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Hepatitis B, C Virus and HIV Co-infection Among Reported Female Cases in South Carolina, 2004 - 2011: An Epidemiological Analysis of Pregnancy Outcomes

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HEPATITIS B, C VIRUS AND HIV CO-INFECTION AMONG REPORTED FEMALE CASES IN SOUTH CAROLINA, 2004 - 2011: AN EPIDEMIOLOGICAL ANALYSIS OF PREGNANCY OUTCOMES

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DEDICATION

To my mother, Efua, my late father, Kofi, my godmother, Rosalind and my siblings.

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ABSTRACT

HIV, hepatitis B and C virus (HBV, HCV) are three of the most common blood-borne infections and they continue to be a major public health problem in the United States (US) and globally. It is not well understood if maternal infection with either HBV or HCV has an adverse impact on pregnancy outcomes as findings from previous studies have provided some mixed results. The overall goal of this study was to assess the risk of preterm birth, low birth weight (LBW), small for gestational age (SGA) and admission into neonatal intensive care unit (NICU) for babies born to HBV- and HCV-infected women. To this end, our objectives were to 1) describe the epidemiology of HBV and HCV and their co-infection with HIV in South Carolina (SC), 2) assess the spatial distribution of HCV infection in SC, and 3) estimate the risk of preterm birth, LBW, SGA, NICU admission in babies born to hepatitis-infected mothers. Linked data from multiple sources for years 2004 to 2011 was utilized and descriptive statistics, Bayesian spatial and logistic regression analyses were conducted to evaluate the objectives of the study. Results revealed substantial variation in the epidemiology of these infections among females in SC to include an emerging epidemic of HCV infections among young white females. The spatial analysis identified Charleston, Darlington, Florence, Georgetown, Greenville, Horry, Oconee, McCormick and Richland counties as high-risk counties for HCV infection. Lastly, results from the logistic regression analysis supported the fact that low birth weight is independently associated with HCV infection during pregnancy, specifically, newly diagnosed mothers. Our

findings are useful for providers to advise infected expectant mothers on the potential risk to their baby. Local and state public health officials can also use these data for taking further public health action and make informed decisions on how to allocate limited resources to help prevent and reduce the spread on HCV and HBV infections within the state.

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List of Abbreviations

AIDS ..... Acquired Immune Deficiency Syndrome

CDC ..... Centers for Disease Control and Prevention

CHESS ..... Carolina's Health Electronic Surveillance System

DNA ..... Deoxyribonucleic Acid

DADE ..... Division of Acute Disease Epidemiology

DAODAS ..... Department of Alcohol and Other Drug Abuse Services

eHARS ..... Enhanced HIV/AIDS Reporting System

HAART ..... Highly Active Antiretroviral Treatment

HIV ..... Human Immunodeficiency Virus

HBV ..... Hepatitis B Virus

HCV ..... Hepatitis C Virus

HCC ..... Hepatocellular Carcinoma

ICD-9 ..... International Classification of Diseases Ninth Revision

SCDHEC ..... South Carolina Department of Health and Environmental Control

STI ..... Sexually Transmitted Infection

MTCT ..... Mother-to-Child Transmission

NICU ..... Neonatal Intensive Care Unit

ORS ..... Office of Research and Statistics

WHO ..... World Health Organization

CHAPTER 1

BACKGROUND AND OBJECTIVES

1.1 Background

Human Immunodeficiency Virus (HIV), hepatitis B and C virus (HBV, HCV) are three of the most common blood-borne infections and are a major public health problem in the United States (US) and globally. Collectively, they cause significant morbidity and mortality from chronic liver diseases, hepatocellular carcinoma (HCC) and opportunistic infections among infected individuals [1-5]. According to the World Health Organization (WHO), approximately 2 billion people worldwide are infected with HBV and more than 240 million of these people live with chronic HBV infection [6]. Likewise, HCV is widespread; the disease kills 350,000 people per year (1% of all deaths worldwide) and there are an estimated150 million people that are chronically infected [7, 8].

1.1.1 Epidemiology of HBV, HCV and HIV Co-infection

Hepatitis simply refers to inflammation of the liver. HBV and HCV infection primarily affects the liver and is usually symptomless for decades. Acute infection with HBV or HCV is short-term (6 months) whereas chronic infection is a lifelong illness that occurs if the infection remains in the body beyond six months. If untreated, the virus causes considerable damage to the liver that can lead to cirrhosis, liver cancer and death. Patterns of HBV infection vary worldwide and its geographic distribution to the prevalence of certain risk factors for HBV infection. In regions of high endemicity such

as Asia and sub-Saharan Africa where HBV prevalence is greater than 8% [9], major risk factors for HBV infection include perinatal transmission, blood transfusions and sexual contact. On the contrary, in regions of low endemicity, intravenous drug use is considered to be leading risk factor for HBV infection. Global variation in HCV prevalence is also evident, as the disease tends to be higher in developing countries, especially those in North Africa. For instance, with nearly 15% of population infected, Egypt has one of worst affected populations in the world [8, 10].

In the US, a region where HBV and HCV infections are considered to be low in prevalence, the Centers for Disease Control and Prevention (CDC) reported 10, 515 new sentinel cases of chronic HBV and 25,974 new sentinel cases of chronic HCV in 2010. It is believed that between 1.25 million and 2 million individuals are infected with HBV in the US, more than 50% of which are of Asian ethnicity [11, 12]. When we consider incarcerated, homeless and active military persons otherwise not found in population-based surveys, the numbers for those affected by HBV and HCV is significantly higher. One study conservatively cited 5.2 million as the true number of persons living with HCV within the US [13]. Within the state of South Carolina (SC), surveillance data for HBV and HCV infections are routinely reported to the Division of Acute Disease Epidemiology (DADE). Between 2004 and 2008, an average of 661 reports of chronic HBV and nearly 20,000 cases of chronic HCV was reported to DADE between the years of 2000 and 2005 [14]. For these same periods, 601 cases of acute HBV and 70 cases of acute HCV infections were reported to DADE. It is worthy to note that because new HCV case are usually asymptomatic, acute HCV infections are rarely identified or reported.

Since its discovery in 1981, at least 60 million people have been infected with HIV and nearly 25 million have died of AIDS [15]. The devastating effect of this pandemic continues to pose a significant public health threat particularly in developing countries; nevertheless, in developed countries where there is increased access to highly active antiretroviral treatment (HAART) for disease management, HIV is no longer the death sentence it used to be. In fact, when detected early, the life expectancy of an HIV infected individual can be restored to near normal through successful HAART treatment. For this reason, HIV is now considered a manageable chronic condition and HIV infected individuals on continued therapy have an improved quality of life and are able to live long productive lives [16, 17]. HIV infected persons are disproportionately affected by viral hepatitis: As of 2009, an estimated 1.2 million persons aged 13 and older residing in the US are living with a diagnosis of HIV infection [18]. Of these, approximately 20-30% are also infected with HCV, while, at least 10% of these HIV-infected individuals are co-infected with HBV [19, 20]. HIV-HBV and HIV/HCV co-infections are highly prevalent because of shared risk factors and common routes of transmission [2, 3, 21]. HIV modifies the natural history of HCV and HBV disease among co-infected individuals; They are more likely to develop chronic hepatitis [22] and have an increased risk of liver-related mortality and morbidity and suffer life-threatening complication beyond those caused by either infection alone [23, 24].

1.1.2 HBV, HCV and HIV Co-infection in Pregnant Women

Within the obstetric population, HBV, HCV and HIV co-infections also affect a significant number of pregnant women. Worldwide, HCV infection in pregnant women varies from 1% to 8% [25]; in the US, the prevalence of HBV infection among women of

childbearing age is estimated to be 0.7% [26], while that of HCV is estimated to be around 1% [27], even though this number is increasing. A recent study in Florida reported an increase in the prevalence of HBV infection among pregnant women from 65.4 to 123.5 per 100,000 births between 1998 and 2007; the same increase was also reported for HCV infection in pregnant women [28]. In high endemic regions such as sub-Saharan Africa, HIV is associated with being HBV- or HCV-positive [29] and among pregnant women, higher HIV co-infection rates have been reported to range from 4.1% -8.9% for HBV and 1.8%-2.1% for HCV [30-33]. In the only known cohort of HIV-infected pregnant women studied in the US, a 1.5% and 4.9% prevalence was reported for HBV-HIV and HCV-HIV infections respectively [34]. Furthermore, Salihu et al. observed an increased risk of HBV and HCV co-infections among HIV/AIDS women when compared to their HIV-negative counterparts in his study [28].

In the absence of contaminated blood transfusions, sexual transmission and intravenous drug use, a substantial proportion of all chronic HBV cases worldwide are attributed to perinatal transmission of HBV. In spite of vaccine availability, infected pregnant women remain an important source for HBV chronic infection as children who acquire the infection at birth through mother-to-child transmission (MTCT) have up to a 90% risk of becoming chronic cases themselves [35]. Therefore, the CDC recommends routine screening for HBV at the time of the first prenatal visit with each pregnancy regardless of vaccination or previous testing [36].

On the contrary, there is no current vaccine for HCV and maternal screening during prenatal visits is risk-based and not universal. Similar to HBV, MTCT of HCV is a major source of new infections among young children and 80% of perinatal cases that

remain HCV RNA-positive after age three develop into chronic HCV cases [37, 38]. In HIV infected pregnant women, maternal co-infection with viral hepatitis facilitates the transmission of HBV or HCV to newborns [39-42] and children born to co-infected mothers have an increased risk of progressing to chronic forms of the disease. Hence, the management of HBV and HCV disease during pregnancy, especially among HIV positive mothers who are co-infected with viral hepatitis remains an important public health issue as reducing perinatal transmission of these diseases is crucial to reducing the global burden of these diseases [43, 44].

1.2 Rationale

There remains a gap in knowledge in how HBV and HCV infection affects pregnancy outcomes. In reality, it is not well understood if mono infections with HBV or HCV have an adverse impact on pregnancy and perinatal outcomes. Previous studies (see Appendix A) from a variety of countries that have investigated this issue have reported inconsistent results.

Majority of the studies that were reviewed used a case-control study design, which provides marginal evidence for establishing a "causal relationship" between maternal HBV or HCV carrier status and any of the adverse pregnancy or perinatal outcomes studied. Furthermore, methodological concerns and limitations noted in these studies further weaken the epidemiological evidence that these studies present. In particular, residual confounding, small and non-representative samples of cases, information and selection bias is likely to have affected the validity of these studies and consequently biased the conflicting results found.

For HBV infected pregnant women, a few studies [45-47] have shown an increased risk for preterm delivery, congenital abnormalities and gestational diabetes while others studies [44, 48] found no such differences. Similarly, studies on HCV infected pregnant women [44, 46, 49, 50] found that the maternal HCV status was associated with a higher risk of low birth weight, preterm delivery, congenital anomalies, cesarean delivery, gestational diabetes and perinatal mortality. In contrast, other studies [51-54] did not detect significant differences in risks associated with these same outcomes (Appendix A).

Across all studies, hepatitis B surface antigen (HBsAg) assay, an administered test used to check for the presence of HBV antibodies, was the measure used to determine HBV exposure status. Being HBsAg positive only indicates active infection, which could mean that the mother has either a chronic or acute infection. Thus, without any information on hepatitis B core antibody (anti-HBc) for the study participants that tested HBsAg positive at the time of pregnancy, it is hard to distinguish between acute and chronic infection status. Moreover, HBsAg provides no indication of past infection or previous infection with hepatitis B. In the same way, an anti-HCV test only indicates exposure to HCV virus and does not distinguish between someone with an active or previous HCV infection; therefore exposure misclassifications error with HBV or HCV status may bias the true risk estimates of pregnancy-related outcomes in this population. Of equal importance, residual confounding from previous or past exposure to HBV infection, which may have been treated or cleared at the time of pregnancy was not accounted for in confounders adjusted for in these studies.

Residual or uncontrolled confounding due to poor and imprecise measurement of confounding variables was also a potential problem in these studies. Most importantly,

the measurements of drug and alcohol use, also strongly related to poor pregnancy outcomes, were not consistently accounted for across all studies. Since drug and alcohol abuse is often underreported during pregnancy, it is likely that residual confounding from these variables occurred and consequently impacted the study results. Furthermore, without adequate control for confounders such as drug and alcohol use, the magnitude of any association between HCV/HBV exposure and pregnancy would be inaccurately quantified, especially if such an association is small. Likewise, the effect of HCV and HBV viral load during pregnancy was not accounted in all the studies. HCV/HBV viral load provides information on the severity of the disease. There is reason to believe that, like HIV, women with a well-controlled HCV/HBV viral load during pregnancy may have better outcomes than women with high viral loads during pregnancy.

The highly selective samples used in some studies [47, 51, 52, 55-57] may have reduced the generalizability to other populations. Even though a few of the studies used population-based samples the remaining studies from other countries were recruited from specialty clinics or single-sites (Appendix A). The sample sizes in these hospital-based cohorts were often small (< 50 cases) and therefore, had insufficient power to detect associations between pregnancy-related outcomes and HBV or HCV carrier status (Appendix A). Additionally, cases differed greatly on a number of characteristics from the selected controls, which reduced their comparability to each other. To illustrate, in a case-control study [52] conducted in Ireland, the birth outcomes of 36 Rhesus negative women infected with HCV (cases) were compared to Rhesus positive women without HCV infection (controls). The authors [52] reported no difference in risk for pre-term delivery. Lack of comparability between the cases and controls is a source of bias and

may have biased the risk estimate towards the null. In another case-control study [49] of HBV and HCV infected pregnant women in Israel, the authors combined HBV and HCV cases in their analysis and found that HBV or HCV carrier status was associated with an increased risk for pre-term delivery, perinatal mortality, congenital malformations and low birth weight. It is therefore difficult to ascertain whether the observed risk is attributable to HCV or HBV infection.

Lastly, in population-based studies where samples from birth certificates were linked to hospital discharge data, the statistical analysis did not account for within-woman (within-subject) correlations resulting from clusters of women who had more than one live birth during the study period. In instances where observations are not independent, a more complex regression model such as generalized estimating equations (GEE) or a mixed model approach is needed to account for the correlations within subjects. Logistic regression, which assumes independent observations, was incorrectly used to analyze the results presented in these studies. Consequently, the standard errors obtained are incorrect and the variability is often overestimated leading to inappropriate inferences and inflated *P* values [58, 59].

Because large numbers of hepatitis infected pregnant women are never identified, practice patterns for optimal management of pregnancies from infected HBV or HCV mothers are yet to be established. Findings from this study can be used to enhance and provide targeted prenatal care services that could significantly improve the quality of birthing outcomes for the baby and mother. Furthermore, a better understanding of how HCV or HBV impacts pregnancy outcomes could lead to useful prevention strategies.

That aside, it is also important to study the magnitude of chronic HCV and HBV infection among pregnant populations and HIV/AIDS population in the state of SC, possibly representing conditions in the southern part of the US. A detailed description of the disease burden within the prenatal population of SC will provide an impetus for prioritizing, and creating targeted interventions. The resulting information is not only useful for health planning and disease control, but it can also be used to improve maternal and child health locally and nationally at the population level. Additionally, it is important to know the geographic and spatial distribution of these infections within the state would provide valuable knowledge for health department personnel, policy makers and health managers to plan and implement interventions and allocate limited health resources.

The primary objective of the proposed project therefore is in threefold focused on the descriptive epidemiology and spatial distribution of these infections in SC as well as an analytic aspect aimed at elucidating how maternal HBV or HCV status during pregnancy affects birth outcomes.

1.3 Objectives

Descriptive epidemiologic study

1. To describe the epidemiology of HBV or, HCV infection and HIV-hepatitis co-infection among reported female cases in SC between years 2004 and 2011.

   Research Question 1.1: What is the prevalence of HBV mono-infection and HBV/HIV co-infection in reported females cases in SC?

Research Question 1.2: What characteristics are associated with HBV mono-infection and HBV/HIV co-infection in reported female cases in SC?

Research Question 1.3: What is the extent of data agreement between the data sources (electronic birth registry and disease surveillance data) used to capture maternal hepatitis B surface antigen (HBsAg) infection status during pregnancy?

Research Question 1.4: What is the prevalence of HCV mono-infection, HCV/HBV and HCV/HIV co-infection in reported female cases in SC?

Research Question 1.5: What are the demographic characteristics, patterns of CD4+ T-lymphocyte count (CD4), sequence of virus diagnosis and risk factors at time of HIV infection among HCV-positive and HCV/HIV positive females in SC?

Geospatial study

2. To assess the spatial distribution of HCV-infected female cases in SC between years 2004 and 2011.

Research Question 2.1: Given the counts of HCV cases reported in each county, do any of the counties have higher counts of disease than what is expected?

Research Question 2.2: What are the demographic characteristics of those areas in SC that exhibit high risks for HCV infection?

Research Question 2.3: Is high drug use activity and other socio-economic or environmental factors explain the observed risks for HCV infection in these counties?

Associations of HBV and HCV with birth outcomes

3. To estimate the association between maternal HBV or HCV status and selected pregnancy outcomes for singleton births that occurred in SC between 2004 and 2011.

   Research Question 3.1: Is being HBV- or HCV-positive during pregnancy associated with an increased risk for the following adverse birth outcomes: preterm birth, low birth weight, small for gestational age and neonatal intensive care admission?

   Research Question 3.2: What is the association of an adverse birth outcome with recently diagnosed infected pregnancies and pregnancies from mothers who are chronic carriers?

CHAPTER 2

HEPATITIS B VIRUS (HBV) AND HBV/HIV CO-INFECTION AMONG REPORTED FEMALE CASES IN SOUTH CAROLINA

2.1 Abstract

The aim of this study was to characterize the burden of hepatitis B virus (HBV) and human immunodeficiency virus (HIV) co-infection, demographic characteristics and the order of HBV/HIV virus diagnosis in women in South Carolina (SC). Additionally, for maternal hepatitis B surface antigen positive (HBsAg+) cases, we evaluated the data agreement between surveillance data for HBV and HIV, linked to birth registry data for years 2004 to 2011. A total of 2,245 female cases of HBV (confirmed and probable) were included. Of these, 1 918 (85%) were chronic HBV (cHBV) cases, 325 (15%) were acute HBV (aHBV) cases and 2 were perinatal cases. Chronic HBV/HIV co-infection made up 4.2% of all cases. HIV was diagnosed first in 74% of cHBV/HIV cases with a median time to HBV diagnosis of 9 years (range, 2-21). Black women represented 78% of all cHBV/HIV cases and heterosexual contact was the most commonly reported mode for HIV transmission (58%). At the time of HIV diagnosis, most cases had HIV viral load counts >100,000 copies/mL and lived in urban areas of the state. Agreement measures for HBsAg+ women reported to surveillance and birth registry records were moderate: Cohen's *Kappa* = 0.49 (95% CI= 0.44-0.54); percent positive agreement = 49%. An increase in efforts to improve screening, reporting and prevention especially among black

women is warranted. Also, reports to disease surveillance of infections diagnosed during prenatal screening needs to be improved.

2.2 Introduction

Hepatitis B virus (HBV) and human immunodeficiency virus (HIV) constitute a major public health concern globally as both infections are a significant cause of morbidity and mortality worldwide. HBV, a leading cause of acute and chronic liver disease, is responsible for approximately 1 million international deaths annually [6, 60]. It is estimated that approximately one third of the world's population (over two billion individuals) have been infected with HBV, and 350 million of these individuals are chronically infected. In the United States (US), a country of low HBV endemicity, approximately 19 000 new cases of acute HBV infections occurred in 2011[61]; moreover, it is believed that between 1.25 and 2 million individuals are chronically infected with HBV [62, 63].

Comparatively, HIV-infection is among the top ten causes of death worldwide, accounting for over 1.5 million deaths annually [64]. Since its discovery in 1981, at least 60 million individuals have been infected and nearly 25 million have died of acquired immunodeficiency syndrome (AIDS) [15]. In the post-HAART (highly active antiretroviral treatment) era, AIDS-related deaths have continued to decline in developed countries and presently, there are more individuals living with HIV as a chronic condition than ever before. Based on a 2011 global estimate, there are 37 million individuals living with HIV [65].

Among unvaccinated HIV-infected individuals, HBV co-infection with HIV is prevalent because of shared risk factors and common routes of transmission. Of the 1.3

million individuals living with an HIV diagnosis in the US as of 2011, at least 10% were co-infected with HBV [20]. Among co-infected individuals, HIV negatively impacts the natural history of HBV disease. These individuals are more likely to develop chronic hepatitis [22] and progress to cirrhosis, have an increased risk of liver-related mortality and morbidity and suffer life-threatening complications beyond those caused by either infection alone [24].

The burden of HBV mono-infection or co-infection with HIV among US women is not well known [66] especially in antenatal populations and among women of childbearing age. More precisely, national estimates [12, 67] of HBV prevalence in US women are based on data from the National Health and Nutrition Examination Survey (NHANES) which excludes high risk populations such as incarcerated and homeless persons or minority populations such as Asians and Pacific Islanders in which the disease is most common [68]. This population-based study overcomes these limitations by including all women, especially those at high risk for disease acquisition.

The aim of this investigation is twofold. First, to describe the characteristics associated with HBV mono-infection and HBV/HIV co-infection (demographics, timing of infection, risk factors and clinical characteristics). Second, to assess the extent of agreement between two data sources (electronic birth registry and disease surveillance data) used to capture maternal hepatitis B surface antigen (HBsAg) infection status during pregnancy.

2.3 Methods

Data sources

Three data sources were used for this study: the South Carolina (SC) Health Electronic Surveillance System (CHESS) and the enhanced HIV/AIDS Reporting System (eHARS) both obtained from the SC Department of Health and Environmental Control (DHEC), and the live birth registry records obtained from the SC Budget and Control Board, Office of Research and Statistics (ORS). The CHESS database containing all the HBV (probable or laboratory-confirmed) cases was linked to eHARS database that contains HIV case reports. The resulting dataset was then linked to the birth registry records to assess agreement for HBsAg-positive cases reported to CHESS. Institutional Review Boards for the SC DHEC, the University of SC Office of Research Compliance and the ORS Data Oversight Committee approved this study.

CHESS data

Acute and chronic HBV infection is mandated by SC law to be reported to DHEC and is recorded in CHESS. This database is part of the Centers for Disease Control and Prevention (CDC) National Electronic Disease Surveillance System (NEDSS), which has been used for disease surveillance and reporting since 2004 [69]. This web-based infrastructure is a passive surveillance system. Following the submission of an initial report and case investigation by the local public health department, a DHEC specialist reviews the investigation to make sure it meets the surveillance case definitions as set forth by the CDC guidelines. A confirmed acute HBV infection was defined as the presence of immunoglobulin M antibody to hepatitis B core antigen (IgM anti-HBc) or HBsAg positive and evidence of an acute illness with discrete onset of symptoms and

jaundice or elevated serum aminotransferase levels (ALT). A probable acute HBV case was defined as a positive result for either IgM anti-HBc or HBsAg with missing or incomplete clinical information. A confirmed case of chronic HBV infection was defined as HBsAg positive, HBV DNA positive, or hepatitis B e antigen (HBeAg) positive two times at least six months apart. Persons testing positive for a single HBsAg or HBV DNA or HBeAg test with either a negative IgM anti-HBc or no IgM anti-HBc test reported were defined as probable chronic HBV cases. CHESS data for cases occurring from January 2004 to December 2011 included the following information: reported age, race, public health region, year case was reported, case investigation status (probable or laboratory confirmed), case zip code, reason for HBV testing and date of diagnosis.

Enhanced HIV/AIDS Reporting System (eHARS)

Since 1986, HIV infection has been reportable by name to SC DHEC and recorded in eHARS. The quality of data from eHARS exceeds the CDC minimum standards on reporting timeliness and completeness [70]. The eHARS data for SC female cases who were diagnosed with HIV infection or presumed to be living with HIV/AIDS by December 2011 included the following: date of birth, race/ethnicity, date of HIV diagnosis, residence at time of diagnosis (rural or urban), risk behavior, HIV/AIDS disease stage, source of report, CD4+ T-cell counts and HIV viral load values and dates of report.

Birth registry data

To determine maternal HBsAg sero-status, the CDC recommends routine testing for all pregnant women during each pregnancy, if at risk for infection during pregnancy and at the time of admission for delivery if a prenatal HBsAg test result is not available

[71]. In 2004, the SC's birth certificate was revised to include maternal HBV and HCV infection present/and or treated during pregnancy. For the purpose of this study, the following information was used for records of all singleton live births that occurred for SC women between the ages of 15 and 49, during January 2004 to December 2011 inclusive: demographic variables of the mother and infant, date of last menstrual period (LMP), pregnancy history, risk factors and infections present during pregnancy, birth weight, gestational age and Apgar score of newborn, breastfeeding, presence of congenital anomalies and fetal death.

Data linkage

ORS created a unique identifier that includes the name, date of birth, social security number, gender and race of each case and this unique identifier was used to link cases across multiple data sets. Figure 2.1 describes the data linkage process used to obtain the final datasets used for analysis. Starting with CHESS data to identify a reference group, female records of confirmed and probable HBV cases that were reported in SC from 2004 to 2011 was linked to eHARS. This step identified the proportion of female cases that were co-infected with HIV. The initial result was HBV and HBV/HIV infected female cases reported in SC during the study period with characteristics relevant to HIV infection status.

Subsequently, the resulting data set was linked to the ORS integrated system to obtain live birth records over the stated study period. This step further identified women who were recorded as being HBsAg-positive during their pregnancy and provided additional data on the proportion of HBV and HBV/HIV infected cases that had live

births during the study period. Trained statisticians from DHEC and ORS performed the record linkage and the final data set contained no personal identifiers.

Statistical analysis

We compared demographic and clinical variables from CHESS and eHARS across groups of women identified as being co-infected with HIV (cHBV/HIV) or mono-infected with either acute (aHBV) or chronic HBV (cHBV). For HBV cases with missing date of diagnosis, the date case was reported to CHESS was used as an approximate diagnosis date instead. Descriptive statistics such as proportions and means were employed to summarize the relative frequencies of HBV and HBV/HIV infected cases within the entire sample. The Chi-square (χ^2) statistic was used to determine if frequency distributions of demographic characteristics differed significantly between disease groups. Continuous data were expressed as median and range or interquartile range (IQR) as appropriate and the Kruskal-Wallis test was used for comparison.

We used Cohen's kappa and positive agreement (P_a) [72] to investigate the degree of concordance between HBsAg-positive cases identified through birth certificate data and those reported through CHESS. This part of our analysis was restricted to birth data from women who had only one singleton pregnancy for the entire study period, as it was difficult to ascertain accurate counts from women who had had more than one singleton pregnancy over the study period. It was particularly challenging in scenarios where women with more than two pregnancies had one pregnancy reported to CHESS during which the mother was identified as being HBsAg-positive but for the remaining pregnancies she was either identified as being HBsAg-negative or her HBsAg-positive

status was not reported to CHESS. All statistical analysis were performed using SAS (version 9.3, SAS institute, Inc.) and DAG_Stat [73].

2.4 Results

During the 8-year study period, a total of 2,245 positive HBsAg notifications consistent with either chronic or acute HBV infection from 2,223 females were reported to CHESS (Figure 2.2). Of the 2,245 cases reported, 1,918 (85%) were chronic HBV (cHBV) infections and 325 (15%) were acute HBV (aHBV) infections. Only two perinatal cases of HBV were reported for the entire study period. Ninety four percent of aHBV were classified as confirmed cases compared to only 65% of cHBV cases met the clinical definition for a confirmed case.

HBV mono-infection individual characteristics

There were 1,754 cHBV and 295 aHBV reports from mono-infected women (Table 2.1). Approximately 281 prevalent cases of HBV were reported each year. Among women with available race information, Black and White women represented 20% and 12% of all HBV cases reported during the study period. Both groups of women were relatively young at the time of HBV notification (aHBV: median age=41 years; cHBV: median age=37 years). Geographically, over the 8-year period, the northeastern region (Pee Dee) of the state reported the largest proportion of aHBV (31%) whereas the central region (Midlands) of the state reported the largest proportion of cHBV (28%) cases.

HBV/HIV co-infection

Of the 1,918 cHBV cases reported, 164 (8.6%) were co-infected. Among co-infected cases, 83 (50.6 %) cases were co-infected with hepatitis C virus (HCV) and 81

(49.4 %) cases were co-infected with HIV (cHBV/HIV). The results of only the HBV/HIV cases are reported here (Tables 2.1 and 2.2). Black women represented 78% of all the cHBV/HIV cases identified and the median age at cHBV notification was 42 years (range 21-63). Heterosexual contact was the most commonly (57%) reported mode for HIV transmission followed by injecting drug use (20%). The median age at HIV diagnosis was 35 years (range, 16-62). The majority of women (58%) within this group lived in urban areas of the state. HIV was diagnosed first in 62 (75%) of the cHBV/HIV co-infected cases and the median time to subsequent HBV diagnosis for these cases was 9 years (range, 2-21). In 22% of cHBV/HIV co-infected cases, both infections were reported in the same year whereas only 4% of co-infected cases had an HBV diagnosis reported first. Twenty-nine percent of the cHBV/HIV co-infected women in our study had a concurrent diagnosis of HIV infection and AIDS within three months whereas 48% were ever diagnosed with an AIDS infection. Triple infection with HBV, HCV and HIV was present in a small number (n=7) of cases reported. A small proportion of aHBV cases were also co-infected; 21(6%) cases also reported an infection with HCV whereas 9 (3%) cases reported a co-infection with HIV.

Linkage between CHESS/eHARS and birth registry data

From the birth registry data, there were 226 894 women with available data on infections presented or treated during pregnancy. Our final sample used for assessing agreement between CHESS and birth registry included 344 HBsAg-positive women from CHESS and 308 (0.13%) HBsAg-positive women identified from the live registry data (Figure 2.3). After linkage, the estimated crude prevalence of HBV infection among pregnant women within our sample was 0.17% (379/226,894). Only 159 (52%) HBsAg-

positive mothers were found reported to CHESS while the remaining 149 (48%) HBsAg-positive mothers from the birth registry data could not be found in CHESS. Conversely, 185 (54%) of HBV infected women from CHESS who had a singleton birth were not identified as being HBsAg-positive mothers on their birth records even though they were reported as being HBV infected prior to their pregnancy.

There was moderate agreement between CHESS and birth certificate data for identifying HBsAg-positive women (Cohen's k = 0.50 [95% CI= *0.47-0.54]).* Percent positive agreement was 49%.

Agreement of HIV cases from the birth data and eHARS could not be ascertained because maternal HIV status is not recorded in the birth registry data. Four (6%) out of the 68 HIV co-infected women who were of childbearing age had one singleton birth.

2.5 Discussion

This study used linked surveillance and birth registry data sources to describe the epidemiology of HBV mono-infected and HBV/HIV co-infection among a population-based sample of women. Overall, we found that approximately 9% of cHBV cases were co-infected with either HIV (4.2%) or HCV (4.3 %). The majority of cHBV/HIV co-infected cases were Black women from urban areas in SC, who self-reported heterosexual contact as the main risk factor for HIV transmission and had low first CD4 counts after HIV was diagnosed. Women between the ages of 20 and 49 reported the highest frequencies of disease occurrence in our study and this observation is consistent with other empirical studies [74, 75] conducted in the US that have found that most HBV infections occur in young adults with sexual contact being one of the most common modes of infection [76]. Within the state, the largest proportion of aHBV cases was reported

from the northeastern region (Pee Dee), which could reflect poor vaccination coverage for aHBV among women in this region.

In low endemic regions such as the US, cHBV/HIV co-infection occurs frequently with estimated prevalences between 5% and 7% [19]. In our study, we observed a moderate prevalence of co-infection with HIV/AIDS and HCV among cHBV infected women reported to CHESS; 4.2% were co-infected with HIV/AIDS, whereas 4.3% had a co-infection with HCV. The majority of co-infected women in our study had an HIV diagnosis preceding an HBV diagnosis, suggesting that both infections were acquired in adulthood and not through perinatal transmission. The 9-year median time between HIV diagnosis and a subsequent chronic HBV diagnosis was a striking element in our study. Routine HBV testing and immunization is recommended for all HIV-infected persons and our finding suggests that there are gaps in compliance with this recommendation. This implies that the HIV infected women who were also co-infected with cHBV lived with undiagnosed viral hepatitis for long periods of time. Thus, opportunities to counsel infected individuals and prevent further transmission were likely to have been missed. Additionally, these results indicates a missed opportunity for those with undiagnosed HBV to be put on appropriate medication that would treat both HIV and HBV as drug resistance and fatal flares of HBV are both potential consequences resulting from choosing the wrong therapy without knowledge of HBV status. Our results points to the importance of routinely testing HIV infected persons for HBV infection and provide HBV immunization for sero-negative individuals.

A large proportion of the HBV/HIV co-infected women in our study presented with low CD4 counts and was diagnosed with AIDS almost immediately upon diagnosis.

Although we cannot be certain of when these cases contracted HIV, the young median age (35 years) and low CD4 counts at HIV diagnosis may suggest long duration of infection. A recent study on missed opportunities for HIV testing among HIV infected women from SC showed that 73% of cases had missed opportunity visits and among the half that were late testers, about 79% were diagnosed with AIDS within a month of receiving their HIV diagnosis [77]. Because we were unable to assess missed opportunities for HIV testing within our sample, we do not know what proportion of HBV/HIV co-infected women with AIDS also had missed opportunity visits for HIV testing.

In this study, among mothers who had one singleton birth, we found moderate agreement between surveillance data and birth certificate data for maternal HBsAg-positive status. Among the prenatal population in SC, HBsAg infection comprised <1% of all cases and the estimated prevalence of HBV infection among pregnant women within our study was 0.17%. This was within the reported range of 0.09-0.27% [12, 28, 44, 48] for US women. Because screening for HBsAg sero-status is universally recommended during pregnancy and at delivery for high risk women [71], we expect to find most, if not all, positive HBsAg cases determined through prenatal screening in the states surveillance system as reporting of HBV cases is required by law. When we assessed the degree of concordance between CHESS and birth certificate data for mothers who had one singleton birth, we discovered that for maternal HBsAg status, CHESS was in moderate agreement with birth certificate data and only 52% of HBsAg-positive cases found on the birth records were reported to CHESS. Surprisingly, even after excluding HBsAg-positive mothers who had births before an HBV diagnosis was reported to CHESS, 54%

of CHESS cases were designated as being HBsAg negative on their birth records and 52% of HBsAg-positive cases from the birth data were not reported to CHESS.

Several reasons may explain this observation. First, designated HBsAg-positive cases per birth certificate could be false positives that were reported to CHESS and were assigned a "suspected" or "not a case" status after a further case investigation. Unfortunately the extent to which this is true could not be assessed in our data, as only probable and confirmed cases were included in study sample. Secondly, we restricted our data to only singleton births. HBsAg sero- positive mothers who had plural births and reported to CHESS were not included in our analysis. Nevertheless, because 54% of mothers who were confirmed as being HBsAg sero-positive were in CHESS but not reported on their birth certificate for that singleton pregnancy raises concerns about the quality of data collected for infections present during pregnancy on the birth certificate. Historically, validation studies [78, 79] conducted on data from U.S. birth registry data have shown it to be a reliable source of information. However, maternal HBV infection present/and or treated during pregnancy was recently added as a data item on the revised birth certificate and the validity and reliability of this measure has not been formally evaluated. Additionally, the high number of HBsAg sero-positive cases not reported to CHESS suggests infrequent passive reporting for HBV within the state and an opportunity to strengthen ties with clinicians and other key partners engaged in disease surveillance reporting.

The findings in this study are subject to at least three limitations. First, the prevalence of HBsAg-positives in our study is very low thus, data agreement results should be interpreted cautiously. Secondly, while HBV screening during pregnancy is

universally recommended in US, it is likely that screening practices differ across providers and this may have resulted in the misclassification of infected but unscreened women in the birth certificate data. Furthermore, as the completeness of surveillance data from CHESS is unknown, the data presented here is not representative of all the HBV infected cases that occurred over the study period. Moreover, our data on HBV and HIV diagnosis date reflects an approximate time for when these conditions were detected and subsequently reported. We cannot determine when the either infections occurred or confirm the order of infection for those women who were co-infected. Finally, CHESS data did not capture several key demographic variables, most especially detailed race information and HBV risk factor data, that could have strengthened our description of this population.

In spite of these limitations there are strengths to our study. This study offers the first description of HBV and HBV/HIV disease burden within the SC female population. Moreover, this study employs a rich variety of data sources and uses a sequential record linkage process that links reported cases of HBV to birth records. Lastly, being able to assess how birth data for maternal HBsAg status compares to reported HBV surveillance data identifies opportunities to enhance and strengthen disease reporting.

In summary, the prevalence of HBsAg infection among pregnant women was within the reported range of previous estimates (0.09-0.27%). HIV and HCV co-infection within this population was substantial and there was moderate agreement between surveillance and birth registry data reported for maternal HBsAg status. HIV co-infected women were largely young black adults who had their HBV diagnosed almost a decade later and lived in urban areas. An increase in efforts to improve screening, reporting and

prevention especially among black women is warranted. Our results also suggest that reports of infections found during prenatal screening to the disease surveillance needs to be improved. More training should be provided for birth record abstractors to promote accurate reporting of this data to surveillance. Clinicians can educate mothers by explaining the importance of data and its widespread use nationally to enhance reporting accuracy. More importantly, using the birth registry data by itself to identify HBsAg positive women may not be adequate and future studies can benefit from using both surveillance data and birth data in identifying HBsAg-positive women.

Table 2.1- Demographics of hepatitis B virus (HBV) and HIV co-infected female cases in South Carolina reported to CHESS and eHARS between 2004 and 2011

		Mono-infection		**Co-infection**	
HBV-related variables[a]	Total n (%)	aHBV n (%)	cHBV n (%)	cHBV/HIV n (%)	P-value
Number of cases	2132	295	1754	83	
Age at HBV, years, median (range)	38 (1-91)	41 (1 - 85)	37 (1 - 91)	42 (21 - 63)	<0.001[b]
≤20	115 (5)	3 (1)	112 (6)	-	<0.001[c]
20-29	503 (24)	46 (16)	450 (26)	7 (8)	
30-39	508 (24)	86 (29)	395 (23)	27 (33)	
40-49	410 (19)	83 (28)	301 (17)	26 (31)	
50-59	311 (15)	43 (15)	248 (14)	20 (24)	
≥60	267 (13)	30 (10)	234 (13)	3 (4)	
Missing		*4 (1)*	*14 (<1)*	*0*	
Year of HBV diagnosis					<0.001[c]
2004	379 (18)	65 (22)	301 (17)	13 (16)	
2005	342 (16)	66 (22)	270 (15)	6 (7)	
2006	321 (15)	42 (14)	265 (15)	14 (17)	
2007	261 (12)	24 (8)	220 (13)	17 (20)	
2008	235 (11)	33 (11)	191 (11)	11 (13)	
2009	230 (11)	23 (8)	197 (11)	10 (12)	
2010	175 (8)	22 (7)	145 (8)	8 (10)	
2011	189 (9)	20 (7)	165 (9)	4 (5)	
Race					
Black	420 (20)	81 (27)	274 (16)	65 (78)	<0.001[c]
White	253 (12)	58 (20)	180 (10)	15 (18)	
Other	174 (8)	11 (4)	160 (9)	3 (4)	
Missing	*1285 (60)*	*145 (49)*	*1140 (65)*	*0*	
Hepatitis B vaccine received indicator					
No	-	150 (51)	-	-	
Yes	-	13 (4)	-	-	
Missing	-	132 (45)			

Table 2.1- Demographics of hepatitis B virus (HBV) and HIV co-infected female cases in South Carolina reported to CHESS and eHARS between 2004 and 2011 *(cont'd.)*

		Mono-infection		**Co-infection**	
HBV-related variables[a]	Total n (%)	aHBV n (%)	cHBV n (%)	cHBV/HIV n (%)	P-value
DHEC region					<0.001[c]
Low country	501 (24)	61 (21)	424 (24)	16 (19)	
Midlands	594 (28)	75 (25)	494 (28)	25 (30)	
Pee Dee	400 (19)	90 (31)	285 (16)	25 (30)	
Upstate	435 (20)	38 (13)	388 (22)	9 (11)	
Missing	202 (9)	31 (11)	163 (9)	8 (10)	
Case classification					
Confirmed	1457 (68)	276 (94)	1135 (65)	46 (55)	<0.001[c]
Probable	675 (32)	19 (6)	619 (35)	37 (45)	

HIV, human immunodeficiency virus; cHBV, chronic hepatitis B virus; aHBV, acute hepatitis B virus; CHESS, Carolina's health electronic surveillance system; DHEC, department of health and environmental control.

*Percentages may not equal to 100 because of rounding.

[a]HBV-related variables were obtained from CHESS surveillance database.

[b]Kruskal Wallis p-value was calculated for continuous values.

[c]Chi-square p-value was calculated for categorical values.

Table 2.2 - Characteristics of chronic hepatitis B and HIV co-infected female cases in South Carolina reported to CHESS and eHARS between 2004 and 2011

	Co-infection
HIV-related variables[a]	cHBV/HIV N (%)
Number of cases	83
Year of HIV diagnosis	
1985-1989	3 (4)
1990-1994	15 (18)
1995-1999	23 (28)
2000-2004	16 (19)
2005-2009	21 (25)
≥ 2010	5 (6)
Age at HIV, years, median (range)	35 (16-62)
≤20	5 (6)
20-29	27 (33)
30-39	19 (23)
40-49	22 (27)
50-59	9 (11)
≥60	1 (1)
Timing of HIV-HBV diagnosis	
HIV reported first	62 (75)
HIV and HBV reported together[b]	18 (22)
HBV reported first	3 (4)
HIV disease stage at diagnosis	
HIV only	19 (23)
HIV and later AIDS	40 (48)
HIV and AIDS diagnosed simultaneously	24 (29)
HIV transmission category	
Injecting drug use	17 (20)
Heterosexual	47 (57)
No identified risk[c]	18 (22)
Other[d]	1 (1)

Table 2.2- Characteristics of chronic hepatitis B and HIV co-infected female cases in South Carolina reported to CHESS and eHARS between 2004 and 2011*(cont'd.)*

	Co-infection
HIV-related variables[a]	cHBV/HIV N (%)
Source of HIV report	
County health department	18 (22)
Hospital	19 (23)
Group practice	12 (14)
Other state[e]	11 (13)
Other[f]	5 (6)
Unknown	18 (22)
Residence at time of HIV diagnosis	
Urban	48 (58)
Rural	19 (23)
Missing	*16 (19)*
$CD4^+$ percentage	
No. of women with data available	81
0-25%	57 (70)
26-40%	21 (26)
≥40%	3 (4)
First viral load group	
No. of women with data available	76
≤ 10,000 copies/mL	25 (33)
> 10,000 copies/mL	51 (67)
First $CD4^+$ count	
No. of women with data available	81
Median (IQR) cells/mm^2	189 (58-494)
First viral load	
No. of women with data available	76
Median (IQR) copies/mL	28561 (4762-114635)

HIV, human immunodeficiency virus; cHBV, chronic hepatitis B virus; IDU, injecting drug use; mL, milliliter; CD4, cluster of differentiation 4;

*Percentages may not equal to 100 because of rounding.

[a]These variables were obtained from the enhanced HIV/AIDs reporting system (eHARS).

[b]HIV and HBV were diagnosed and reported in the same year.

[c]Adults with no risk factors reported (n=4) or no identified risk factors (n=14).

[d]Other risk category includes heterosexual who had sexual intercourse with a high-risk individual (e.g., IDU, male bisexual, transfused individual, HIV-positive individual)

[e]Other state includes reports from other states.

[f]Includes blood banks/business (n=1); private physician (n=1); state (n=2); department of mental health (n=1);

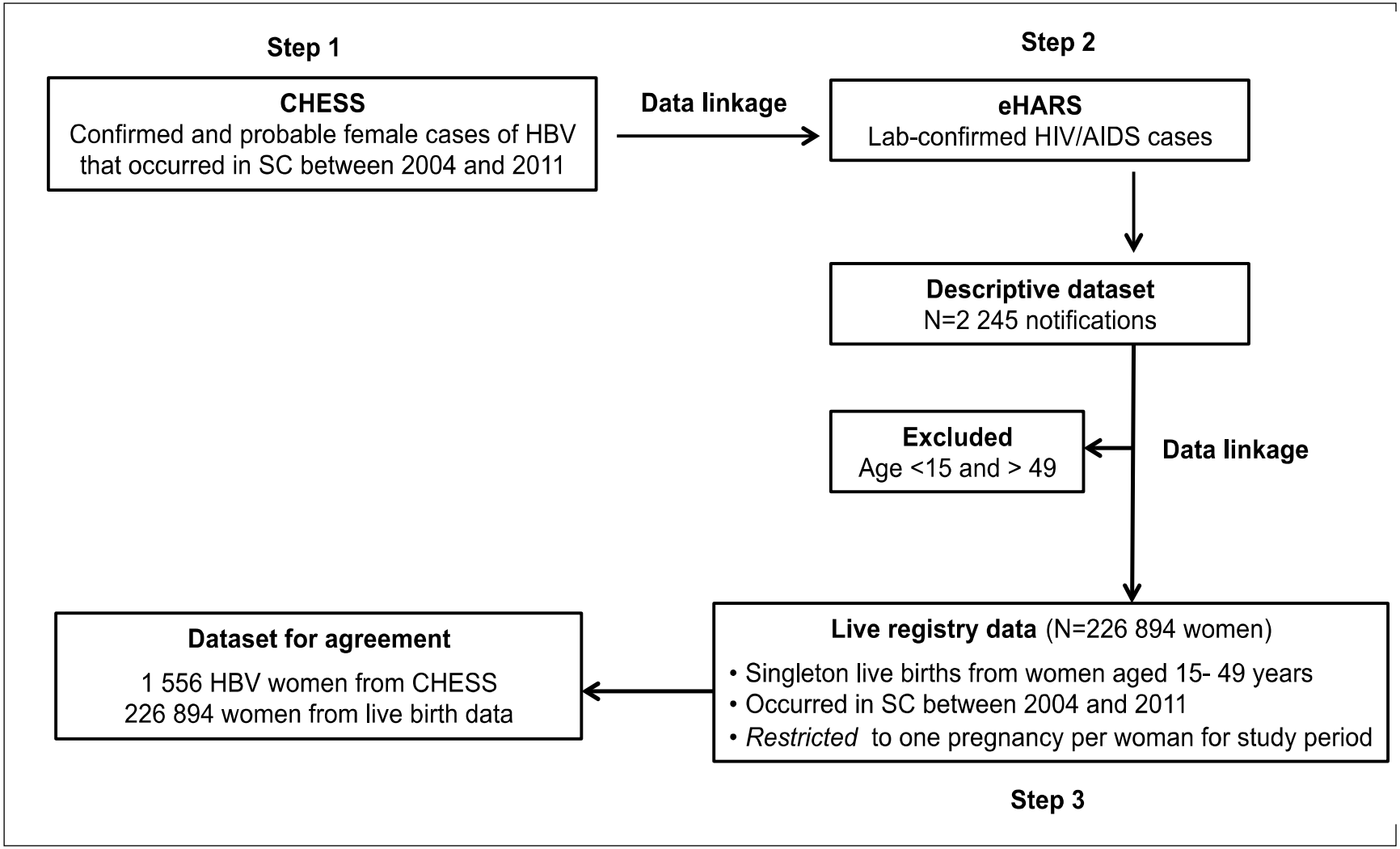


Figure 2.1 Data sources and linkage process

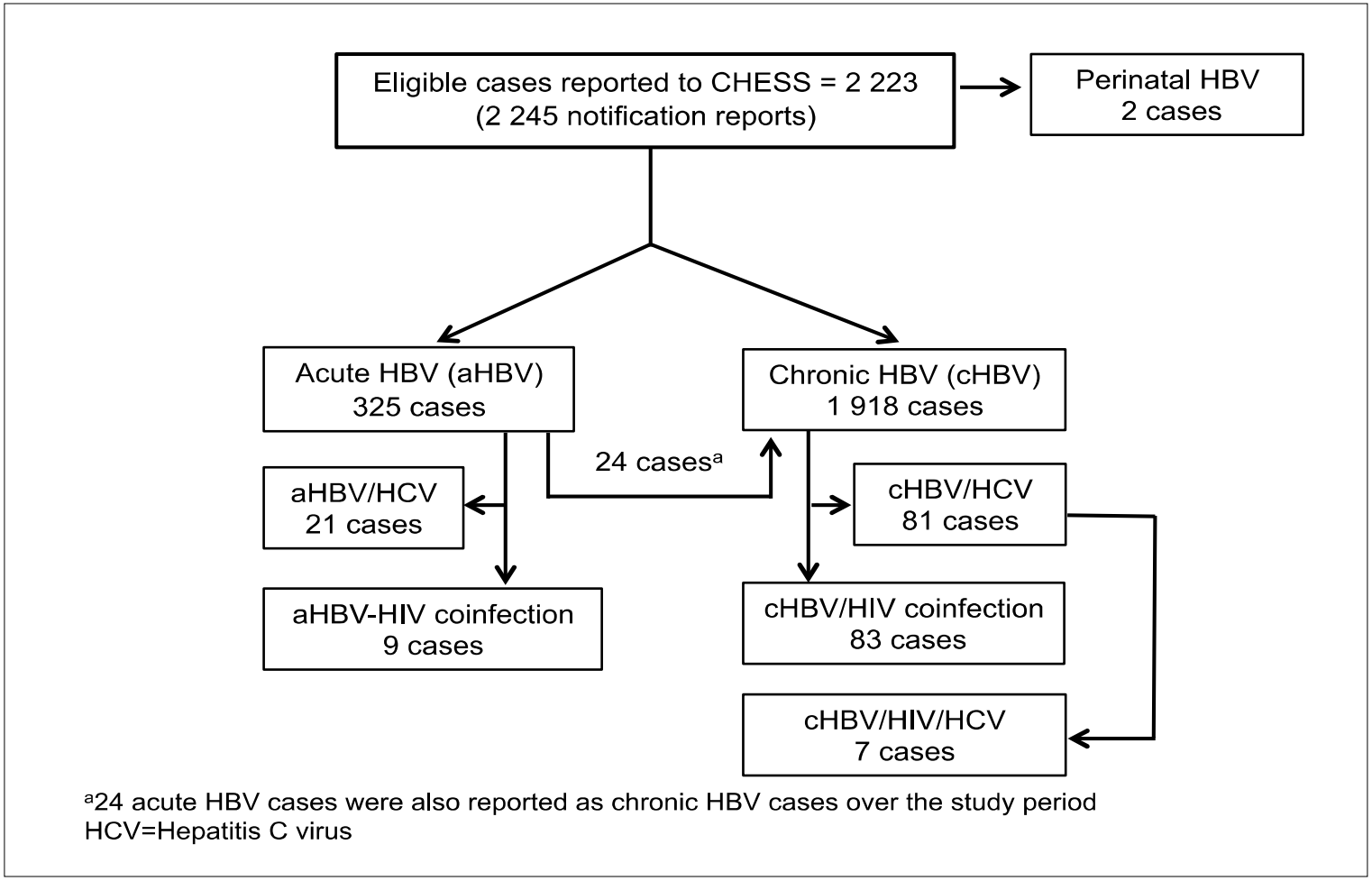


Figure 2.2 Sample population and flow for hepatitis B virus (HBV) female cases from CHESS linked with HIV data from eHARS; January 1, 2004 to December 31, 2011.

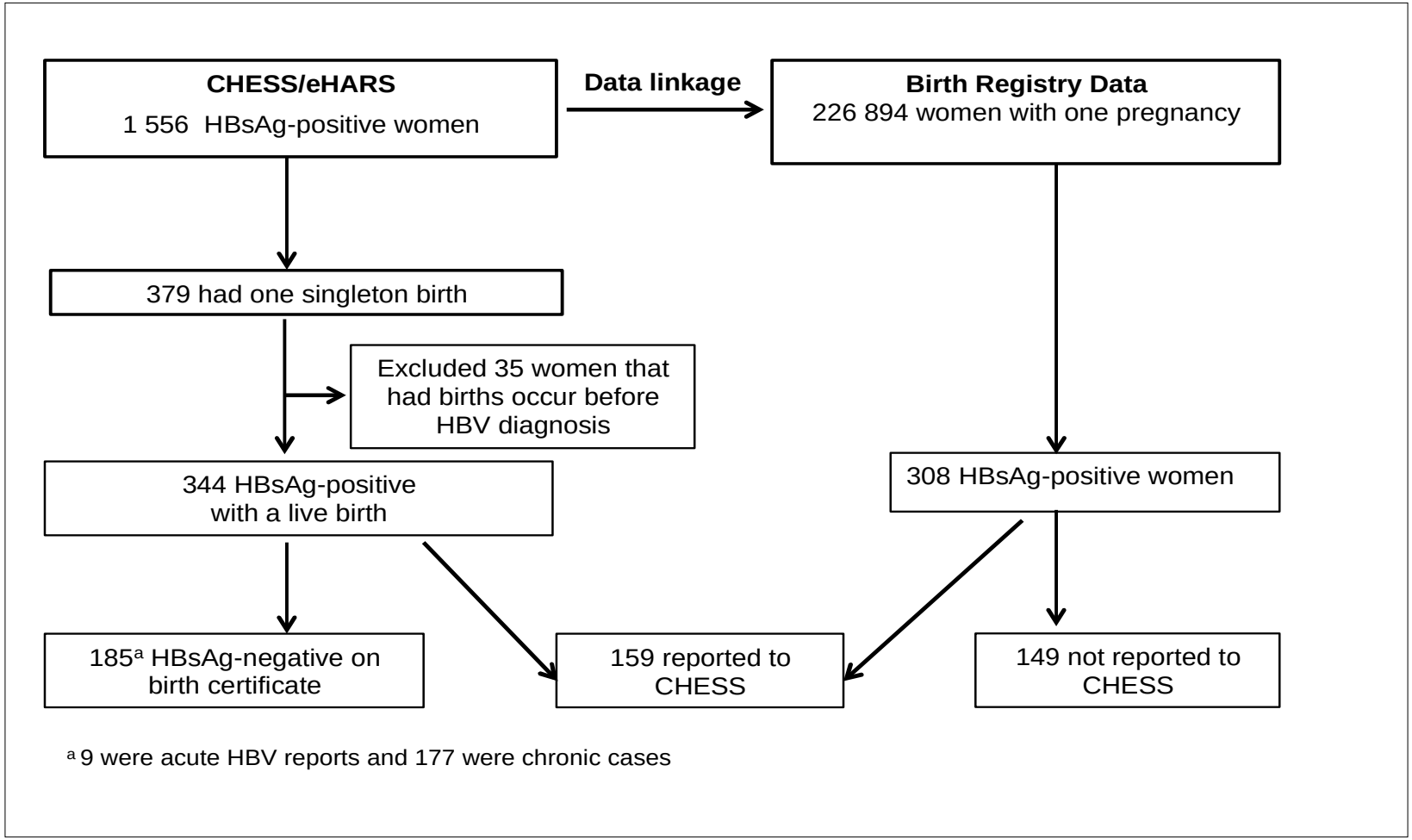


Figure 2.3 Sample population for hepatitis B virus (HBV) female cases from CHESS/eHARS linked with birth registry; January 1, 2004 to December 31, 2011.

CHAPTER 3

HEPATITIS C VIRUS (HCV), HCV/HEPATITIS B VIRUS (HBV) AND HCV/HIV CO-INFECTION AMONG REPORTED FEMALE CASES IN SOUTH CAROLINA

3.1 Abstract

Few data exist on the magnitude of Hepatitis C virus (HCV) mono-infection, and its co-infection with hepatitis B virus (HCV/HBV) and human immunodeficiency virus (HCV/HIV) within the US female population. This study describes the burden of HCV, HCV/HBV and HCV/HIV co-infection, demographic characteristics and the order of HCV/HIV virus diagnosis in women in South Carolina (SC). The study used a linked dataset of surveillance data that was reported from HCV-, HBV- and HIV-infected female cases that occurred in SC between 2004 and 2011. We identified a total of 10,208 HCV-positive reports. Ninety-five percent were mono-infected with HCV, followed by 4% who were co-infected with HCV/HIV and 1% with HCV/HBV infection. HCV mono-infected cases overall were predominantly middle-aged White women. However, after stratifying our results by age for those with available race information (40%), we observed an increase over the study period in the number of HCV infections reported for White adolescents and young adults aged 15-25 years old. HCV/HIV co-infected cases tended to be Black middle-aged women from urban areas who reported either intravenous drug use (IDU) or heterosexual contact as their main risk factor for HIV transmission.

HIV was diagnosed first in 79% of HCV/HIV co-infected cases and 62% of HCV/HBV co-infected cases had both infections reported within the same year. Our findings suggest a need for resources to be directed at improving screening and prevention efforts among middle-aged White women, Black women and young persons between the ages of 15 and 25 years.

3.2 Introduction

Hepatitis C virus (HCV) infection is the most common chronic blood-borne infection in the United States (US) and remains a global leading cause of liver-related morbidity and mortality [80, 81]. The estimated number of HCV-infected individuals worldwide is staggering. Between 130-170 million, 2-3% of the world's population, are chronically infected with HCV [82]. In the US, taking into account institutionalized, incarcerated and homeless persons, there are at least 3.5 million individuals who are infected with chronic HCV [83, 84]. In one recent study, when active military service personnel, nursing home residents and immigrants were accounted for, as many as 5.2 million individuals in the US were reported to be living with chronic HCV infection [13].

Among individuals infected with human immunodeficiency virus (HIV), co-infection with HCV is very common as these two infections share common risk factors for transmission. Of the estimated 1.3 million HIV-infected Americans, about 25% are co-infected with HCV and among HIV patients who have a history of either intravenous drug use (IDU) or hemophilia, HCV/HIV co-infection rates ranges from 70 to 95% [20, 21] [19]. For individuals living with both viruses, HIV adversely affects the natural history of HCV disease [85, 86]. Thus, co-infection is associated with severe disease, high HCV viral loads, a faster progression to liver disease and an increased rate of decompensated liver-

related mortality[3, 23, 24, 85 87, 88]. These adverse clinical outcomes are also seen among those co-infected with both HCV and hepatitis B virus (HBV). Compared to a single hepatitis infection, co-infection with HCV and HBV is associated with a higher prevalence of liver cirrhosis, liver decompensation as well as an increased risk of developing liver cancer [89-91].

In order to evaluate the burden and trends of HCV adequately, HCV prevalence should be stratified by age, ethnicity and gender [82]. However, unanswered questions exist concerning the epidemiology of HCV, HCV/HIV and HCV/HBV infection within the female population. Specifically, for women in their childbearing years and those who are pregnant, the prevalence of HCV has not been well-studied [28]. Estimates from the National Health and Nutrition Examination Survey (NHANES) estimates HCV prevalence in US women at close to 1% [27, 84], whereas estimates using US birth data have yielded prevalence rates that fall between 0.06 and 0.2% [28, 44, 50]. Yet, these data do not take into account certain populations, such as homeless or incarcerated persons, that are at high risk for HCV infection [13]. Additionally, the completeness of reporting HCV infection on the US birth certificate is unknown and because universal screening of HCV during pregnancy is not mandatory, ascertainment bias could likely influence these HCV prevalence estimates from birth certificates [50].

Surveillance data offer an alternative opportunity to overcome some of these limitations through the use of a population-based sample. Beyond being a valuable epidemiologic tool for descriptive analysis, surveillance data avoids some biases found in population surveys in that data are reported from all sources, including hard to reach populations [92]. To the best of our knowledge, there are no studies that have used

surveillance data to characterize the burden of HCV, HCV/HIV and HBV-HCV infection within a female population.

In this study, we used data collected through South Carolina's (SC) viral hepatitis and HIV/AIDS surveillance system to report on the prevalence, demographic characteristics, patterns of CD4+ T-lymphocyte count (CD4), sequence of virus diagnosis and risk factors at time of HIV infection among HCV-positive females in SC. In our previous study [93], we described characteristics associated with HBV and HBV/HIV co-infection and assessed the extent of agreement between the electronic birth registry and disease surveillance data.

3.3 Methods

Data sources

Two data sources were obtained from the SC Department of Health and Environmental Control (DHEC) and used for this study: the South Carolina (SC) Health Electronic Surveillance System (CHESS) and the enhanced HIV/AIDS Reporting System (eHARS). The CHESS database containing all the HCV and HBV (probable or laboratory-confirmed) cases was linked to eHARS database that contains HIV case reports. Approval was received from SC DHEC and the University of SC Office of Research Compliance.

CHESS data

In SC, all positive laboratory results (confirmed and probable) indicating HCV infection are required by law to be reported to SC DHEC and are recorded in CHESS [69]. This web-based infrastructure is a passive surveillance system and is part of the Centers for Disease Control and Prevention (CDC) National Electronic Disease Surveillance

System (NEDSS) which has been used for disease surveillance and reporting since 2004 [94] . A trained DHEC specialist reviews all positive HCV tests recorded in CHESS to ensure that each notified case meets the case definition for HCV as set forth by the CDC guidelines. In accordance with these surveillance guidelines, a confirmed chronic HCV case (past or current infection) was defined as a positive anti-HCV assay with either a positive nucleic acid test (NAT) result or a positive recombinant immunoblot assay (RIBA) test to further confirm HCV infection. Conversely, all positive anti-HCV assay reports where neither a NAT nor RIBA test was conducted or reported to SC DHEC and did not meet the case definition for an acute HCV case were defined as probable chronic HCV cases. Because no laboratory distinction can be made between a previous or current infection and includes about 20% of persons who resolved their infections, confirmed chronic HCV cases represent "past or present" HCV infection [95].

For our analysis, all confirmed or probable female cases with a report date between January 1st 2004 and December 31st 2011 were extracted from CHESS along with demographic data on the reported age, race and zip code. To identify HCV/HBV co-infected cases, the same inclusion criteria were applied to extract HBV infected cases from CHESS. This data were described elsewhere [93].

Enhanced HIV/AIDS Reporting System (eHARS)

HIV is a mandatory reportable disease in SC and since 1986, all newly identified cases of HIV infection who are residents of SC has been reported to the eHARS. Recorded in the eHARS database are demographic variables, CD4 counts and HIV viral loads. Based on a routine assessment of the database for accuracy and completeness, the quality of data from eHARS exceeds the CDC minimum standards on reporting

timeliness and completeness; 95% within six months of a diagnosis and 98% completeness based on comparison with other data sources [SC DHEC, unpublished data, 2010]. For our analysis, female cases of HIV/AIDS who were reported to eHARS by December 2011 were eligible to be selected for potential linkage to CHESS cases.

Data linkage

A trained statistician from DHEC performed the data linkage for this study. Using probabilistic matching methods, HCV-positive cases from CHESS were linked to HIV positive records from eHARS. Each record was matched on gender, name, race, social security number and date of birth. After linkage the final dataset contained no identifiers.

Statistical analysis

We compared demographic differences for HCV- and HIV-related variables across groups of women identified with HCV mono-infection, HCV/HIV or HCV/HBV co-infection over the 8-year study period. Frequencies and percentages for each level of categorical variables were calculated and the Chi-square (χ^2) statistic was used for comparison. Continuous data such as age and CD4 counts were expressed as median and range or median and interquartile range (IQR) as appropriate.

We determined the sequence of virus diagnosis for both HCV/HIV and HCV/HBV co-infected cases by obtaining the difference in time between the year either HIV or HBV was reported and the year HCV was reported. The prevalence of HBV infection among those infected with HCV was calculated as the proportion of HCV cases with a positive hepatitis B surface antigen report (HBsAg) in CHESS during the study period. HBsAg positive cases from CHESS included probable or confirmed cases that

were either acute or chronic HBV infections. All data were analyzed using SAS (version 9.3, SAS Institute Inc.) and R statistical program [96].

3.4 Results

A total of 10,208 reports from female cases of HCV were received in CHESS over the 8-year study period (Figure 3.1). Of these reports, 11 (<1%) were acute HCV cases and the remaining 10,197 were chronic HCV cases. Our analysis was limited to the portion of the sample that had a chronic HCV infection (Table 3.1 and 3.2).

HCV mono-infection

Of the total 10,197 chronic HCV cases reported, 9,664 (97%) were mono-infected and of these, 8,469 (88%) cases met the clinical definition for a confirmed case. The median age at HCV notification was 48 years (range 1-79 years). Forty percent (3,856) of mono-infected cases had available race information. Among these, 27% were White and 12% were Black. An average of 1,208 prevalent cases were reported each year with the western (Upstate) and central (Midlands) regions of the state reporting the largest proportions (26% and 21%) of monoinfected cases respectively.

When the age distribution for the number of monoinfected cases were stratified by race (for those with available race information) and compared for years 2004 and 2011, we noted a difference by race (Figure 3.2). For White females, the mean age decreased from 45 years in 2004 to 44 years in 2011 while the variance increased from 139.6 in 2004 to 195.7 in 2011. For Black females, the mean age increased from 50 years in 2004 to 55 years in 2011 whereas the variance increased slightly from 131.6 in 2004 to 139 in 2011.

HCV/HIV co-infection

HCV/HIV co-infection prevalence in this sample was 4% (95% CI: 3.9% - 4.7%) and the median age at the time of HCV diagnosis was 48 years (range, 18-75 years). The majority of co-infected cases were Black (76%) whereas 21% were White. Almost half of HCV/HIV co-infected cases (46%) reported IDU as the main risk factor for HIV transmission and this was followed by 38% of cases that reported heterosexual exposure as a risk factor. The majority of cases (59%) resided in urban areas whereas over 50% of the HIV reports were from hospitals and county health departments. HIV was diagnosed first in 340 (79%) cases and among these cases, the median time to subsequent HCV diagnosis was 9 years (range, 1-23 years). Although 16% had both infections reported in the same year, 5% of HCV/HIV cases had an HCV diagnosis reported first. AIDS disease stage was diagnosed in 42% of HCV/HIV cases whereas only 34% were HCV/HIV cases without AIDS. At the time of HIV presentation, the median age was 40 years (range, 16-69 years), and the median CD4 cell count and viral load were 307 cells/µL (IQR 156-528 cells/µL) and 14,000 copies/mL (IQR 1,780-73,860 copies/mL), respectively.

HCV/HBV co-infection

There were 101 (7%) cases of HCV that were co-infected with HBV. Seven of these cases, also had an infection with HIV, i.e., these individuals had a triple infection with HCV, HIV and HBV. Of the 94 cases that remained, 20 (21%) were an acute HBV infection while 74 (79%) had a chronic infection with HBV. At the time HCV was reported, the median age was 49 years (range, 21-79) and 84% met the clinical definition for a confirmed HCV case. When we considered the 40 (43%) cases with available race information, notifications from White women made up the largest proportion (26%).

HCV and HBV infections were reported within a year of each other in majority (62%) of the cases and only 16% had their HBV infection reported first.

3.5 Discussion

Our data showed that for the 40% of HCV mono-infected cases with available race information, middle-aged White women were predominant and who were most likely to reside in the western (Upstate) and central (Midlands) regions of the state. These findings are consistent with what is already known about HCV infection from national data. The NHANES data from 1999-2002 showed that anti-HCV prevalence was highest among individuals between the ages of 40 and 49 years [84]. Additionally, a recent NHANES study using data from 2001-2010 revealed that more than two-thirds (70.1%) of US sero-prevalent HCV cases belonged to 1945-1965 birth cohort [97]. In our study, 65% HCV mono-infected cases were in the 40-59 years age group that corresponds to 1952-1970 birth cohort. Within this cohort, persons born between 1945 and 1964 were between the ages of 40 and 59 in 2004. From the NHANES data, even though the national prevalence of females infected with HCV is estimated to be around 1.1%[84], this data covers only non-institutionalized persons meaning that active military personnel, incarcerated, homeless, hospitalized individuals are excluded from this estimate [13]. Furthermore, epidemiologic data on HCV mono-infection and HCV/HBV or HCV/HIV co-infection in female populations are rare. Because women constitute a large proportion of the total adult population, monitoring HCV prevalence trends, as has been previously done with the HIV epidemic, is useful for assessing the extent of HCV infection within the general population. To the best of our knowledge, this study represents one of the largest cohorts of HCV-positive women whose co-infection status was identified using

surveillance data.

Our findings add to previous evidence about HCV infection to reveal that there has been a substantial increase from 2004 to 2011 in the number of HCV infections in adolescents and young adults between the ages of 15 and 25 years. When we compared the age distribution for cases reported in 2004 and those reported in 2011, we observed an increase in the variance for 2004 and 2011. Similar observations were also reported from three studies [1, 98, 99] that used HCV surveillance data from Massachusetts, New York and Wisconsin. In these studies, the young adults were predominantly White residents in rural and urban communities and IDU was associated with the observed increase [1, 98, 99]. In our study, when we looked at age distribution by race for cases with available race information, the results for White women appeared to be evident than those for Black women. It should be noted that since race information was missing for over 57% of reported HCV cases, caution should be applied to the interpretation of these results. Furthermore, since we lacked data on HCV risk history for these cases reported, we were unable to assess if IDU explained the observed increase in the number of HCV cases reported for young adult and adolescents in 2011.

HCV/HIV co-infection was present in 4% of all the chronic HCV cases. These were primarily Black middle-aged women from urban communities in SC who had their HIV infection identified first, reported IDU as the main risk factor for HIV transmission and had a median CD4 count of 307 cells/mm^2 (IQR 156-528 cells/mm^2) at baseline testing. Our results are comparable to findings from a US study that used HIV-infected women visiting a prenatal clinic and reported an HCV/HIV prevalence of 4.9% [34]. Conversely, other US epidemiological studies on HCV/HIV co-infection have yielded

prevalences between 16% and 36% [100-102], although these studies were conducted primarily in HIV-positive cohorts that were disproportionately male. We obtained the number of women reported to be living with HIV/AIDS in SC as of December 2011 to determine the proportion of HIV infected women that are co-infected with HCV. We estimated that 9.4% (432/4,578) of HIV positive women are co-infected with HCV/HIV.

Because of shared routes of transmission for both HCV and HIV infections, it is not surprising that in our study, IDU and heterosexual contact were the most common self-reported HIV risk factor. HIV was diagnosed first in 79% of the cases and the 9-year median time between HIV and a subsequent chronic HCV diagnosis is a significant finding. CDC and the US Preventive Services Task Force recommend HCV screening in HIV infected individuals at the time of entry into health care but does not recommend a frequency after baseline screening. Our finding here could help make the case for recommending routine HCV screening amongst HIV-positive individuals, especially those known to be injection drug users. Early detection of HCV infected individuals can prevent further transmission, help select the appropriate medication for treatment and consequently reduce HCV-related mortality within this population.

One explanation for why HCV was reported much later in the majority of our HCV/HIV co-infected cases is that HIV increases susceptibility of infected women to sexually acquired HCV [103], thus, it is likely the HCV infection was acquired as a consequence of being infected with HIV. In one cross-sectional study among HIV-positive women reporting no history of IDU, heterosexual contact with a male drug injector was associated with being HCV positive [104]. Conversely, in a Canadian study that used surveillance data from both genders, the authors reported HCV diagnosed first in

52% of their cases and this was independently associated with IDU behavior [105]. Although we were unable to assess the extent to which IDU or heterosexual contact was a risk factor for HCV transmission in this study, it is likely that both heterosexual contact and IDU were risk factors in HCV acquisition.

Lastly, 1% of our cases were co-infected with HCV/HBV and this estimate was comparable to an estimate of 1.4% recently reported by Tyson et al. [106]. In other US studies [27, 107, 108] higher prevalences for past HBV exposure among HCV cohorts have been reported to range from 25%-65%. Our HCV/HBV co-infected women had their HBV diagnosed first and this is likely due to universal screening practices for HBV infection during obstetric care. In contrast to Bini et al. [107] who reported HCV/HBV co-infection to be highest amongst individuals with age less than 40 years, we found that 67% of our HCV/HBV cases were between the ages of 40 and 59 years old.

Our findings here are limited because the completeness of HCV surveillance data from CHESS is unknown. Also, our HCV data is biased towards persons more likely to have health insurance and to be receiving health care. Thus, this data may not be a representative sample of all the HCV-infected cases that occurred over the study period. We could not estimate the prevalence of HCV infection in our study due to the lack of a true denominator for our surveillance cases. Furthermore, our data on diagnosis date for HCV, HBV and HIV infection reflects approximate times for when these conditions were detected and subsequently reported. However, we cannot determine when these infections occurred or confirm the order of either HCV/HIV or HCV/HBV infection for those who were co-infected. Finally, several missing data from key demographic variables, such as

race/ethnicity and HCV risk factor, in the CHESS database may have weakened our description of this population.

Our study offers the first description of HCV/HIV and HCV/HBV co-infection prevalence within the SC female population. The use of statewide surveillance data to ascertain the co-infection status of HCV-infected female cases is another strength of this study. Finally, our study represents one of the largest cohorts of HCV-infected females in the US. Characteristics of these HCV mono-infected and co-infected women can be used to target screening and prevention efforts at the local and state level.

In summary, our results appear to be consistent with what is already known about HCV infection. HCV mono-infected cases were predominantly middle-aged White women whereas those co-infected with HCV/HIV were largely Black middle-aged women from urban areas who reported either IDU or heterosexual contact as their main risk factor for HIV transmission. There was a substantial increase in the number of HCV infections reported for adolescents and young adults between the ages of 15 and 25 years. Our co-infection prevalence was close to the reported range of previous estimates of 4.9%- 36% and 1.4%-65% for HCV/HIV and HCV/HBV respectively.

The findings suggest a need for resources to be directed at improving screening and prevention efforts among Black and White middle aged women and most especially, in young persons between the ages of 15 and 25 years. Over three-thirds of the HCV/HIV infected women in our study belonged to the 1945 to 1965 birth cohort. These individuals benefit from combined testing for HIV and HCV infections. Not only will this approach be cost-effective, it can lead to the timely identification of HCV/HIV co-infected individuals. HIV-infected individuals with IDU as a risk factor or heterosexual contact

with male IDU should be routinely screened for HCV because of the risk of ongoing exposure to HCV. Because HCV risk behavior and detailed race information were unavailable for analysis in our HCV surveillance data, initiatives to fund and improve HCV case reporting data are warranted.

Table 3.1- Demographics of hepatitis C (HCV), hepatitis B virus (HBV/HCV) and HIV co-infected female cases in South Carolina reported to CHESS and eHARS between 2004 and 2011

	Co-infection		**Mono-infection**	
HCV-related variables[a]	HCV/HBV n (%)	HCV/HIV n (%)	HCV n (%)	P-value[c]
Number of cases	94	432	9664	
Age at HCV, years, median (range)	49 (21 - 79)	48 (18 - 75)	48 (1 - 99)	
≤20	0	1 (<1)	136 (1)	<0.001
20-29	5 (5)	15 (3)	755 (8)	
30-39	13 (14)	57 (13)	1229 (13)	
40-49	33 (35)	190 (44)	3157 (33)	
50-59	30 (32)	145 (34)	3113 (32)	
≥60	12 (13)	22 (5)	1219 (13)	
Missing	*1 (1)*	*2 (<1)*	*55 (<1)*	
Year HCV was reported				0.018
2004	13 (14)	54 (13)	1014 (10)	
2005	20 (21)	60 (14)	1385 (14)	
2006	13 (14)	65 (15)	1447 (15)	
2007	14 (15)	62 (14)	1299 (13)	
2008	9 (10)	70 (16)	1293 (13)	
2009	12 (13)	50 (12)	1048 (11)	
2010	8 (8)	47 (11)	1054 (11)	
2011	5 (5)	24 (6)	1124 (12)	
Race				
Black	13 (14)	330 (76)	1184 (12)	<0.001
White	24 (26)	92 (21)	2562 (27)	
Other	3 (3)	7 (2)	110 (1)	
Missing	*54 (57)*	*3 (1)*	*5808 (60)*	
Case classification				
Confirmed	79 (84)	381 (88)	8469 (88)	0.53
Probable	15 (16)	51 (12)	1195 (12)	
DHEC region				
Low country	21 (22)	91 (21)	1752 (18)	<0.001
Midlands	30 (32)	134 (31)	2073 (21)	
Pee Dee	13 (14)	82 (19)	1706 (18)	
Upstate	15 (16)	59 (14)	2530 (26)	
Missing	*15 (16)*	*66 (15)*	*1603 (17)*	

Table 3.1- Demographics of hepatitis C (HCV), hepatitis B virus (HBV/HCV) and HIV co-infected female cases in South Carolina reported to CHESS and eHARS between 2004 and 2011 *(cont'd.)*

	Co-infection		**Mono-infection**	
HCV-related variables[a]	HCV/HBV n (%)	HCV/HIV n (%)	HCV n (%)	P-value[c]
Timing of HCV/HBV diagnosis				
HBV reported first	16 (16)			
HCV and HBV reported concurrently[b]	63 (62)			
HCV reported first	22 (22)			

HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus; CHESS, Carolina's Health Electronic Surveillance System; DHEC, Department of Health and Environmental Control
*Percentages may not equal to 100 because of rounding.
[a]HBV-related variables were obtained from CHESS surveillance database.
[b]HBV and HCV were reported to CHESS within the same year of diagnosis.
[c]Pearson Chi-square value

Table 3.2- Characteristics of hepatitis C and HIV co-infected female cases in South Carolina reported to CHESS and eHARS between 2004 and 2011

	Co-infection
HIV-related variables[a]	cHCV/HIV (N %)
Total number of cases	432
Year of HIV diagnosis	
1985-1989	26 (6)
1990-1994	81 (19)
1995-1999	96 (22)
2000-2004	108 (25)
2005-2009	92 (21)
≥ 2010	29 (7)
Age at HIV, years, median (range)	40 (16-69)
≤20	11 (3)
20-29	56 (13)
30-39	144 (33)
40-49	154 (36)
50-59	56 (13)
≥60	9 (2)
Timing of HIV-HCV diagnosis	
HIV reported first	340 (79)
HIV and HCV reported together[b]	67 (16)
HCV reported first	25 (5)
HIV disease stage at diagnosis	
HIV only	149 (34)
HIV and later AIDS	181 (42)
HIV and AIDS diagnosed simultaneously	102 (24)
HIV transmission category	
Injecting drug use	197 (46)
Heterosexual	166 (38)
No identified risk[c]	68 (16)
Other[d]	1 (<1)
Residence at time of HIV diagnosis	
Urban	254 (59)
Rural	102 (24)

Table 3.2. Characteristics of hepatitis C and HIV co-infected female cases in South Carolina reported to CHESS and eHARS between 2004 and 2011 *(cont'd.)*

	Co-infection
HIV-related variables	cHBV/HIV (N%)
Source of HIV report	
County health department	97 (22)
Hospital	125 (29)
Group practice	49 (11)
Other state[e]	54 (13)
Other[f]	28 (6)
Unknown	79 (18)
$CD4^+$ percentage	
No. of women with data available	424
0-25%	258 (60)
26-40%	124 (29)
≥40%	42 (10)
First viral load group	
No. of women with data available	381
≤ 10,000 copies/mL	174 (40)
>10,000 copies/mL	207 (48)
First $CD4^+$ count	
No. of women with data available	427
median (IQR) cells/μL	307 (156-528)
First viral load	
No. of women with data available	381
median (IQR) copies/mL	14000 (1780-73860)

HIV, human immunodeficiency virus; HCV, hepatitis C virus; HBV, hepatitis B virus; CD4, cluster of differentiation 4; mL, milliliter; IDU, injecting drug use.

*Percentages may not equal to 100 because of rounding.

[a]These variables were obtained from the enhanced HIV/AIDS Reporting System (eHARS).

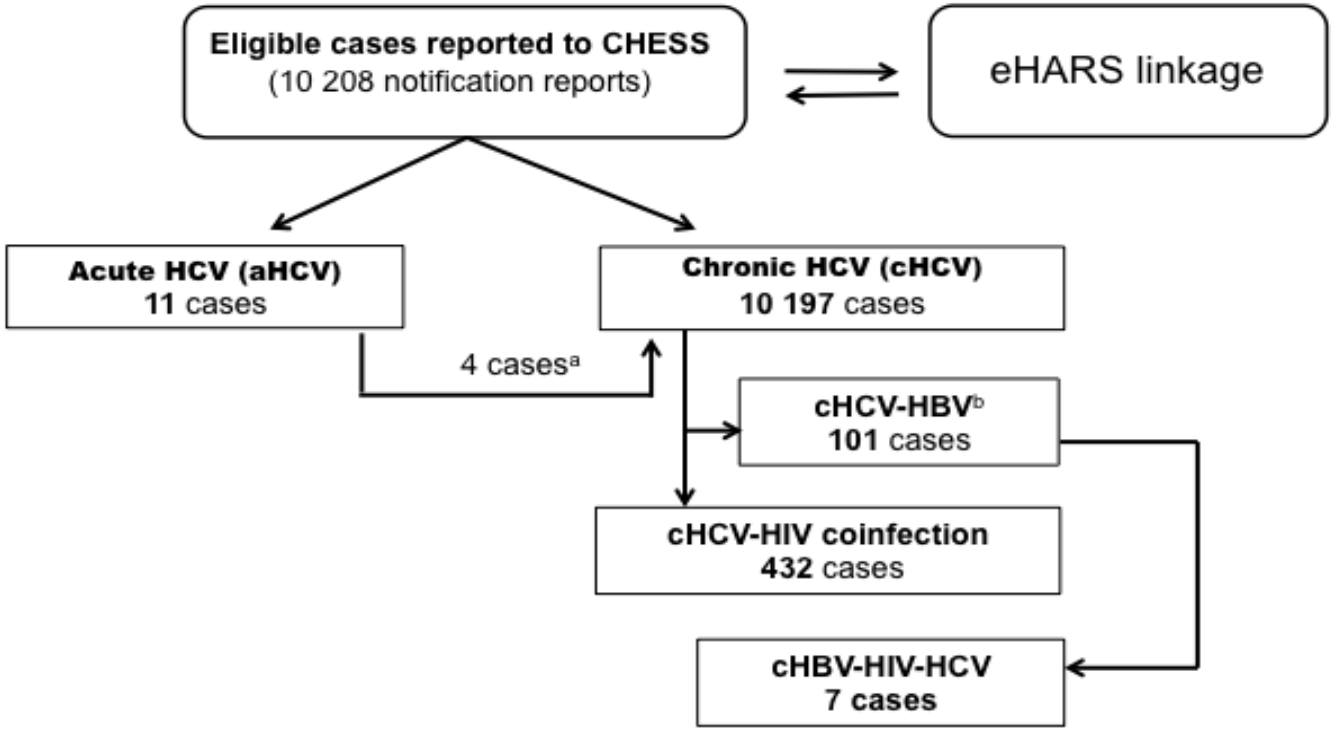
[b]HIV and HCV were diagnosed and reported in the same year.

[c]Adults with no risk factors reported (n=17) or no identified risk factors (n=51).

[d]Other risk category includes heterosexual who had sexual intercourse with a high-risk individual (e.g., IDU, male bisexual, transfused individual, HIV-positive individual)

[e]Other state includes reports from other states.

[f]Includes blood banks/business (n=5); private physician (n=5); state (n=17); department of mental health (n=1)



[a] 4 acute HCV cases were also reported as chronic HCV cases over the study period
[b] 20 of these acute HBV cases 74 of the remaining cases were chronic HBV cases
HBV=Hepatitis B virus

Figure 3.1 Sample population and flow for hepatitis C virus (HCV) female cases reported to CHESS linked with HIV data from eHARS; January 1, 2004 to December 31, 2011

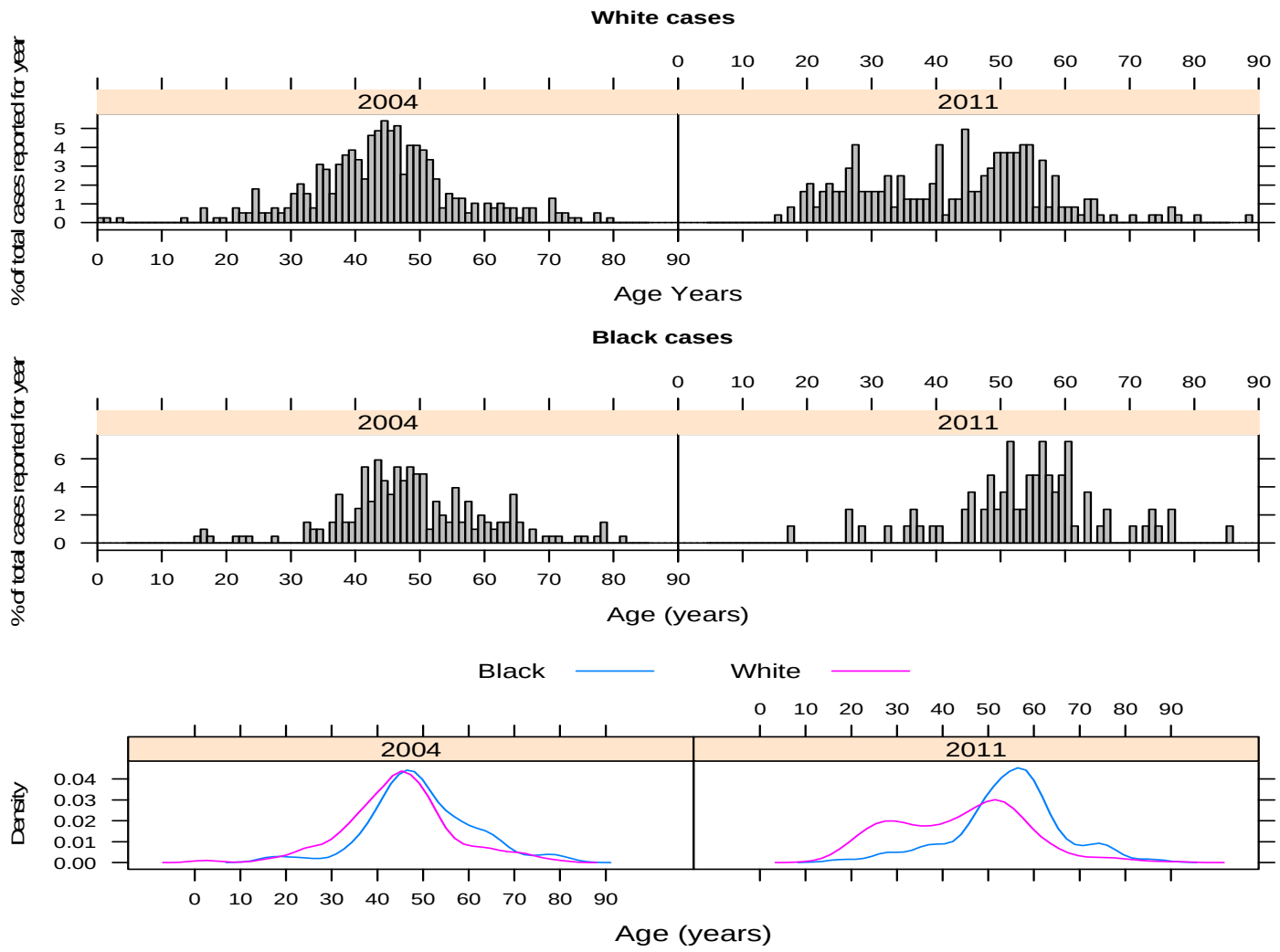


Figure 3.2 Age dis
female cases of he

CHAPTER 4

SPATIAL ANALYSIS OF HEPATITIS C VIRUS AMONG REPORTED FEMALE CASES IN SOUTH CAROLINA: AN ECOLOGICAL STUDY

4.1 Abstract

Chronic Hepatitis C virus (HCV) is a continuing global public health threat affecting millions worldwide and in 2007 the number of HCV-related deaths exceeded the number of HIV-related deaths in the United States. The purpose of this study was to investigate the spatial distribution of reported female cases of HCV in South Carolina (SC) so as to identify areas with high risk for HCV infection and describe their characteristics for targeted public health action. Additionally, we assessed if the number of drug abuse treatment admissions, an indicator for drug use, was a potential explanatory covariate for HCV risk in these areas. We evaluated aggregated counts of reported HCV-infected female cases that occurred in SC between 2004 and 2011. Using a Bayesian hierarchical spatial model that included potential confounders, a map with smoothed standardized morbidity ratio's (SMR) for HCV disease was created for each of the 46 counties in SC. Of the 10, 197 HCV-infected reports received for the study period, 8,511 (83.5%) reports with geographical information were used for our spatial analysis. There was significant variation in the HCV risk among the counties in SC. Nine out of the fourteen counties with a smoothed SMR >1 were statistically significant. These high-risk

counties were mainly located along the coastal, midland and mountain regions of the state. Even though six of these high-risk counties were areas with metropolitan centers, the remaining three were federally designated rural counties that had low per capita incomes and a large proportion of its residents living in poverty. We found no link between the number of drug abuse treatment admissions and HCV risk among these counties. Our results establish that there are areas in SC where the observed count for HCV infections is higher than expected. Targeted public health action is needed to help reduce the risk of the disease in these areas, especially in those rural counties. Future research should consider other unmeasured factors so as to better understand the underlying cause for high HCV risk in these counties.

4.2 Introduction

Chronic Hepatitis C virus (HCV) is the most common blood-borne infection and the leading indication for liver transplantation in the United States (US) [109, 110]. There are at least 3.5 million US residents who are infected with HCV [83, 84]. Of the three types of viral hepatitis (hepatitis A, B, and C), HCV accounted for the most deaths and had the highest death rate between years 2006 and 2010 [61, 111]. As of 2007, the number of HCV-related deaths in the US exceeded the number of HIV-related deaths [5].

HCV is largely transmitted through percutaneous exposure to infected blood and injecting drug use (IDU) is often the principal risk factor for disease transmission. Thus, a substantial proportion of 'newly diagnosed' HCV infections are confined to individuals who have a history of injecting drugs or are current injecting drug users (IDUs) [97]. National trends reveal an emerging epidemic of HCV infections among young non-urban IDU's across the country [1, 98, 112]. In South Carolina (SC), surveillance data from a

descriptive study that used reported HCV-infected female cases uncovered a similar pattern; there was a substantial increase in the number of HCV infections reported for white females between the ages of 15 and 25 years after comparing 2004 data to 2011 data [113]. In spite of these findings the spatial epidemiology of these HCV-infected cases have not been investigated and it is unknown if these reported HCV cases occur more in rural SC as has been previously reported in other US states [1, 98, 99].

Disease mapping provides a visual representation of how disease is geographically dispersed. Assessing the geographic distribution of disease cases, especially those recorded through disease surveillance, has the potential of identifying areas of unusual high risk so that public health action may be taken [114]. Such initial work can enable better resource allocation and efficient risk assessment as well as enhance policy decision-making [114]. Furthermore, disease mapping may generate new causal hypothesis that can be used to provide context for future analytical studies [115].

Increasingly in spatial epidemiology, Bayesian small area risk models have been consistently used to map disease risks as well assess associations between potential explanatory covariates and disease risk estimates. Yet, there is only one US study [116] to date that has employed the use of these Bayesian disease mapping techniques to evaluate the geographic distribution of HCV cases reported through disease surveillance.

Using previously reported data [113], we conducted an ecological spatial analysis of prevalent HCV females cases in SC from 2004 to 2011 to identify which counties in SC exhibit elevated risks for HCV infection and to describe the population characteristics of these identified high-risk areas. Additionally, we assessed the total number of drug abuse

treatment admissions within these counties as a potential explanatory covariate for HCV disease risk.

4.3 Methods

Hepatitis C data

The SC Division of Acute Disease Epidemiology (DADE) provided the viral hepatitis data for this analysis. We included all confirmed or probable female cases of HCV with a report date between January 1st, 2004 and December 31st, 2011 along with demographic data on the reported age, race, zip code and county of residence. The case definitions used here and database from which these cases were extracted from have been described elsewhere [113]. Approval was received from SC Department of Health and Environmental Control (SCDHEC) and the University of SC Office of Research Compliance.

Drug abuse treatment admission data

Drug abuse treatment admission is an indicator of illicit drug use several studies used it to monitor national trends in drug use and abuse have [117-119]. Aggregated county data on the number of admissions for drug abuse treatment came from the Department of Alcohol and other Drug Abuse Services (DOADAS). Publicly funded drug abuse treatment facilities in SC are required to report patient information recorded at the time of intake to DOADAS. Reported data elements include the patient's primary or secondary substances of abuse, the route of intake, age, gender, race, county of residence, type of treatment and prior treatment admissions. DAODAS data covers all admissions rather than individuals, therefore, one individual may be represented multiple times in the

dataset. For the purpose of our analysis, we only considered unique admissions for where the primary, secondary or tertiary substance of abuse involves cocaine, methamphetamine, opiates, sedatives or stimulant use. Only treatment admissions for SC female residents that occurred from 2005 to 2011 were used for our analysis. Data from 2004 was unavailable and therefore not included in our analysis. We excluded any treatment admissions for patients whose primary or secondary substance abuse problem was listed as alcohol, marijuana or hashish.

Geographic location and population data

Our geographical unit of analysis was the county and we considered all 46 counties within the state for our spatial analysis. Data describing the population and socio-economic conditions within each county were obtained from the US Census Bureau, USA counties data file download [120] and included as potential confounders of HCV disease risk in our Bayesian hierarchical model. After review of literature, our list of potential confounders included the proportion of White female residents (race) in 2007, proportion of persons aged ≥ 24 with a bachelor's degree or higher (education) between 2005 and 2009, percentage of foreign born residents from 2005-2009, as an indicator of resident immigrant population and percentage of people of all ages living in poverty in 2007. Population counts of females residing in each county were total average female population count from 2004 to 2011, and this was also obtained from US Census Bureau. These data were used to calculate indirectly standardized morbidity ratios (SMR) described below. The geographic boundary file used in this was study was downloaded from the SCDHEC geographic information systems data-clearing house.

Spatial analysis

This study is ecological and investigates the spatial distribution of HCV infection within the state of SC. We performed our spatial analysis of reported HCV-infected cases in three steps: First, we estimated the expected number of HCV cases in each county. Expected counts are based on the size of the population living in each county. Secondly, we calculated the standardized morbidity ratio (SMR) for HCV cases in each county, by dividing the observed counts of HCV-infected cases by the expected number. SMR values above one represent areas with elevated levels of disease risk whereas values below one indicate an area of reduced disease risk. Lastly, using a full Bayesian approach, a geographically weighted Poisson model with a random spatial effect term was applied to 'smoothen' the raw SMRs before mapping [121]. This last step was repeated for an unadjusted model, a model that only included our main covariate of interest and a final model that included all the potential confounders and our main covariate of interest.

Bayesian spatial smoothing of SMRs for small area disease mapping reduces random fluctuation of rates from unstable SMRs due to small counts and small population sizes [114, 122-124]. Since HCV counts are often small and rare, case counts were modeled with a Poisson distribution. We used a Bayesian hierarchical model with a log-link, proposed by Besag, York and Molli□ (BYM model) in 1991 [125], to fit the raw SMR's with our covariate of interest (total number of drug treatments) and potential confounders. The BYM model is a hierarchical model that uses a conditional auto-regressive distribution and incorporates the effect of neighboring areas under study [126 124, 125]. Put differently, the BYM model shrinks unstable risks toward the local mean risk by "borrowing" information between neighboring areas [127]. We standardized all our

covariates by subtracting the mean and then dividing the result by its standard error. We implemented the BYM model in WinBUGS [128] using Monte Carlo Markov Chain (MCMC) simulation, in which samples are generated from a posterior distribution given observed values. We generated 200,000 iterations with the first 20,000 discarded as "burn-in" values. The estimated mean relative risks and parameters from these samples along with their corresponding 95% credible intervals were computed and mapped. To ensure that our model converged the time series plots produced in WinBUGS were visually checked and assessed. Significant high-risk areas were determined from 95% credible intervals obtained with WinBUGS using our full Bayes BYM model. All of our spatial analysis and graphing were completed with R statistical program [96] version 2.12.

4.4 Results

Our initial dataset consisted of 10,197 reports of chronic HCV-infected female cases that were reported to DADE between 2004 and 2011. Of these, 1,686 (16.5%) cases were missing geographical location information and were excluded from our analysis. Our final data used for the spatial analysis consisted of 8,511 reports. Eighty-eight percent (n = 7,473) met the clinical definition for a confirmed case and 40% were assessed by either a RIBA or RNA test. The mean age of all the cases was 47.7 years. None of the 46 counties had zero observed counts of HCV infection and counties with the highest concentration of HCV reports matched up to major metropolitan areas in SC (Figure 4.1).

The posterior means and Deviance information criterion (DIC) values from our Bayesian hierarchical model are summarized in Table 4.1. From this table, we selected the most parsimonious model with the smallest DIC value that converged. This final

model contained our standardized main covariate variable of interest (total number of drug treatment admissions) and potential confounders (race, education, proportion of foreign-born residents and poverty). From this analysis, no significant associations between total number of drug treatment admissions and HCV infection risk were detected.

Unsmoothed raw SMR's for HCV infection ranged from 0.11 to 3.26. However, because these raw estimates can be very imprecise due to areas with small populations and are affected by possible spatial correlation between disease risks in nearby areas, we used our Bayesian model described above to produce smoothed estimates of disease risk. Several counties with significant risks for HCV infection emerged (Figure 4.2) from this analysis. Our smoothed relative risks ranged from 0.26 to 2.82 and high-risk areas for HCV infection were observed in the coastal, midlands and Piedmont (mountain) regions of the state. Based on our computed credible intervals from the BYM model, nine out of the fourteen counties with an SMR >1, were statistically significant. Specifically, the counties of Charleston, Darlington, Florence, Georgetown, Greenville, Horry, Oconee, McCormick and Richland showed a significant high risk for HCV infection. The socio-economic characteristics of these areas are summarized in Table 4.2. Compared to the per capita income of $33,388 from 2012 [129] for the entire state, four of the nine counties had lower per capita incomes. Three counties (McCormick, Georgetown, Oconee) were federally designated rural counties whereas the remaining counties were counties with metropolitan centers. Of note, McCormick county exhibited the highest risk for HCV infection (SMR=2.82) even after the data has been spatially filtered. This county also had

the largest percentage of people of all ages living in poverty and the lowest percentage of persons, 24 or older, with at least a college degree.

4.5 Discussion

We investigated the spatial epidemiology of HCV infections in South Carolina (SC) as reported to disease surveillance between 2004 and 2011 using Bayesian smoothing techniques. The results revealed that there is substantial variation in HCV infection risk among the counties in SC and several of these counties were identified as high-risk areas. These high-risk counties were a mixture of metropolitan and rural areas distributed across the state. We did not find a significant relationship between number of drug abuse treatment admissions reported in these counties and the HCV disease risk. Additionally, we detected no relationship between HCV risk and confounding covariates for which we adjusted in the BYM model.

Even though it has been well established that injecting drug use (IDU) is a leading risk factor for HCV infection in developed countries, the number of drug abuse treatment admissions in our Bayesian model did not explain the observed spatial variations in HCV infections in SC. One explanation to this finding is that our aggregated counts of drug abuse treatment admissions may not accurately reflect the extent of illicit drug use within counties in SC. Since only publicly funded treatment centers report their data to DOADAS, data from privately funded treatment centers are not included in these counts. Furthermore, the treatment population represented in the DOADAS data set may not be representative of all patients undergoing drug abuse treatment in SC. Lastly we could not confirm if the this data comprised of only injector admissions.

Yet, the fact that there was little change in the SMR's after adjusting for potential confounders (race, percent foreign born, education and poverty) and applying smoothing, is an important observation in itself. This implies that there are other unobserved factors that might be account for the high HCV prevalence in these areas and will require further investigation. Up until recently, HCV infection related to IDU risk behavior was understood to occur more in metropolitan centers as it is where drug trade is high and readily available. However this notion is quickly changing. Three (33%), out of the nine high-risk counties we identified were federal designated rural counties which, corresponds to recent reports of an emerging HCV epidemic in rural and suburban communities within the US [1, 98, 112]. It is believed that this emerging problem may be related to the national opioid epidemic seen largely in young injectors in nonurban areas [130, 131].

The interpretation of our findings must also consider some weaknesses. First, since small area analysis are ecological approaches, results obtained from this aggregated levels of observation cannot be used to make assumptions regarding individual risks as the result may not hold true at individual levels. Secondly, the geographic resolution at which this study was carried out may have impacted our results, as aggregating data to different areal arrangements (e.g. census or neighborhood tracts) may lead to different results which may affect the interpretation of our findings [127]. Another limitation to consider is the fact that about 16% of all the HCV cases reported for study period were excluded because of missing location data. These exclusions may have impacted the observed HCV prevalence. Lastly, the HCV surveillance cases used here are a mixture of asymptomatic individuals with risk factors who have been screened for disease and those

showing signs of chronic liver disease. Therefore, it is likely that the data to some extent, may reflect screening practices and initiatives rather than true prevalence or incidence of HCV infection in various regions [116].

Taken these limitations into account, we were able to identify counties in SC with significant HCV infection risks that warrant further investigations. The characteristics of these significant high-risk areas described here should also motivate more targeted prevention efforts to be undertaken within the state of South Carolina. Even though we were unable provide a reasonable explanation as to why McCormick county exhibited an unusually high SMR, this finding warrants further investigation by public health officials in order to understand the underlying cause(s) for this observation.

Table 4.1- Final Besag,York and Molli (BYM) model for reported female cases of hepatitis C virus (HCV) infection, South Carolina, 2004-2011, posterior means and 95% credible interval

Parameter	Posterior mean	95 % Credible Interval
Total number of Drug abuse treatment admissions	1.01	0.97-1.05
Proportion White	1.00	0.97-1.04
Proportion aged ≥ 25 years with at least a college degree or higher	1.02	0.99-1.06
Proportion of foreign residents	0.97	0.95-1.00
Proportion of all ages living below poverty	0.98	0.95-1.02
Model	**Included covariate**	**DIC**
1. Unadjusted	None	389.692
2. Adjusted for Drug	Drug	389.304
3. Adjusted for all covariates	Drug, White, Foreign, Poverty, Education	388.88

Table 4.2- Characteristics of counties in South Carolina with significant smoothed risks for hepatitis C infection

County	Number of HCV cases	Average female population (2004-2011)	Per Capita income (2011)	% Poverty (2007)[a]	% White (2007)	% Educated[b]	% Foreign born residents	Number of drug abuse treatment admissions (2005-2011)	Smoothed SMR
SC	**8,522**	**2,063,083**	**33,388**	**14.30**	**68.7**	**23.5**	**4.4**	**68,010**	**-**
McCormick	57	4,659	27,509	19.6	50.7	14.9	1.6	88	2.8
Florence	383	66,662	34,450	17.8	57.5	20.6	2.4	1,913	1.44
Richland	932	165,940	36,347	12.7	50	36.6	5.1	4,455	1.34
Darlington	177	35,513	29,355	18.7	56.9	17.1	1.6	1,651	1.31
Georgetown	152	29,097	38,403	17.7	65.1	22	3.1	682	1.28
Oconee	169	33,661	31,964	13.9	90.4	21	3.3	1,420	1.24
Charleston	787	160,182	41,656	15.2	65.5	36.7	5	5,273	1.19
Horry	561	100,095	29,148	14	83	21	6.2	2,757	1.17
Greenville	950	194,834	37689	12.2	78	29.1	7.8	7, 001	1.15

SMR= standardized morbidity ratio; HCV=hepatitis C virus; SC=South Carolina.

[b] Proportion of people with age ≥ 25 with a college degree or more

[a] Proportion of people of all ages living in poverty in 2007.

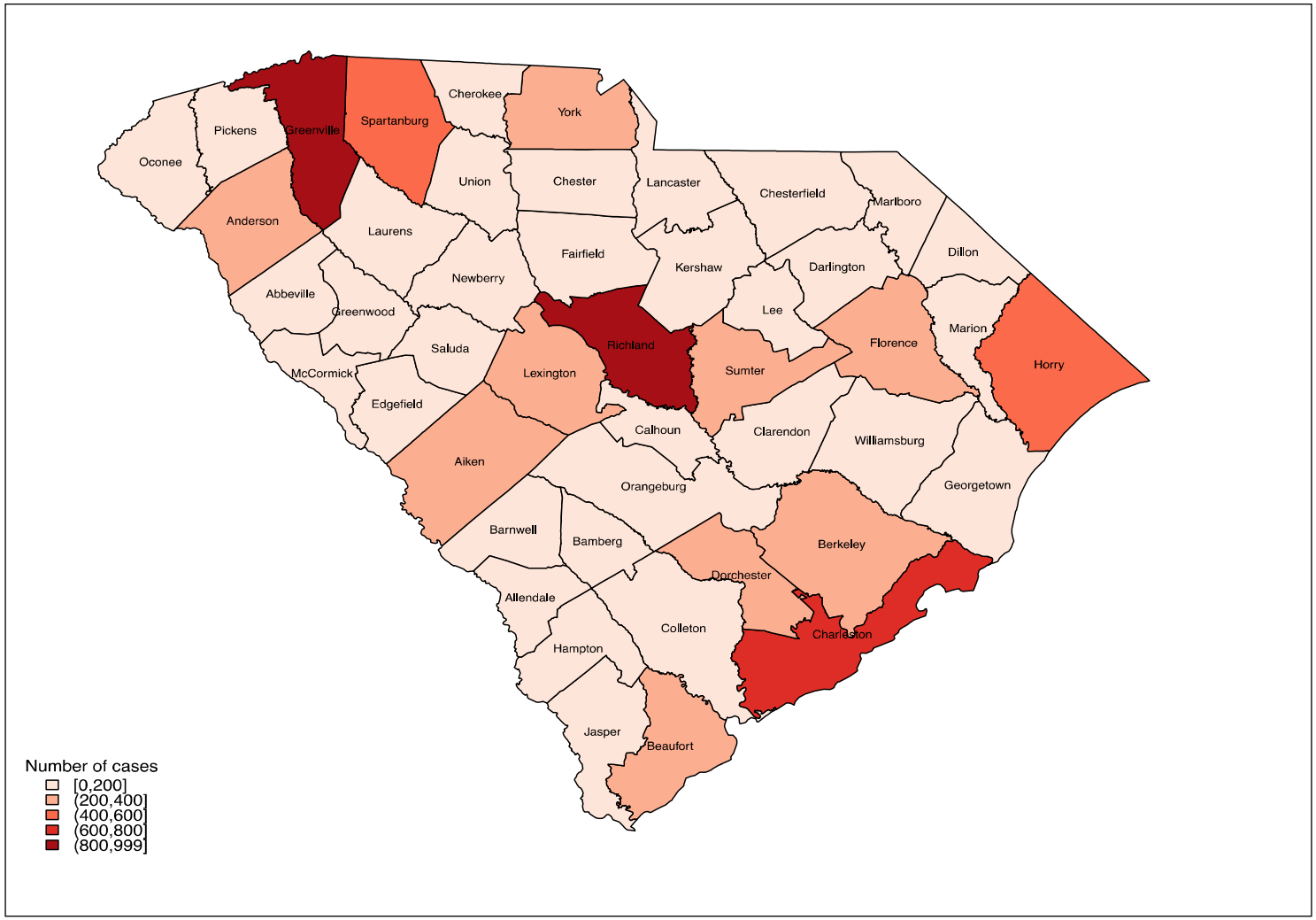


Figure 4.1 Map of South Carolina showing raw counts of reported female cases of hepatitis C infection per county, 2004-2011.

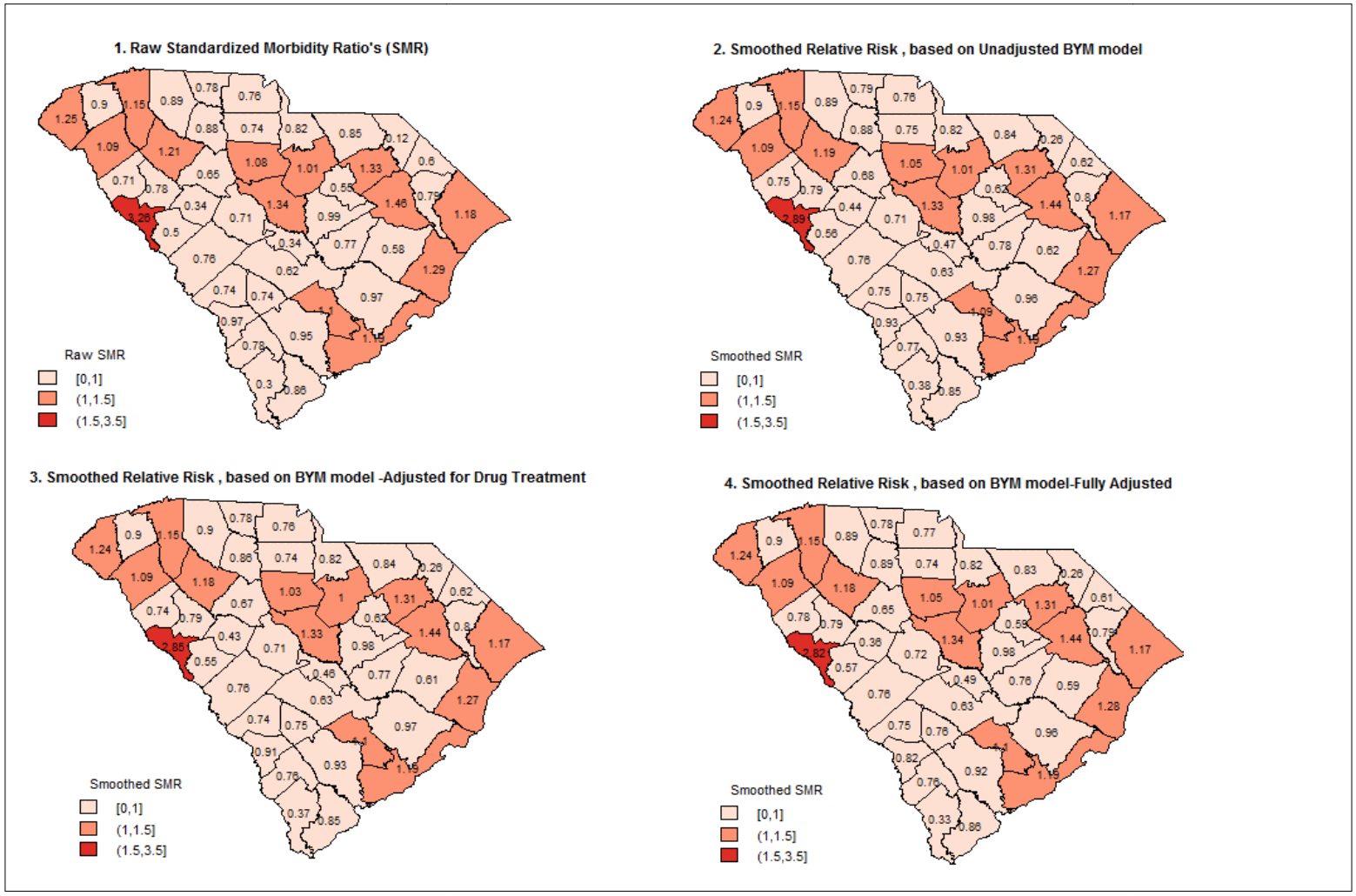


Figure 4.2 Standardized morbidity ratios (SMR's) and smoothed relative risks for reported hepatitis C virus female cases of hepatitis C viral infections in South Carolina, 2004-2011

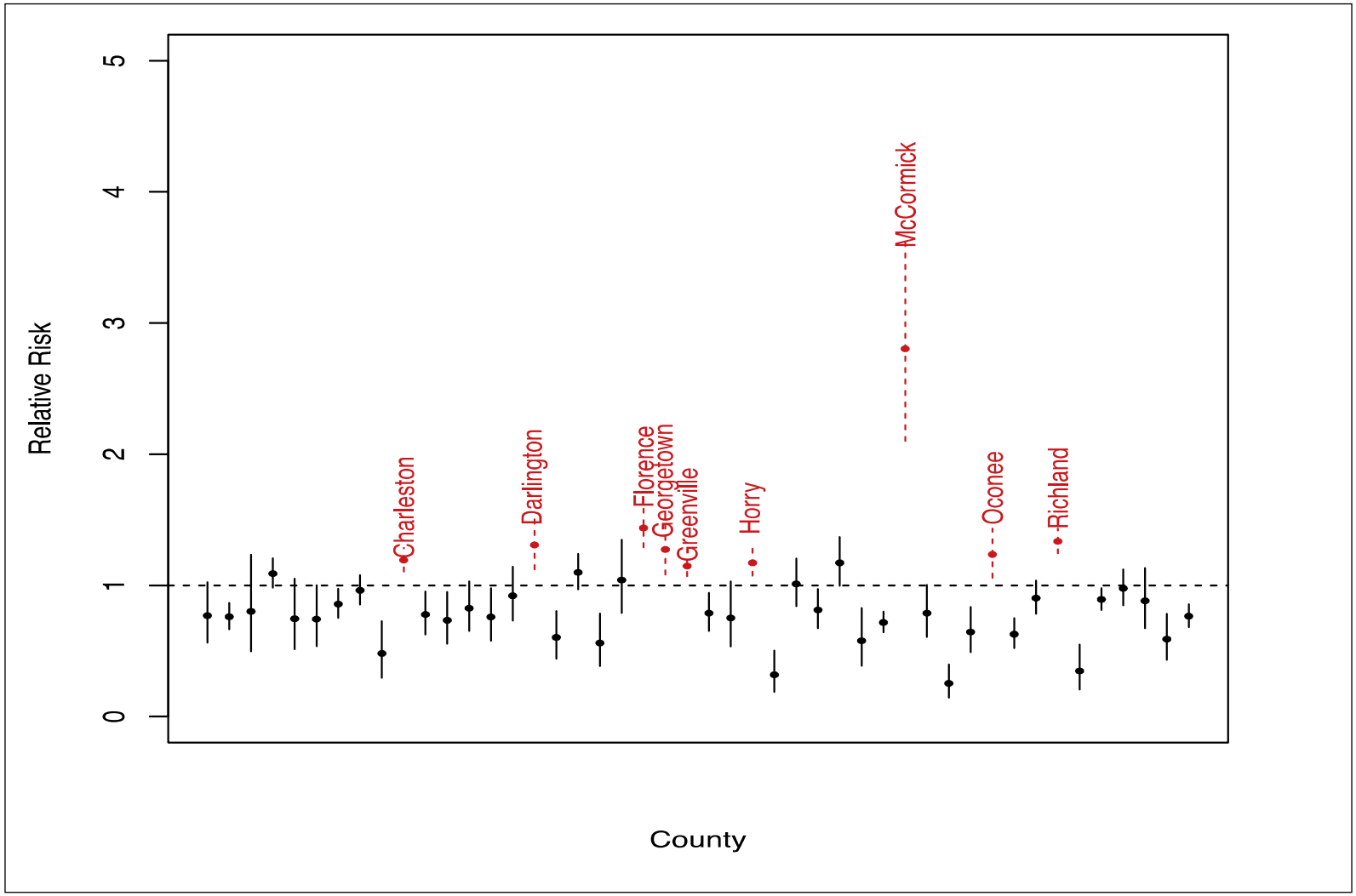


Figure 4.3 95% credible intervals of the relative risks obtained from BYM model

CHAPTER 5

PREGNANCY OUTCOMES IN WOMEN INFECTED WITH HEPATITIS B OR C VIRUS

5.1 Abstract

The objective of this study was to estimate the association between maternal hepatitis B or C (HBV, HCV) infection status during pregnancy and preterm birth, small for gestational age (SGA), low birth weight (LBW) and neonatal intensive care unit (NICU) admission. We utilized data from a cohort of singleton pregnancies from women, aged 15-49, whose births were recorded in the South Carolina birth registry between 2004 and 2011. Restricting our analysis to women who contributed more than one pregnancy over the study period, we used logistic regression to analyze pregnancy outcomes after a subsequent pregnancy after considering infection status in a prior pregnancy. A total of 438,208 singleton pregnancies in women aged 15-49 years were recorded in the SC birth registry over the 8-year study period. Of these, 211,457 (48.3 %) pregnancies were from women who contributed two or more consecutive pregnancies prospectively and 95,291 (21.7%) pregnancies were subsequent pregnancies that were used for the analysis. Among pregnancies that were studied, 276 (0.29%) were HCV-infected and 236 (0.25%) were HBV-infected. After adjusting for known confounders babies born to HCV-infected mothers whose status changed from a non-diseased state in their previous pregnancy, to a diseased status in their subsequent pregnancy had higher odds of LBW (OR=2.07, 95% CI 1.28- 3.37) after being compared to non-infected cases.

No increase in odds was identified for HBV mothers. Our results supports an association between LBW and HCV infection, specifically for mothers who transitioned from a non-infected status state in their previous pregnancy, to an infected status during their subsequent pregnancy in our study.

5.2 Introduction

Approximately one third of the world's population have been infected with Hepatitis B virus (HBV) and between 130-170 million, 2-3% of the world's population, are chronically infected with hepatitis C virus (HCV) [82]. Together, both infections constitute a major global health problem as they cause significant liver-related morbidity and mortality among those infected [60, 80]. In low endemic regions, such as the United States (US), HBV and HCV affect a considerable proportion of women. Based on data from the National Health and Nutrition Examination Surveys (NHANES), chronic HBV infection affects about 0.19% of women whereas approximately 1.1% are chronically infected with HCV [12, 84].

There have been varied reports on the prevalence of HCV and HBV infection in pregnant women and in women of childbearing age. Within the US, around 0.06 to 1% of pregnant women are said to be infected with HCV [28, 44, 48, 50, 132] whereas 0.09% to 5.7 % of antenatal women are infected with HBV[26, 28, 44, 48, 93, 133]. Even though these numbers appear to be small, they correspond to several thousands of HCV- and HBV-infected pregnant women who deliver at risk babies in the US annually. For instance, in one study that used birth registry data from 22 US states, it was reported that about 16,608 women who had babies in 2006 were HBV-infected [26].

The literature on how pregnancy outcomes are impacted by these viral infections remains inconclusive. Current knowledge linking preterm birth, small for gestational age (SGA), low birth weight (LBW) and neonatal intensive care unit (NICU) admission to maternal HBV or HCV infection is controversial, as these results have been mixed. While some studies have found an increased risk for preterm birth [44, 45, 47], SGA [44, 50], LBW [44, 48, 50] and neonatal intensive care unit (NICU) admission[50 50]in HCV- and HBV-positive women, other studies [28, 44, 50, 51, 57] have found differently. For example, three studies [45, 55, 134] that examined preterm births found no increased risk among mothers who tested positive to hepatitis B surface antigen (HBsAg) whereas two other studies [45, 47] reported an increased risk for preterm births among HBsAg positive women. With the exception of a few papers [28, 44, 50], most studies used small sample sizes, which limited their generalizability. Even more importantly, ICD-9 codes were used to ascertain disease exposure status and/or other potential confounders and it is likely biases from residual confounding and inaccurate exposure assessment were introduced into these studies.

Hence, more information from large, population studies that overcome some these limitations are needed to better understand how being HCV- or HBV-positive during pregnancy may impact birth outcomes. Additionally, the conventional statistical approaches used in previous studies [44, 50] have ignored correlations resulting from the clustering of multiple pregnancies from the same mother. Also, the fact that infected cases may belong to groups of “recently diagnosed” or ‘chronic carrier’ cases have been overlooked. Assuming that there is a carryover effect from a prior infected pregnancy or ongoing treatment, the risk of an adverse pregnancy outcome may be different for newly infected cases compared to those cases with a prior infected pregnancy.

In the present study, we sought to estimate the association between maternal HBV or HCV status with preterm birth, SGA, LBW and NICU admission among a retrospective cohort of antenatal women from the South Carolina (SC) birth registry data. Our approach was to assess if there was a difference in the risk (which is equal to the odds given that these outcomes are rare) for an adverse pregnancy outcome for "recently diagnosed" and 'chronic carrier' cases of maternal HCV or HBV infection compared to subsequent non-infected pregnancies.

5.3 Methods

This secondary data analysis utilized data from the SC birth registry, where data pertaining to all live births are recorded, the South Carolina (SC) Health Electronic Surveillance System (CHESS), a database that contains surveilled female cases (probable and confirmed) infected with HCV or HBV, and the Department of Alcohol and Other Drug Abuse Services (DOADAS), which contains patient level information on treatment admissions for substance abuse. Detailed information on the methods used to link birth registry data to CHESS is reported elsewhere [93, 113] Furthermore, an assessment of the concordance between these two data sources for maternal HBsAg infection status showed that the agreement was moderate and that our sensitivity for finding HBsAg positive cases in the birth registry was enhanced through the linkage [93].

Approval for this study came from the Institutional Review Boards for the SC DHEC, the University of SC Office of Research Compliance and the SC Budget and Control Board, Office of Research and Statistics (ORS) Data Oversight Committee. From the birth registry data, we selected all singleton pregnancies from women, aged 15-49, whose births were recorded between 2004 and 2011. After linkage to CHESS we

additionally linked the birth registry/CHESS file to substance abuse treatment admissions data from DAODAS. All publicly funded drug abuse treatment facilities in SC are required to report patient information recorded at the time of intake to DOADAS. Reported data elements include the patient's primary or secondary substances of abuse, the route of intake, age, gender, race, county of residence, type of treatment and prior treatment admissions. Since information on alcohol use that is recorded on the birth certificate is known to be unreliable [79], linkage to DAODAS enabled us to obtain additional information on the alcohol and drug abuse/use history of subjects in the birth registry. We only used treatment admissions data for SC female residents that occurred from 2005 to 2011, as data from 2004 was unavailable for linkage.

Exposure definition

Maternal HCV or HBV status was ascertained from the linked CHESS/birth registry data. The case definitions used to describe probable or confirmed cases of HCV and HBV from CHESS have been described elsewhere in detail [93, 113]. Our exposed cohort was made of singleton pregnancies where the mother was known to be either HBV or HCV positive prior to or during that observed pregnancy. We considered a case positive if it was reported to CHESS prior to or during the year of childbirth. Additionally, we also included positive cases from the birth data that were not reported to CHESS as being HCV or HBV positive. Pregnancies that occurred before a notification was made in CHESS or were not positive on the birth certificate were considered negative and these pregnancies made up our non-infected cohort. Any pregnancies that had an unknown HBV or HCV infection status were excluded.

Pregnancy outcomes

We had four main outcomes of interest in this study and these were preterm birth, low birth weight (LBW), small for gestational age (SGA) and neonatal intensive care unit (NICU) admission. A recent validation of the SC birth certificate data showed that obstetric estimate of gestational age, birth weight in grams and NICU admission were among the variables with excellent agreement and sensitivity [135]. Obstetric estimation of gestational age has also been previously validated in the US birth registry data [136]. Preterm birth was ascertained from obstetric estimate of gestational age in weeks and infants were considered preterm if they were born before 37 weeks. Any births with a gestational age of ≤ 20 weeks were excluded from this study, as these births are often not viable. We defined LBW as < 2,500 grams at the time of birth. SGA, a measure of fetal growth restriction, was assessed as birth weight below the 10th percentile for gestational age according to fetal sex on standardized weight charts developed by Alexander et al. [137].

Maternal characteristics

Maternal covariates of interest were abstracted from the linked birth registry/DAODAS file and these were included as potential confounders in our analysis. We categorized our potential confounders into two main groups: socio-demographic confounders and risk factor confounders. These potential confounders were selected based on a review of the literature, biological plausibility and on whether or not they were statistically significant in our univariate analysis. Socio-demographic confounders included maternal age (<20 vs. 20-29 vs. ≥ 30 years), race/ethnicity (non-Hispanic white vs. non-Hispanic Black vs. Hispanic vs. Other), education (< high school vs. high school

vs. beyond high school), Women and Infant Care (WIC) program participation (yes vs. no), payer source (Medicaid vs. private insurance vs. self pay vs. other) and adequacy of prenatal care (inadequate vs. intermediate vs. adequate vs. adequate plus vs. unknown). Adequacy of prenatal care was determined by using the revised graduated index proposed by Kotelchuck, which has been found to describe the level of prenatal care utilization among high-risk groups quite well [138, 139].

All of the risk factor related variables were dichotomized as yes vs. no. Risk factor confounders consisted of maternal tobacco use during pregnancy, presence of a sexually transmitted infection (STI), previous adverse outcome, other morbidities and history of alcohol or drug abuse. The presence of an STI was assessed as presence of any of the following infections during pregnancy; syphilis, gonorrhea, chlamydia and genital herpes. For previous adverse outcome, which also reflected the reproductive history of each case, we created a composite variable to represent a previous preterm birth or previous poor pregnancy outcome to include a perinatal death, small-for-gestational age and intra uterine growth restriction. By including prior adverse birth outcomes in the model, we focus on the risk that is related to a change of the infection status. Other pregnancy morbidities were considered present if any of the following conditions were checked on the birth certificate: pre-pregnancy hypertension, pre-pregnancy hypertension, gestational hypertension, fertility treatment, previous cesarean, gestational diabetes and vaginal bleeding. Women were classified as having a history of drug or alcohol abuse if they were found in the DAODAS database and reported alcohol, cocaine, methamphetamine, opiates, sedatives or stimulant use as either their primary, secondary or tertiary substance of abuse at the time of treatment admission and also determined their

primary route of drug of use. Lastly, we considered the parity of the pregnancies and interval between their prior and subsequent pregnancy as continuous variables in our analysis.

Statistical analysis

Our analysis was restricted to a subset of women who had two or more subsequent pregnancies captured in our dataset over the eight-year study period. From this group, we assessed pregnancy the incidence of preterm birth, LBW, SGA and NICU admission as it pertained to maternal HCV and HBV infection (Figure 5.1). We categorized our exposure group into three levels based on their exposure status at the time of their initial and subsequent pregnancy. Our reference group consisted of those pregnancies that had no disease in their initial and subsequent pregnancy (non-diseased). Our "recently diagnosed" group included those mothers who were without disease at the time of their initial pregnancy and then positive at the time of their subsequent pregnancy. Lastly, our 'chronic carriers' disease group, was defined as all those who had HBV or HCV disease in both their initial and subsequent pregnancy.

We used the Pearson Chi-square (χ^2) statistic to compare socio-demographic and risk factor variables between non-infected and infected pregnancies. Descriptive statistics were presented as number (percentage) for categorical variables and in mean (range) for continuous variables such as parity and interval between pregnancies. As we were only assessed outcomes for one time point (t=1), only one pregnancy was contributed by each woman to the dataset, thus, we had no issue with clustering from multiple pregnancies from women who contributed several pregnancies over the study period.

Multivariable logistic regression model using PROC GENMOD in SAS, was used to model the effect of 'recently diagnosed' and 'chronic carrier' infections of HCV and HBV disease on preterm birth, LBW, SGA and NICU admission. We included our main exposure of interest as categorical variable with three levels (non-diseased vs. 'recently diagnosed' vs. 'chronic carrier') into our regression model with non-diseased group serving as our baseline reference group. In order to see how our parameter estimates changed, with the addition of confounding variables to the model, we used a forward stepwise modeling approach that entered a block of variables at a time. Consequently, three models were fitted for each outcome, per disease (HCV or HBV). Since past reproductive history is strongly associated with birth outcomes [140] our crude model included our main covariate adjusted for previous adverse pregnancy outcome, parity and interval between initial and subsequent pregnancy. In this first model, the unadjusted odds ratios (ORs) were calculated for the association between each outcome and our main covariate variable. Next, the ORs in the second model were additionally adjusted for socio-demographic confounding variables. Finally, the ORs in our fully adjusted model included risk factor variables and all the variables contained in second model. All statistical tests were performed using SAS (version 9.3, SAS institute, Inc.).

5.4 Results

There were 438,208 singleton pregnancies in women aged 15-49 years recorded in the SC birth registry over the 8 study years, 2004- 2011. After excluding cases, which were co-infected with both HCV and HBV (n=30), 438,178 pregnancies remained. Of these, 211,457 (48.3 %) pregnancies were from women who contributed two or more consecutive pregnancies prospectively during the observation period. At the time of

subsequent pregnancy (t=1), we had 95, 291 (21.7%) pregnancies (Figure 5.1). Among the pregnancies that were studied, 276 (0.29%) were HCV-infected and 236 (0.25%) were HBV-infected. Removing pregnancies with missing SGA (n=31), LBW (n=7), payment source for delivery (n=646), WIC usage (n=6), parity (n=45), race (n= 195), maternal education (n=321) and tobacco use during pregnancy (n=66) left a total of at least 93, 814 pregnancies for our multivariate analysis.

Table 5.1 summarizes the differences between HCV-, HBV- and non-infected pregnancies in terms of selected socio-demographic and risk factor characteristics at the time of a subsequent pregnancy. Compared to mothers with non-infected pregnancies, HCV-infected mothers were young adults; and were more likely to be of Black non-Hispanic race, participate in WIC, use Medicaid payment for delivery, smoke during pregnancy and to receive a lower level of prenatal care. They were also more likely to have a history of alcohol and drug abuse. HBV-infected mothers were also young adults. They were more likely to be of Hispanic race, have at least a high school education, participate in WIC, use Medicaid as a source of payment for delivery and have tested positive for an STI.

When we compared the frequencies of adverse pregnancy outcomes between non-infected pregnancies and infected pregnancies (Table 5.2), those that were HCV-infected were more likely than non-infected pregnancies to have a LBW, small for gestational age and an admission to the NICU unit. These significant differences were not observed for HBV infections.

Crude and adjusted OR's for the association between preterm birth, NICU admission, LBW, SGA and HCV or HBV infection are summarized in Tables 5.3 and

5.4. Our analysis revealed a significant relationship between delivering a baby with low birth weight and maternal HCV infection among the 'recently diagnosed' group. After adjusting for potential confounders, HCV-infected cases who went from a non-diseased state in their previous pregnancy, to a diseased status in their subsequent pregnancy had higher odds of LBW (OR=2.07, 95% CI 1.28- 3.37) after being compared to non-infected cases. After adjusting for risk factors, the association for preterm birth and SGA related to HCV-infection in the 'recently diagnosed' group became marginally significant respectively (OR= 1.85, 95% CI: 0.95-3.6, p-value=0.06; and OR=1.85; 95% CI: 0.95-3.60, p-value =0.07). We found no significant associations for HCV infection and NICU admission. Likewise, when we examined the models for HBV-infected cases, we found that being HBV-infected, be it a 'recently diagnosed' or a 'chronic carrier' case, did not confer an additional risk for LBW, SGA, preterm birth and NICU admission.

5.5 Discussion

Our analysis of data from the SC birth registry revealed that being a 'recently diagnosed' HCV-infected case was independently associated with LBW but not preterm birth, SGA and NICU admission. We also found no significant associations between HBV infection and these outcomes.

As I have already noted, the few studies of HCV infection and adverse birth outcomes have provided controversial results. Two large population-based US studies found that HCV-infected mothers were at an increased risk of delivering LBW and SGA babies and babies who were admitted into NICU [44, 50]. Conversely, findings from Haider et al. [56], Jaffery et al.[57] and Hillemanns et al. [52] showed that being HCV-infected during pregnancy is not associated with delivering preterm or LBW babies. What must be noted

in these latter studies is that they were conducted in antenatal clinics that attended to 'high-risk' prenatal clients. Therefore, selection bias and use of small sample sizes could have affected their results. Our analysis drew from a large population-based cohort of pregnant women and assessed the change in infection status as exposure. While our approach to analysis was different from that used in previous studies, our overall finding with HCV infection is consistent with the findings of Connell et al. [44] and Pergam et al. [50], who both used birth registry data.

We were surprised not to detect a difference in risk for those 'chronic carrier' patients, that is, those that had a positive HCV or HBV status in their initial and subsequent pregnancies. Yet, no such significant associations were revealed in our analysis. One likely reason is that, we did not have a sufficient number of events in this group to be able to detect a significant effect. Another plausible explanation could be that after the discovery of their infection status, patients may have undergone antiviral therapy to control and stabilize their viral disease before conceiving again. Some studies that demonstrated improved outcomes in infected individuals who have undergone interferon therapy and are without persistent viremia [141, 142]. Therefore, if these patients had low viremia in their subsequent pregnancies it is unlikely the disease had any impact on their pregnancy outcome. Unfortunately, since our data did not include any information about HCV or HBV viremia or viral load during pregnancy, we had no way of confirming this speculation.

Earlier studies on HBV infection and birth outcomes have found significant risks for preterm birth [45, 47] and SGA [44] whereas other studies [44, 45, 55, 134] that looked at preterm births and LBW found no increased incidence among mothers who tested positive to

HBsAg. This study demonstrated a null effect for preterm birth, SGA, LBW, NICU admission and HBV infection. Though our results differ from the earlier non-US studies that have come from small centers, our finding for HBV is similar to the only other US study that used birth registry data. With the exception of SGA, Connell et al. found no significant risks associated with being HBV infected during pregnancy. Even though both virus primarily infect hepatic cells, they are virologically distinct and display numerous clinical differences [143]. For example, most adults infected HBV are able to clear their infection spontaneously, resulting in lifelong protective immunity whereas 60-80% of adults with HCV fail to control the infection and develop chronic disease [143]. A plausible explanation to this observation may lie in the divergent immune responses produced by HCV and HBV. Studies have already linked circulating pro-inflammatory cytokines from maternal innate and adaptive immune responses to adverse pregnancy outcomes [144-146]. Accumulating evidence suggests that there is a lack of interferon response during HBV acute infection resulting from the inactivation of various pathways that will normally induce interferon and cytokine production[147]. In other words, HBV 'evades' the innate immune response by not inducing it to act whereas HCV induces a strong innate and adaptive immune response [148, 149] which leads to interferon and cytokine production during the initial stage of infection. From this knowledge, it can be gathered that the 'stealth' of HBV may perhaps be the reason why no effect was seen for HBV infection.

Our study has limitations that should be acknowledged. First, our approach to this analysis only included outcomes after the subsequent pregnancies that were observed prospectively. These pregnancies may not necessarily have be the second pregnancy of that mother as its possible they had other pregnancies that were not captured in our

observation window. We acknowledge the fact that our use of the term ‘‘recently diagnosed’’ especially for HCV-infected cases does not truly reflect ‘new cases’ of infections. Rather, these are past or present infections that went undiagnosed for years. The fact that our infected pool of cases was largely made up of chronic cases reported surveillance underscores this point. In our data set, 49% and 42% of “recently diagnosed” HBV and HCV cases had their diagnosed within 2 years after an initial uninfected pregnancy. Among these “recently diagnosed” pregnancies, the frequency of preterm birth and LBW were consistently higher for HCV infected cases compared to non-infected cases whereas the frequency of SGA was higher among HBV infected cases compared to non-infected cases. In addition, because there is no universal screening for HCV, the HCV-positive cases in our data were most likely identified through provider initiated risk-based screening. Consequently, the HCV cases here are a mixture of those who exhibit high risk factors and those experiencing symptoms of early liver disease. Lastly, another limitation to consider is the fact that our data contained no information on hepatitis viremia (viral load) or treatment status. Therefore, we were not able to assess these variables in our study. We also had no information on the HIV/AIDS status of these mothers thus we were unable to adjust for the effect of this disease in our analysis.

In spite of these limitations, there are several strengths to this study. Our approach to analysis used here enabled us to assess if the risks for ‘newly diagnosed’ and ‘chronic carrier’ cases of disease were different. Also, by linking birth data to surveillance data, we were able to improve our sensitivity for case finding in the birth data, thus the potential for misclassification of maternal disease status was greatly reduced. Further linkage to substance abuse treatment data allowed us to ascertain maternal drug and

alcohol use. These are variables that would otherwise not be available in the birth certificate data. Lastly, our sample of subsequent pregnancies was comparable to all the singleton births (see Appendix D) that occurred in SC over the study period. If we consider the state of South Carolina as a sampling unit of Southern US, our data may well be representative of the demographic composition of women in residing in this region of the US. Therefore our results are generalizable to populations in the south with similar demographics. .

In summary, our data supports an association between LBW and HCV infection, specifically for mothers who were 'recently diagnosed' in our study. These findings have some implications for HCV-positive women entering into prenatal care. LBW is an important risk factor for infant mortality [150, 151] and from a practice point of view, this information is useful for providers to advise infected expectant mothers on the potential risk to their baby. Although universal screening for HCV infection during pregnancy is not currently recommended in the US, given our findings, additional steps, such as improving nutrition and receiving adequate prenatal care can be taken to help reduce the effect of this disease on pregnancy outcome. The current interferon therapy for HCV infection is not indicated for pregnant women and there is no vaccine to prevent perinatal HCV infection, however that may soon change. When that time arrives, linkage to care during pregnancy may help reduce the risk of this disease on low birth weight. But until such a time, future studies should consider investigating how a patient's viremia affects pregnancy outcomes. Finally, more population-based studies with more power are needed to determine if 'chronic carriers' of disease poses a higher risk.

Table 5.1- Characteristics of HCV-infected and HBV-infected pregnancies in South Carolina, 2004 -2011

	Non-infected number (%)	**HCV+ number (%)**		**HBV[a] + number (%)**	
	n=(94, 870)	**(n= 275)**	**P-value[b]**	**(n=235)**	**P-value[b]**
Socio-demographic variables					
Age in years, median (range)	26 (15 - 49)	27 (17 - 41)	**0.006[c]**	27 (17-43)	**0.001[c]**
< 20 years	6556 (7)	14 (5)	0.24	11 (5)	**0.047**
20-29 years	58467 (62)	164 (60)		134 (57)	
≥ 30 years	29757 (31)	97 (35)		90 (38)	
Race/ethnicity			**<.0001**		**<.0001**
non-Hispanic White	8669 (9)	12 (4)		20 (9)	
non-Hispanic Black	52306 (55)	187 (68)		60 (26)	
Hispanic	32064 (34)	69 (25)		103 (44)	
Other	1546 (2)	7 (3)		51 (22)	
Maternal education			**0.0013**		**0.0063**
< High school	21938 (23)	77 (28)		66 (28)	
High school	24965 (26)	90 (33)		77 (33)	
Beyond high school	47558 (50)	106 (39)		91 (39)	
Did mother use WIC			**0.029**		0.308
No	44516 (47)	105 (38)		96 (41)	
Yes	48624 (51)	163 (59)		134 (57)	
Unknown	1634 (2)	7 (3)		5 (2)	
Payment source for delivery			**<.0001**		0.05
Medicaid	49508 (52)	182 (66)		141 (60)	
Private Insurance	35296 (37)	71 (26)		66 (28)	
Self-pay	5947 (6)	10 (4)		16 (7)	
Other	3385 (4)	10 (4)		9 (4)	
APCU index[e]			**<.0001**		**0.06**
Inadequate	20309 (21)	92 (33)		67 (29)	
Intermediate	6635 (7)	25 (9)		19 (8)	
Adequate	27826 (29)	64 (23)		65 (28)	
Adequate plus	39464 (42)	93 (34)		82 (35)	
Unknown	546 (<1)	1 (<1)		2 (<1)	

Table 5.1- Characteristics of HCV-infected and HBV-infected pregnancies in South Carolina, 2004 -2011 *(cont'd.)*

	Non-infected number (%)	**HCV+ number (%)**		**HBV[a] + number (%)**	
	n=(94, 870)	**(n= 275)**	**P-value[b]**	**(n=235)**	**P-value[b]**
Risk factor variables					
Maternal smoking during pregnancy			**<.0001**		0.106
No	82282 (87)	150 (55)		206 (88)	
Yes	12432 (13)	125 (45)		28 (12)	
Maternal STI during pregnancy[d]			0.27		**0.016**
No	88094 (93)	251 (91)		209 (89)	
Yes	6686 (7)	24 (9)		26 (11)	
Previous adverse outcome			**0.033**		0.688
No	84739 (89)	235 (85)		212 (90)	
Yes	10041 (11)	40 (15)		23 (10)	
Risk factors present in pregnancy			0.338		0.39
No	64590 (68)	180 (65)		154 (66)	
Yes	30190 (32)	95 (35)		81 (34)	
History of alcohol abuse[f]			**<.0001**		**<.0001**
Yes	93125 (98)	237 (86)		223 (95)	
No	1655 (2)	38 (14)		12 (5)	
History of drug use[f]			**<.0001**		**0.03**
No	92383 (97)	196 (71)		224 (95)	
Yes	2397 (3)	79 (29)		11 (5)	
Primary route of drug use			**<.0001**		
Injection or intramuscular	107 (4)	29 (35)		-	
Other	2290 (96)	51 (65)		11 (100)	
Interval between pregnancies, median (range), years	2 (<1-7)	3 (<1-7)		2 (<1-7)	
Parity, median (range)	1 (1-22)	2 (1-13)		1 (1-8)	

CHESS=South Carolina Health Electronic Surveillance System; BC = birth certificate (registry) data; HBV= hepatitis B virus; HCV=hepatitis C virus, STI= sexually transmitted infections; WIC=women, infant and children nutrition program, APCU= adequacy of prenatal care utilization.

[a] These include 37 pregnancies confirmed in CHESS as acute HBV cases.

[b] Pearson Chi-square test

[c] Kruskall Wallis test

[d] STI infections include presence of either chlamydia, gonorrhea, syphilis or genital herpes infection for that pregnancy

[e] Adequacy of prenatal care utilization index as defined by Kotelchuck (1994)

[f] Data from Department of Drug, Alcohol and Other Drugs. Indicates if patient has received treatment services for drug or alcohol addiction

Table 5.2 - Frequency of adverse birth outcomes at the time of a subsequent pregnancy by exposure to viral hepatitis: South Carolina, 2004-2011.

Adverse birth outcome	Non-infected (N = 94, 870)	HCV + (N = 275)	P value[a]	HBV[b] + (N =235)	P value[c]
Preterm birth					
No	85567 (90)	238 (87)	**0.037**	211 (90)	0.79
Yes	9213 (10)	37 (13)		24 (10)	
Low birth weight, grams					
No	87933 (93)	240 (87)	**0.002**	217 (92)	0.95
Yes	6840 (7)	35 (13)		18 (8)	
Small for gestational age					
No	86009 (91)	235 (85)	**0.0093**	208 (89)	0.46
Yes	8740 (9)	40 (15)		27 (11)	
Newborn Admission to NICU					
No	90325 (95)	256 (93)	0.08	217 (92)	**0.03**
Yes	4455 (5)	19 (7)		18 (8)	

NICU= Neonatal intensive care unit. CHESS= South Carolina Health Electronic Surveillance System; BC = Birth certificate (registry) data; HCV=hepatitis C virus; BC = Birth certificate (registry) data; HBV= hepatitis B virus.

[a]Pearson Chi-square test comparing HCV infected pregnancies to non-infected pregnancies.

[b]These include 37 pregnancies confirmed in CHESS as acute HBV cases.

[c]Pearson Chi-square test comparing HBV infected pregnancies to non-infected pregnancies

*Frequencies may not equal the total N shown because of missing numbers not shown in table.

Table 5.3- Multivariate logistic regression analysis of subsequent pregnancy outcomes after maternal hepatitis C viral infection.

	Model 1[a]		**Model 2[b]**		**Model 3[c]**	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
SGA (n=93,829)						
Non disease- non disease (n=93,557)	1.00		1.00		1.00	
Newly diagnosed (n=124)	**1.95 (1.22-3.13)**	**0.0051**	**2.09 (1.29-3.36)**	**0.0024**	1.51 (0.93-2.45)	0.09
Chronic carriers (n=148)	1.39 (0.86-2.26)	0.17	1.41 (0.87-2.31)	0.158	1.10 (0.67-1.80)	0.68
AIC	*57704*		*55362*		*54892*	
Low birth weight (n=93,851)						
Non disease- non disease (n= 93,579)	1.00		1.00		1.00	
Newly diagnosed (n=124)	**2.51 (1.58-4.00)**	**0.0001**	**2.80 (1.73-4.52)**	**<.0001**	**2.07 (1.28-3.37)**	**0.0030**
Chronic carriers (n=148)	1.14 (0.64-2.03)	0.64	1.17 (0.65-2.10)	0.59	0.84 (0.46-1.53)	0.58
AIC	*47990*		*45071*		*449595*	
Preterm (n=93,856)						
Non disease- non disease (n=93, 584)	1.00		1.00		1.00	
Newly diagnosed (n=124)	1.58 (0.97-2.56)	0.06	**1.66 (1.01-2.73)**	**0.04**	1.47 (0.89-2.43)	0.12
Chronic carriers (n=148)	1.02 (0.60-1.72)	0.92	1.03 (0.60-1.75)	0.91	0.83 (0.48-1.4)	0.51
AIC	*58866*		*55402*		*55060*	
NICU Admission (n=93,856)						
Non disease- non disease (n=93, 584)	1.00		1.00		1.00	
Newly diagnosed (n=124)	1.6 (0.83-3.06)	0.15	1.63 (0.85-3.15)	0.13	1.39 (0.72-2.69)	0.32
Chronic carriers (n=148)	1.23 (0.6-2.4)	0.54	1.20 (0.60-2.38)	0.59	0.98 (0.49-1.95)	0.95
AIC	*35040*		*34215*		*33965*	

SGA= small for gestational age; NICU=neonatal intensive care unit; CI= confidence interval; AIC=Akaike information criterion.

[a]Model 1: Adjusted for parity, previous adverse pregnancy outcome, interval between first and second pregnancy

[b]Model 2: Model 1 + socio-demographic variables (age, insurance status, race, education, adequacy of prenatal care received, WIC status)

[c]Model 3: Model 2 + risk factors (smoking , history of alcohol abuse, history of drug use, morbidity)

Table 5.4- Multivariate logistic regression analysis of subsequent pregnancy outcomes after maternal hepatitis B viral infection.

	Model 1[a]		Model 2[b]		Model 3[c]	
	OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
SGA (n=93,787)						
Non disease- non disease (n=93,557)	1.00		1.00		1.00	
Newly diagnosed (n=63)	**2.05 (1.08-3.93)**	**0.03**	1.85 (0.95-3.6)	0.06	1.85 (0.95-3.60)	0.07
Chronic carriers (n=167)	1.03 (0.66-1.73)	0.89	0.94 (0.55-1.58)	0.82	0.92 (0.54-1.55)	0.75
AIC	*57656*		*55318*		*54888*	
Low birth weight (n=93,809)						
Non disease- non disease (n=93,579)	1.00		1.00		1.00	
Newly diagnosed (n=63)	1.28 (0.54-2.97)	0.56	1.11 (0.47-2.62)	0.81	1.07 (0.455-2.55)	0.87
Chronic carriers (n=167)	0.88 (0.4-1.64)	0.71	0.84 (0.43-1.56)	0.58	0.81 (0.40-1.49)	0.49
AIC	*47904*		*44990*		*44588*	
Preterm (n=93, 814)						
Non disease- non disease (n=93,584)	1.00		1.00		1.00	
Newly diagnosed (n=63)	1.44 (0.70-2.94)	0.31	1.31 (0.63-2.71)	0.46	1.29 (0.62-2.68)	0.49
Chronic carriers (n=167)	0.82 (0.47-1.42)	0.49	0.84 (0.47-1.46)	0.52	0.81 (0.4-1.42)	0.47
AIC	*58821*		*55360*		*55053*	
NICU Admission (n=93,814)						
Non disease- non disease (n=93,584)	1.00		1.00		1.00	
Newly diagnosed (n=63)	2.05 (0.87-4.78)	0.09	1.96 (0.83-4.60)	0.12	1.82 (0.77-4.30)	0.17
Chronic carriers (n=167)	1.43 (0.77-2.64)	0.25	1.48 (0.79-2.75)	0.21	1.488 (0.8-2.7)	0.21
AIC	*35014*		*34192*		*33957*	

SGA= small for gestational age; NICU=neonatal intensive care unit; CI= confidence interval, AIC=Akaike information criterion.

[a]Model 1: Adjusted for parity and previous adverse pregnancy outcome and interval between first and second pregnancy)

[b]Model 2: Model 1 + socio-demographic variables (age, insurance status, race, education, adequacy of prenatal care received, WIC status)

[c]Model 3: Model 2 + risk factors (smoking , history of alcohol abuse, history of drug use, morbidity and presence of STI)

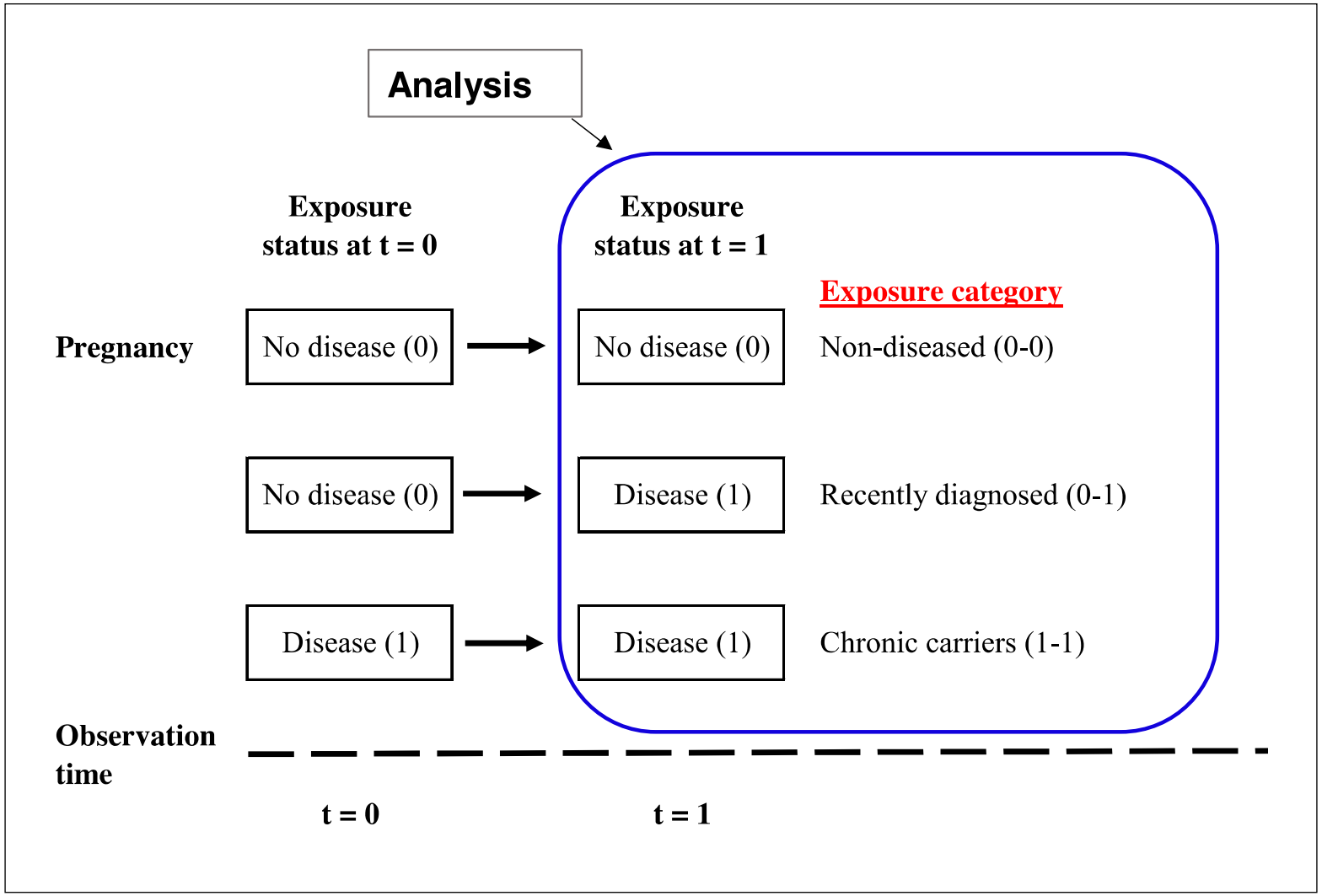


Figure 5.1 Study design used for analyzing subsequent pregnancies in South Carolina, 2004-2011

CHAPTER 6

SUMMARY AND CONCLUSIONS

Descriptive studies

Both descriptive studies provided a characterization of the Hepatitis B and C virus (HBV, HCV) mono-infection and HBV/HIV, HCV/HIV and HBV-HCV co-infections among females in South Carolina. There was significant variation in the epidemiology of these infections in SC. In the HBV descriptive study, we estimated the prevalence of HBsAg among pregnant women to be 0.17% and found that HBV/HIV co-infection was substantial. Approximately 9% of chronic HBV cases in the study period were co-infected with either HIV (4%) or HCV (5%). Chronic HBV/HIV co-infected cases were more likely to be Black women from urban areas in SC, who reported heterosexual contact as the main risk factor for HIV transmission. These HBV co-infected cases also had low first CD4 counts after HIV diagnosis and there was a 9-year median time between HIV diagnosis and a subsequent HBV diagnosis. Taken together, these findings suggest that there are gaps in compliance with the recommended routine HBV screening and immunization for HIV-infected persons. Additionally, the findings indicate a missed opportunity for those with undiagnosed HBV to be put on appropriate medication that would treat both HIV and HBV. Women between the ages of 20 and 49 reported the highest frequencies of HBV infections and within the state, the largest proportion of acute

HBV infections reported from the Northeastern region (Pee Dee) of the state. We also found moderate agreement between CHESS and the birth registry data when we compared the degree of concordance for HbsAg positive cases reported during pregnancy. From these results we determined that disease surveillance of infections diagnosed during prenatal screening needed improvement. Additionally, our findings are suggestive to increase efforts to improve screening, reporting and prevention, especially among black women.

In the HCV descriptive study we focused on describing the disease burden and characteristics associated with HCV, HCV/HIV and HCV-HBV co-infection. Results from this study revealed an emerging epidemic of HCV infections among young white females between the ages of 15 and 25 years in recent years. However, a large burden of HCV mono infection was still found in middle-aged white women. Four percent of cases were co-infected with HCV/HIV and they were more likely to black, whereas 1% of HCV cases were co-infected with HCV-HBV and they were more likely to be White. These findings suggest a need for resources to be directed at improving screening and prevention efforts among Black and White middle aged women and most especially, in young persons between the ages of 15 and 25 years. Also because HCV risk behavior and detailed race information were unavailable for analysis in our HCV surveillance data, initiatives to fund and improve HCV case reporting data are warranted.

Spatial analysis of HCV infections

An investigation into the spatial epidemiology of HCV infections in SC showed considerable differences in how HCV is distributed across the state. Our Bayesian spatial analysis identified several counties as high-risk areas for HCV infection. These counties,

namely Charleston, Darlington, Florence, Georgetown, Greenville, Horry, Oconee, McCormick and Richland, represent a mixture of metropolitan and federally designated rural areas. McCormick county exhibited the highest risk for HCV infection even after the standardized morbidity ratio (SMR) had been spatially smoothed. This county also had the largest percentage of people of all ages living in poverty and the lowest percentage of persons, 24 or older, with at least a college degree. Our report of high HCV risks seen in rural SC corresponds to other recent reports of an emerging HCV epidemic in rural communities within the US which has been largely attributed to the increasing number of injecting drug users (IDU) in these areas.

Even though we assessed drug treatment admissions data as potential explanatory covariate for HCV infection in the spatial model, it did not explain the observed spatial variation. This implies that other unobserved factors that might account for the high HCV prevalence observed in these areas exists and will require further investigation. The infection prevalence map based on our spatial analysis provides a visual representation of how HCV disease is geographically dispersed. Information from the high-risk areas identified can used for policy decision-making and taking public health action. In addition, information from spatial and descriptive analysis can use to allocate resources more efficiently to help prevent and reduce the spread on HCV disease within the state.

Birth outcomes study

Even though the estimated national prevalence of HCV and HBV infections in the antenatal population may seem small, these prevalence correspond to several thousands of infected women who deliver babies annually and therefore constitute a public health problem. One important finding from our study of birth outcomes is that low birth weight

is independently associated with HCV infection during pregnancy. Specifically, HCV-infected women who transitioned from a non-diseased status to a diseased status in their subsequent pregnancy had significant higher odds of delivering babies that had a low birth weight. We found no significant associations between HCV infection, SGA, preterm birth and NICU admission. Also, no effect was detected for 'chronic carrier' women who were positive for HCV infection in their initial and subsequent pregnancies. We also found that being HBV-infected, be it a 'recently diagnosed' or 'chronic carrier' case, did not confer an additional risk for LBW, SGA, preterm birth and NICU admission.

LBW is an important risk factor for infant mortality and from a practice point of view this information is useful for providers to advise infected expectant mothers on the potential risk to their baby. Additional population-based studies with more power are needed to determine if 'chronic carriers' of viral hepatitis poses a higher risk and future studies should consider investigating how a patient's viremia affects pregnancy outcomes.

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APPENDIX A.

SUMMARY OF LITERATURE REVIEW FINDINGS

Table A.1 Summary of literature review findings by epidemiologic study design and location

Author, year published and location	Study design	Statistical Analysis	Sample size (Disease prevalence)
Lobstein et al.,[55] (2011) Germany	Retrospective cohort	T-test and Mann Whitney test with Bonferroni correction	39[a] (0.48%)
Elefsiniotis et al.,[47] (2010) Greece	Retrospective cohort	Logistic regression	70[a] (3.8%)
Saleh-Gargari et al.,[152] (2009) Iran	Case-control	Multinomial logistic regression	450[a]
Lao et al.,[153] (2007) China	Case-control	Logistic regression	1138[a] (8.3%)
Tse et al.,[45] (2005) China	Case-control	Logistic regression	253[a]
To et al.,[154] (2003) Hong Kong	Case-control	Not reported	1340[a] (9.7%)
Wong et al.,[134] (1999) Hong Kong	Case-control	Unpaired t-test, Mann Whitney test	824[a] (11.6%)
Haider et al.,[56] (2009); Pakistan	Case-control	2 tailed t-test	23[b] (8.0%)
Pergam et al.,[50] (2008) USA	PB retrospective cohort	Mantel-Haenszel stratified analysis	506[b] (0.2%)
Jaffery et al.,[57] (2005) Pakistan	Case-control	Logistic regression	31[b] (3.27%)
Jabeen et al.,[51] (2000) Ireland	Case-control	Not reported	26 [c]
Hillemanns et al.,[52] (2000) Germany	Case-control	Mann Whitney test MH chi-square test	35 [d] (0.94%)

Table A.1 Summary of literature review findings by epidemiologic study design and location *(cont'd.)*

Author, year published and location	Study design	Statistical Analysis	Sample size (Disease prevalence)
Connell et al.,[44] (2011) USA	PB retrospective cohort	Logistic regression	1458[e], 999[f], (0.09%) (0.06%)
Reddick et al.,[48] (2011) USA	Case-control	Logistic regression	814[e], 555[f],
Safir et al.,[49] (2010) Israel	PB retrospective cohort	Logistic regression	749[g] (0.4%)

Abbreviations: US=United States, MV=multivariable; PB=Population-based; MH= Mantel-Haensel; PCR=polymerase chain reaction; [a] HBsAg assessed with Elisa assay; [b] Elisa and PCR confirmed anti-HCV test ; [c] HCV RNA positive; [d] RIBA confirmed anti-HCV test [e]Clinically diagnosed HBV from ICD-9-CM codes; [f]Clinically diagnosed HCV from ICD-9-CM codes; [g] Anti-HCV or HBsAg positive cases

Table A.2 Summary of literature review findings by study outcomes

	Hepatitis B virus		Hepatitis C Virus	
Maternal outcomes		**N**		**N**
Gestational diabetes	↔ ↑	(5)	↔ ↑	(3)
Premature rapture of membranes	↔	(3)	↔	(2)
Preterm premature rapture of membranes	↑	(1)		
Pre-eclampsia	↔ ↑ ↓	(5)	↔	(2)
Intrauterine growth restriction	↔	(1)	↔	(2)
Cesarean delivery	↔ ↓	(2)	↔ ↑	(5)
Perinatal outcomes				
Preterm birth	↔ ↑ ↓	(5)	↔ ↑	(3)
Small for gestational age	↔	(3)	↑	(2)
Low birth weight	↔	(2)	↔ ↑	(5)
Neonatal jaundice	↔	(2)		
Apgar score (1 min)	↔ ↑	(3)	↔	(2)
Assisted ventilation	↔	(1)	↑	(1)
Spontaneous abortion			↔	(1)
Congenital abnormalities	↔ ↑	(3)	↑	(2)
NICU admission	↔ ↑	(2)	↑	(1)
Still birth	↑	(1)		

N= number of studies reviewed * Highlighted cells represent studied outcomes with varied result

APPENDIX B.

CHARACTERISTICS OF SINGLETON PREGNANCIES INFECTED WITH HEPATITIS B OR C VIRUS, SOUTH CAROLINA, 2004-2011

Table B.1 Characteristics of singleton pregnancies infected with Hepatitis B or C virus compared to non-infected pregnancies, South Carolina, 2004-2011

	HCV + number (%)		**HBV+ number (%)**		**Non infected number (%)**	
	CHESS (n=623)	**BC (n=283)**	**CHESS (n=647)**	**BC[a] (n = 266)**	**(n = 436,389)**	P-value[b]
Age in years, median (range)	28 (15 - 44)	26 (15 - 42)	28 (15 - 46)	27 (16 - 43)	26 (15 - 49)	<0.0001[c]
< 20 years	37 (6)	31 (11)	51 (8)	14 (5)	57388 (13)	<0.0001
20-29 years	343 (55)	159 (56)	339 (52)	150 (56)	250132 (57)	
≥ 30 years	243 (39)	93 (33)	257 (40)	102 (38)	128869 (30)	
Race/ethnicity						
Non-Hispanic White	479 (77)	164 (58)	122 (19)	79 (30)	240905 (55)	<0.0001
Non-Hispanic Black	105 (17)	82 (29)	286 (44)	112 (42)	143767 (33)	
Hispanic	22 (4)	21 (7)	36 (6)	27 (10)	41164 (9)	
Other	16 (3)	15 (5)	197 (30)	46 (17)	9121 (2)	
Maternal education						
< High school	204 (33)	71 (25)	192 (30)	68 (26)	100545 (23)	<0.0001
High school	206 (33)	81 (29)	186 (29)	76 (29)	112169 (26)	
Beyond high school	211 (34)	128 (45)	263 (41)	121 (45)	222319 (51)	
Did mother use WIC						
Yes	434 (70)	151 (53)	371 (57)	143 (54)	234108 (54)	<0.0001
No	173 (28)	123 (43)	265 (41)	111 (42)	194816 (45)	
Unknown	16 (3)	9 (3)	11 (2)	12 (5)	7465 (2)	
Payment source for delivery						
Medicaid	473 (76)	148 (52)	352 (54)	149 (56)	216579 (50)	<0.0001
Private Insurance	95 (15)	97 (34)	200 (31)	58 (22)	162793 (37)	
Self-pay	29 (5)	18 (6)	61 (9)	27 (10)	28608 (7)	
Other	25 (4)	15 (5)	29 (4)	27 (10)	23881 (5)	
Did mother smoke during pregnancy						
Yes	342 (55)	74 (26)	58 (9)	46 (17)	56283 (13)	<0.0001
No	281 (45)	209 (74)	588 (91)	219 (82)	379845 (87)	
STI present during pregnancy[d]?						
Yes	69 (11)	19 (7)	75 (12)	31 (12)	30546 (7)	<0.0001
No	554 (89)	264 (93)	572 (88)	235 (88)	405843 (93)	

Table B.1 Characteristics of singleton pregnancies infected with Hepatitis B or C virus compared to non-infected pregnancies, South Carolina, 2004-2011 *(cont'd.)*

	HCV + number (%)		HBV+ number (%)		Non infected number (%)	
	CHESS (n=623)	**BC (n=283)**	**CHESS (n=647)**	**BC[a] (n = 266)**	**(n = 436,389)**	P-value[b]
Parity						
Nulliparous	158 (25)	120 (42)	207 (32)	82 (31)	182088 (42)	<0.0001
Multiparous	465 (75)	163 (58)	439 (68)	184 (69)	254201 (58)	
History of alcohol abuse[e]						
Yes	108 (17)	12 (4)	21 (3)	13 (5)	7123 (2)	<0.0001
No	515 (83)	271 (96)	626 (97)	253 (95)	429266 (98)	
History of drug use[e]						
No	394 (63)	266 (94)	631 (98)	254 (95)	427210 (98)	<0.0001
Yes	229 (37)	17 (6)	16 (2)	12 (5)	9179 (2)	
Primary route of drug use						
Injection /intramuscular	79 (34)	4 (24)	0	1 (8)	482 (5)	<0.0001[f]
Other	150 (68)	27 (76)	16 (100)	11 (92)	8697 (95)	
BMI pre-pregnancy, kg/m^2						
Underweight	36 (6)	10 (4)	37 (6)	15 (6)	18526 (4)	0.234
Normal weight	272 (44)	123 (43)	275 (43)	105 (39)	180693 (41)	
Overweight	158 (25)	73 (26)	145 (22)	63 (24)	107923 (25)	
Obese	143 (23)	74 (26)	180 (28)	79 (30)	120239 (28)	
Gestational weight gain[g]						
Adequate	126 (20)	58 (20)	160 (25)	64 (24)	100113 (23)	<0.0001
Inadequate	209 (34)	78 (28)	195 (30)	80 (30)	108535 (25)	
Excessive	197 (32)	100 (35)	203 (31)	88 (33)	160718 (37)	
Missing	*91 (15)*	*47 (17)*	*89 (14)*	*34 (13)*	*67023 (15)*	
Previous adverse outcome[h]						
No	533 (86)	253 (89)	567 (88)	235 (88)	398887 (91)	<0.0001
Yes	90 (14)	30 (11)	80 (12)	31 (12)	37502 (9)	
Risk factors present in pregnancy						
No	408 (65)	214 (76)	452 (70)	194 (73)	329348 (75)	<0.0001
Yes	215 (35)	69 (24)	195 (30)	72 (27)	107041 (25)	
APCU index[i]						
Inadequate	224 (36)	74 (26)	162 (25)	85 (32)	87457 (20)	<0.0001
Intermediate	51 (8)	20 (7)	49 (8)	19 (7)	31960 (7)	
Adequate	118 (19)	80 (28)	178 (28)	54 (20)	124432 (29)	
Adequate plus	226 (36)	106 (37)	250 (39)	104 (39)	188974 (43)	
Unknown	4 (<1)	3 (1)	8 (1)	4 (2)	3566 (<1)	

CHESS=South Carolina Health Electronic Surveillance System; BC = birth certificate (registry) data; HBV= hepatitis B virus; HCV=hepatitis C virus, BMI=body mass index; STI= sexually transmitted infections;

Characteristics of singleton pregnancies infected with Hepatitis B or C virus, South Carolina, 2004-2011 *(cont'd)*

WIC=women, infant and children nutrition program, APCU= adequacy of prenatal care utilization.
[a] These include 37 pregnancies confirmed in CHESS as acute HBV cases.
[b] Pearson Chi-square test
[c]Kruskall Wallis test
[d]STI infections include presence of either chlamydia, gonorrhea, syphilis or genital herpes infection for that pregnancy
[e]Data from Department of drug, alcohol and other drugs. Indicates if patient has received treatment services for drug or alcohol addiction
[f]Fisher exact test
[g]According to the Institute of Medicine guidelines
[h] Adequacy of prenatal care utilization index as defined by Kotelchuck (1994)

APPENDIX C.

SAS OUTPUT FREQUENCIES FOR PREGNANCY OUTCOMES BY HEPATITIS B OR C INFECTION STATUS AT THE TIME OF A SUBSEQUENT PREGNANCY

SAS output frequencies

Hepatitis C Cases

	Small for gestational age		
newgroup_hcv	**No**	**Yes**	**Total**
No disease	84947	8610	93557
Newly diagnosed	103	21	124
Chronic carriers	129	19	148
Total	85179	8650	93829

	Low birth weight		
newgroup_hcv	**No**	**Yes**	**Total**
No disease	86871	6708	93579
Newly diagnosed	102	22	124
Chronic carriers	135	13	148
Total	87108	6743	93851

	Preterm		
newgroup_hcv	**No**	**Yes**	**Total**
No disease	84533	9051	93584
Newly diagnosed	104	20	124
Chronic carriers	132	16	148
Total	84769	9087	93856

	NICU		
newgroup_hcv	**No**	**Yes**	**Total**
No disease	89214	4370	93584
Newly diagnosed	114	10	124
Chronic carriers	139	9	148
Total	89467	4389	93856

Hepatitis B Cases

	Small for gestational age		
newgroup_hcv	**No**	**Yes**	**Total**
No disease	84947	8610	93557
Newly diagnosed	52	11	63
Chronic carriers	151	16	167
Total	85150	8637	93787

	Low birth weight		
newgroup_hcv	**No**	**Yes**	**Total**
No disease	86871	6708	93579
Newly diagnosed	57	6	63
Chronic carriers	156	11	167
Total	87084	6725	93809

	Preterm		
newgroup_hbv	**No**	**Yes**	**Total**
No disease	84533	9051	93584
Newly diagnosed	54	9	63
Chronic carriers	153	14	167
Total	84740	9074	93814

	NICU		
newgroup_hbv	**No**	**Yes**	**Total**
No disease	89214	4370	93584
Newly diagnosed	57	6	63
Chronic carriers	156	11	167
Total	89427	4387	93814

APPENDIX D.

ASSESSMENT OF SELECTION BIAS

Table D.1 Comparison of maternal characteristics between all prospectively observed women with singleton pregnancies, all women with subsequent pregnancies and study sample at the time of a subsequent pregnancy, South Carolina, 2004-2011

Maternal characteristic	**All Women (N=438,208)**	**Women with subsequent pregnancies (N=211,457)**	**Study sample at time of subsequent pregnancy (N= 95,291)**
Age at delivery in years, median (range)	26 (15 - 49)	25 (15 - 49)	26 (15 - 49)
<20 years	57521 (13)	28838 (14)	6581 (7)
20-29 years	251113 (57)	130370 (62)	58766 (62)
>=30 years	129544 (30)	52124 (25)	29944 (31)
Race/Ethnicity			
Hispanic	41268 (9)	19133 (9)	8701 (9)
Non-Hispanic White	241736 (55)	114466 (54)	52553 (55)
Non-Hispanic Black	144342 (33)	73603 (35)	32236 (34)
Other	9391 (2)	3494 (2)	1605 (2)
Education			
< High school	101069 (23)	56384 (27)	22081 (23)
High school	112708 (26)	55287 (26)	25133 (26)
Beyond High school	223033 (51)	98964 (47)	47755 (50)
WIC usage			
No	195476 (45)	92998 (44)	44718 (47)
Yes	235190 (54)	114660 (54)	48921 (51)
Payment source for delivery			
Medicaid	217681 (50)	113223 (54)	49832 (52)
Private Insurance	163240 (37)	73949 (35)	35433 (37)
Self-pay	28739 (7)	14007 (7)	5973 (6)
Other	23974 (5)	7980 (4)	3404 (4)
Smoking			
No	381120 (87)	182752 (86)	82639 (87)
Yes	56795 (13)	28452 (13)	12585 (13)
Any STI present?			
No	407439 (93)	195637 (93)	88555 (93)
Yes	30739 (7)	15695 (7)	6736 (7)

Table D.1 Comparison of maternal characteristics between all prospectively observed pregnancies, women with subsequent pregnancies and study sample at time of subsequent pregnancy, South Carolina, 2004-2011 *(cont'd.)*

Maternal characteristic	All Women (N=438,208)	Women with subsequent pregnancies (N=211,457)	Study sample at time of subsequent pregnancy (N= 95,291)
Pre-pregnancy BMI			
Underweight, BMI<18.5	18623 (4)	9232 (4)	3620 (4)
Normal weight, 18.5<=BMI<25	181460 (41)	87672 (41)	37148 (39)
Overweight, 25<=BMI<30	108349 (25)	52034 (25)	24063 (25)
Obese, BMI>=30	120707 (28)	57965 (27)	28350 (30)
Previous adverse pregnancy outcome			
No	400449 (91)	192036 (91)	85186 (89)
Yes	37729 (9)	19296 (9)	10105 (11)
Risk factors present in pregnancy			
No	330594 (75)	158170 (75)	64925 (68)
Yes	107584 (25)	53162 (25)	30366 (32)
History of alcohol use			
No	430905 (98)	207415 (98)	93586 (98)
Yes	7273 (2)	3917 (2)	1705 (2)
History of drug use			
No	428730 (98)	205557 (97)	92804 (97)
Yes	9448 (2)	5775 (3)	2487 (3)
Adequacy of prenatal care			
Missing	3584 (<1)	1648 (<1)	549 (<1)
Inadequate	87996 (20)	45407 (21)	20468 (21)
Intermediate	32098 (7)	15601 (7)	6679 (7)
Adequate	124854 (28)	60105 (28)	27955 (29)
Adequate plus	189646 (43)	88571 (42)	39640 (42)

*Percentages may not equal to 100 because of rounding.

BMI=body mass index; STI= sexually transmitted infections; WIC=women, infant and children nutrition program.