, PhD, Priti R. Patel, MD, and Anne C. Moorman, MPH.

Authors’ Affiliations: Centers for Diseases Control and Prevention (IWA, DBN, YK, TM-H, PAK, SK, PRP, ACM); Emory University
School of Medicine, Division of Renal Medicine, Atlanta, GA (IWA); Healthcare-Associated Infections Program, California Department of Public Health (JR); Orange County Public Health, Santa Ana, CA (MZ); New York State Department of Health, Central Islip (JG); New York State Department of Health, Albany, NY (EC); Communicable Disease Service, New Jersey Department of Health, Trenton (AEP, PAK); School of Public Health, Rutgers University, Newark, NJ (AEP); Florida Department of Health, Tallahassee, FL (MC); and New York State Department of Health, New Rochelle, NY (EA).

Current affiliation for DBN: Piedmont Athens Regional Medical Center, Athens, GA.

Address for Correspondence: Ibironke W. Apata, MD, US Centers for Disease Control and Prevention; 1600 Clifton Rd, Mailstop A-31, Atlanta, GA 30322. E-mail: iba2@cdc.gov

Authors’ Contributions: Research idea and study design: IWA, DN, SK, PRP, ACM; data acquisition: YK, TM-H, JR, MZ, JG, EC, AEP, PAK, MC, EA; data interpretation: YK, TM-H, SK; supervision or mentorship: PRP, SK. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Support: None.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Acknowledgements: The authors thank all those in the health departments who contributed to the public health investigations.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the opinion of the CDC. Use of trade names and commercial source is for identification only and does not constitute endorsement by the US Department of Health and Human Services, or the US CDC.

Peer Review: Received February 27, 2019. Evaluated by 2 external peer reviewers, with direct editorial input from an Associate Editor and the Editor-in-Chief. Accepted in revised form July 20, 2019.

REFERENCES