Impact of a vaccine intervention on county-level rates of acute hepatitis B in West Virginia, 2011–2018

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Abstract

The rate of acute hepatitis B in West Virginia (WV) has been increasing since 2006. To reduce new infections, WV implemented a vaccine intervention (WV Pilot Project), which provided over 10,000 doses of hepatitis B vaccine to at-risk adults in 18 counties. The objectives of this study were to describe yearly changes in acute hepatitis B incidence and assess county-level impact of the WV Pilot Project using geospatial methods. County rates of acute hepatitis B and vaccine doses per 100,000 population were visualized biannually from 2011 to 2018. Local indicators of spatial autocorrelation were used to detect county-level clustering. Significant differences in the median rate of acute hepatitis B pre and post intervention in counties receiving vaccine were evaluated using Wilcoxon signed-rank test and bootstrapping. A Bland-Altman graph visualized significant differences in county-level rates of acute hepatitis B before and after the WV Pilot Project compared to the statewide estimate. Analyses identified significant geographic clustering of acute hepatitis B in southern WV across all four time-periods. Nine of the 18 (50%) counties receiving vaccine had significant declines in acute hepatitis B incidence compared to the statewide mean difference estimate. Findings suggest that increased dissemination of hepatitis B vaccine through local health departments and existing harm reduction services can reduce the incidence of acute hepatitis B in states such as WV, which have been disproportionately affected by substance misuse.

Keywords

Hepatitis B; Hepatitis B vaccine; Cluster analysis; Vaccine intervention

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1. Introduction

Hepatitis B is a liver disease resulting from infection with the hepatitis B virus (HBV). Complications of infection include fulminant hepatitis, cirrhosis, liver failure, hepatocellular carcinoma, and death (Ganem and Prince, 2004). The virus is spread through contact with blood and body fluids, is highly infectious, and environmentally stable on hard surfaces for more than seven days (Than et al., 2019). In the United States, major risk factors for infection include sexual exposure and injection drug use (Centers for Disease Control and Prevention, 2015; Schillie et al., 2018). People who inject drugs (PWID) are at an increased risk of acquiring hepatitis B infections through sharing of equipment to inject drugs and sexual contact (Schillie et al., 2018; Walsh et al., 2014). Estimates of the noninstitutionalized civilian United States population indicate that approximately 20 to 27% of PWID have lab markers consistent with past or present HBV infection compared to just 4.6% in the general population (Ioannou, 2011; Shing et al., n.d.).

Over the past three decades, the incidence of new HBV infections in the United States has declined 75% due to universal vaccination of infants at birth, catchup vaccinations of adolescents, and human immunodeficiency virus (HIV) prevention efforts in men who have sex with men and PWID (Van Buren and Schaffner, 1991; Centers for Disease Control and Prevention, 1999; Centers for Disease Control and Prevention, n.d.-a). However, the increase in substance misuse and injection drug use over the past decade has resulted in a resurgence of acute cases of hepatitis B among at-risk groups especially in parts of Appalachia (Schillie et al., 2018; Racho, n.d.; Harris et al., 2016). Despite the decreasing trend nationwide, the rate of acute HBV infections in West Virginia (WV) has steadily increased since 2006. In 2016, WV's rate of acute HBV infections was 14.7 per 100,000 population, almost 15 times the national average of 1 per 100,000 population (Centers for Disease Control and Prevention, n.d.-a; Anil and Simmons, 2016). Appalachian states, in particular Kentucky, Tennessee, and West Virginia, have been disproportionately affected by opioid misuse (Harris et al., 2016). From 2009 to 2013, the three states reported a 114% increase in the number of reported acute hepatitis B cases (Harris et al., 2016). The majority of these cases occurred in non-Hispanic whites, ages 30 to 39, with 75% of all cases reporting injection drug use as a risk factor (Harris et al., 2016). From 2012 to 2016, injection and non-injection drug use were the two most commonly reported risk factors among people with acute hepatitis B in WV (Anil and Simmons, 2016; West Virginia Office of Epidemiology and Prevention Services, 2018).

The CDC’s Advisory Committee on Immunization Practices (ACIP) currently recommends adults with risk factors, including recent or current injection drug use, receive hepatitis B vaccination due to increased risk for HBV infection (Schillie et al., 2018).

In January 2013, the West Virginia Bureau for Public Health, Office of Epidemiology and Prevention Services (WV OEPS) initiated the West Virginia Hepatitis B Vaccination Pilot Program (WV Pilot Project), part of a larger CDC funded HepB Vaccine Pilot Program implemented in 14 local and state health departments nationwide (Bridges et al., 2019). The goal of the two-year project in WV was to decrease the number of new HBV infections by providing over 10,000 doses of vaccine to at-risk adults in 18 counties with higher rates of
acute hepatitis B (Harris et al., 2016; West Virginia Office of Epidemiology and Prevention Services, 2015). Vaccine was administered to adults considered at-risk for HBV infection at sites where universal HBV vaccination is recommended including HIV clinics, local health department (LHD) STD clinics, and LHD community partnerships with local substance use treatment centers and correctional facilities (Bridges et al., 2019; West Virginia Office of Epidemiology and Prevention Services, 2015; Mast et al., 2006).

The objectives of this study were to describe yearly changes in county-level acute hepatitis B incidence and assess the impact of the WV Pilot Project using geospatial methods.

2. Methods

For this retrospective study, 2011–2018 acute hepatitis B data and the number of HBV vaccine doses provided to WV Pilot Project counties were obtained from WV OEPS. Acute hepatitis B case counts by county are the result of cases identified through the Nationally Notifiable Disease Surveillance System and were limited to those meeting the CDC's confirmed acute hepatitis B case definition; defined as “a case that meets the clinical case definition, is laboratory confirmed, and is not known to have chronic hepatitis B” (Centers for Disease Control and Prevention, n.d.-b). Case data were incorporated into two-year estimated rates based on the years of vaccine distribution to counties participating in the WV Pilot Project; prior to vaccine distribution (2011–2012), during vaccine distribution (2013–2014 and 2015–2016), and following vaccine distribution (2017–2018). Geospatial methods, including mapping and cluster analyses, were used to examine changes in the distribution of acute hepatitis B in WV in relation to vaccination efforts. County rates were estimated in ArcMap 10.5.1 (ESRI Redlands, CA) using mid-year U.S. Census population estimates and joined to a WV counties shape file (U.S. Census Bureau Population Division, n.d.; WV GIS Technical Center, 2019). Rate per 100,000 population of acute hepatitis B for each period were visualized using a quartile classification to highlight spread of the data, with darker colors indicating higher rates of acute hepatitis B. Vaccine doses per 100,000 population were calculated by dividing the total number of doses received by each county by their total population and multiplying by 100,000. The resulting rates were visualized using graduated symbols, with larger symbols indicating greater distribution of vaccine doses.

Local Empirical Bayes Moran’s I and local indicators of spatial autocorrelation (LISA) maps were included to identify county-level acute hepatitis B clusters during each time-period using GeoDa 1.12 (GeoDa Center, AZ). To perform the cluster analyses, two-year case counts were set as the event variable, and midyear county-level census estimates were set as the base variable. A queen's contiguity weight was specified to maximize neighbors involved and cluster analyses results were permuted 99,999 times to increase robustness of analyses and identify statistically significant areas of high county-level acute hepatitis B rates (Hendricks and Mark-Carew, 2017). Statistical significance was assessed at the 0.05 alpha level. The null hypothesis for the local cluster analysis was a random pattern of county-level rates of acute hepatitis B with no local spatial association (Anselin, 1995).

A Wilcoxon signed-rank test was used to detect a significant change in the median rate of acute hepatitis B per 100,000 population in WV Pilot Project counties before (2011–2014)
and after (2015–2018) the intervention. Due to the small sample size of counties included in the analysis, bootstrapping was used to estimate the median rate change and 95% confidence interval, and to validate estimates from the Wilcoxon signed-rank test. A Bland-Altman graph, which plots the difference between two paired measurements against its mean, was used to visualize significant differences in county-level rates of acute hepatitis B per 100,000 population in all WV counties before and after the WV Pilot Project (Giavarina, 2015).

To assess statistical significance at the 0.05 alpha level, the statewide mean difference and corresponding 95% confidence interval (CI) were plotted. Counties with differences in rates of acute hepatitis B outside the upper or lower bounds of the 95% CI were considered significant.

3. Results

County-level rates of acute hepatitis B per 100,000 population and the rate of vaccine doses per 100,000 are displayed in Fig. 1 (Data available in Supplementary Files 1 and 2). Overall, rates of acute hepatitis B were highest in southern WV across the four time-periods. Zero case counts were present in 21 of 55 (38%) WV counties in 2012–2013, decreasing to 10 of 55 (18%) by 2017–2018 (Supplementary File 1). The highest rates of acute hepatitis B were observed in the southern counties, while the lowest rates were observed in northern counties. Over the four time-periods, progressive increases in rates of acute hepatitis B were observed in southern adjacent counties. Vaccine doses per 100,000 population ranged from 54.1 to 4486.4. Vaccine distribution was limited to 18 counties based upon population size and rates of acute hepatitis B (Supplementary File 2). The rate of vaccine doses per 100,000 indicates the magnitude of vaccine doses distributed in relation to the county population with higher rates indicating a larger proportion of the population potentially receiving vaccine.

County-level clustering in rates of acute hepatitis B in relation to vaccine doses per 100,000 population are displayed in Fig. 2. Analysis of county-level clustering takes into account rates in adjacent counties and identifies definite hotspots and coldspots or groups of counties (cluster) with high or low rates of acute hepatitis B. While counties in clusters changed somewhat over each time period, in general, hotspots (high-high clusters) indicating statistically significant clustering of high county-level rates of acute hepatitis B, were detected in southern WV during all time-periods (n = 7 in 2011–2012, n = 9 in 2013–2014, n = 9 in 2015–2016, and n = 8 in 2017–2018). Over the four time-periods, the high-high clusters increased to include adjacent counties to the north and west, indicating progressive expansion into counties neighboring the initial multi-county hotspot. Of the nine counties identified in the 2013–2014 hotspot, seven (78%) received vaccine doses. Cold spots (low-low clusters) indicating statistically significant clustering of low county-level rates of acute hepatitis B, were detected in northern and eastern WV counties during all time-periods (n = 10 in 2011–2012, n = 9 in 2013–2014, n = 10 in 2015–2016, and n = 9 in 2017–2018).

The median hepatitis B rate difference before and after the WV Pilot Project (calculated using the Wilcoxon signed-rank test and bootstrapping) for participating counties was an increase of 1.21 per 100,000 population (95% CI, –13.29, 21.93) following the intervention, however the increase was not significant (p-value = .90). Due to the small sample size of WV Pilot Project counties included in the analysis (n = 18), bootstrapping was used to
estimate the median rate difference along with a 95% CI. This resulted in a median rate
decrease of -4.16 of acute hepatitis B cases per 100,000 population (95% CI, – 33.07, 19.36)
following the intervention. The Bland-Altman mean difference analysis found the statewide
mean difference before and after the intervention was an increase of 10.80 cases per 100,000
population (95% CI, 0.80, 20.79). County-level differences in rates of acute hepatitis B
before and after the WV Pilot Project and the statewide mean difference and 95% CI are
displayed in Fig. 3 (Data available in Supplementary File 3). Twelve of the 18 WV Pilot
Project counties (67%) had a rate difference lower than the statewide estimate indicating
a reduction in the rate of acute hepatitis B following vaccine distribution compared to the
statewide mean difference. Of these, nine (50%) had statistically significant declines as
indicated by a rate difference below the lower bound of the statewide 95% CI. However,
four (22%) of the 18 WV Pilot Project counties had statistically significant increases in rates
of acute hepatitis B following the intervention compared to the statewide mean difference.
Of the 37 non-Pilot Project counties, 8 (22%) experienced a statistically significant decrease
and 11 (30%) a statistically significant increase as indicated by values below and above the
95% CI respectively.

4. Discussion

In this study, we found the incidence rate of acute hepatitis B increased steadily across
WV with rates peaking in 2015–2016 and then slightly declining in 2017–2018. One of
the most notable findings of this study was the shift in counties identified as hotspots
through cluster analyses across the four time-periods. This shift suggests counties at risk
for HBV transmission are changing and additional efforts are needed in emerging hotspots.
Two counties identified as hotspots in all four time-periods did not receive vaccine through
the WV Pilot Project demonstrating a missed opportunity to vaccinate at-risk individuals.
All counties identified as a hotspot in the 2017–2018 cluster analysis may benefit from
enhanced hepatitis B surveillance and increased efforts to prevent new HBV infections.

While the median difference calculated using both the Wilcoxon signed-rank test and
bootstrapping estimates found non-statistically significant changes in the median rate of
acute hepatitis B in WV Pilot Project counties, the median difference estimate obtained
via bootstrapping indicates a decrease of - 4.16 cases per 100,000 population (95% CI,
– 33.07, 19.36) after WV Pilot Project implementation. Due to the small sample size of
counties included in the analysis, the bootstrapping estimate most likely provides a better
approximation compared to the estimate obtained from the Wilcoxon signed-rank test.

Another notable finding was the significant decrease in the rate difference before and after
the WV Pilot Project (as indicated by values below the statewide mean difference 95% CI)
in nine participating counties - Berkeley, Hancock, Harrison, Jefferson, Mason, McDowell,
Mercer, Mingo, and Wyoming. While eight of the 37 (22%) non-Pilot Project counties
experienced a similar decrease, a significant decrease was observed in 50% of WV Pilot
Project counties. These findings indicate that the WV Pilot Project may have reduced the
number of new HBV infections in at-risk adults especially in the southern part of WV where
the greatest acute hepatitis B rate differences were observed. In total, 12 of the 18 WV
Pilot Project counties had acute hepatitis B rate differences below the WV mean difference
and while not all of the results were statistically significant, these findings point to the effectiveness of the WV Pilot Project in reducing or stabilizing rates in these counties.

From 2013 to 2015, the WV Pilot Project administered over 10,000 doses of HBV vaccine to adults considered at risk for HBV infection in 18 counties. At-risk adults were reached through local health department STD clinics, correctional facilities, substance use treatment centers, and HIV care facilities (Bridges et al., 2019; West Virginia Office of Epidemiology and Prevention Services, 2015). Completion of the three-dose series was cited as a challenge throughout the project (West Virginia Office of Epidemiology and Prevention Services, 2015). In WV, of those who initiated the vaccine series, 59% received the second dose, and 32% completed the three-dose series (West Virginia Office of Epidemiology and Prevention Services, 2015). Although some protection is conferred through receipt of one or two doses of hepatitis B vaccine, people who use drugs may have an altered immune response and therefore less likely to be protected after receiving just one or two doses (Tran et al., 2012). Failure to complete the series, coupled with lower immune response may have resulted in less at-risk individuals protected against HBV infection, thus reducing the impact of the WV Pilot Project.

4.1. Strength and limitations

Strengths of this study include the use of geospatial modeling, including cluster analyses, to examine trends in acute hepatitis B over eight years in WV. Hotspots identified in the cluster analyses indicate a statistically significant high county rate of acute hepatitis B in relation to the surrounding counties representing a non-random pattern. Another strength is the use of bootstrapping, which provides a better approximation of the median pre and post intervention due to the small sample size of counties included in the estimation. Finally, the use of Bland-Altman analysis to calculate and plot the difference in rates of acute hepatitis B before and after the WV Pilot Project for comparison with the statewide mean difference and 95% CI, provides a method to assess if the rate differences for individual counties were statistically significant.

Potential limitations of this study include a lack of county-specific data regarding the number of participants who completed vaccination through the WV Pilot Project. However, vaccine doses per 100,000 population in each county is an indication of the volume of vaccine distributed in relation to the total population for that county. It is also unknown if people who initiated or completed the series developed immunity as post-serological testing was either not done or data were not available. Previous studies have shown that immune response to hepatitis B vaccine is lower in people with altered immune function including PWID, so not everyone vaccinated may have developed immunity (Tran et al., 2012). Additionally, the 2018 acute hepatitis B case counts from WV OEPS used in all calculations were provisional and thus subject to change. Forty-four of the 55 WV counties have populations under 55,000 making the rates easily influenced by small case counts. Combined time-periods were used in order to stabilize rates, but small counties were still subject to large rates based on few cases of acute hepatitis B. Finally, many factors may have resulted in either an increase or decrease in the incidence rates of acute hepatitis B infections between the time-periods therefore making it difficult to determine the overall
impact the WV Pilot Project on incidence rates. The first WV harm reduction program with syringe exchange opened in 2015 after the WV Pilot Project, and in 2017 there were 12 such programs (White Paper: The Need for Harm Reduction Programs in West Virginia, 2017). Overall efforts to reduce the effects of substance misuse in WV may have reduced the number of new acute hepatitis B infections. However, to our knowledge there have been no new statewide hepatitis B vaccine initiatives since the WV Pilot Project.

5. Conclusion

Hepatitis B is a vaccine preventable disease, yet many at-risk adults remain unvaccinated and susceptible to infection. Ongoing harm reduction efforts, including syringe exchange programs, STD clinics, and LHD partnerships with community programs serving at-risk adults, should incorporate hepatitis B testing and vaccination to reduce the number of new HBV infections. Geographic information systems can guide surveillance efforts, placement of prevention services, and direct future interventions by identifying trends and changes in new HBV infections in WV.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.
West Virginia county-level rates of acute hepatitis B from 2011 through 2018 and vaccine doses per 100,000 population. Darker colors and larger circles indicate a higher rate of acute hepatitis B and vaccine doses per 100,000 population respectively.
* The WV Pilot Project concluded in 2015.
Fig. 2.
West Virginia acute hepatitis B cluster analyses and vaccine doses per 100,000 population. High-high counties, depicted in black, are hotspots or a group of counties with high rates of acute hepatitis B. Low-low counties, depicted in dark grey, are coldspots or a group of counties with low rates of acute hepatitis B. High-low and low-high counties are spatial outliers indicating a county with a high rate surrounded by counties with low rates or a county with a low rate surrounded by counties with high rates of acute hepatitis B.

* The WV Pilot Project concluded in 2015.
Fig. 3.
Bland-Altman graph depicting the difference in acute hepatitis B rates per 100,000 population in WV Pilot Project and non-Pilot Project counties compared to the mean difference for all of West Virginia before and after WV Pilot Project implementation. Values above or below the 95% CI have statistically significant differences greater than or less than the mean difference for West Virginia.