An Age-Period-Cohort Analysis of the Impacts of Hepatitis B Vaccines on Hepatocellular Carcinoma in the United States

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Abstract

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Background:

The hepatitis B vaccine was licensed in 1986 and between 1986 and 1991 was only recommended for use in high-risk individuals. The hepatitis B vaccine recommendation was revised in 1991 to include children under the age of 18, and was revised again in 1994 when it became part of the childhood immunization schedule. Due to the high incidence of perinatal infections the vaccine recommendation was most recently revised in 2005 to include a birth dose.

In the United States, chronic hepatitis B infection accounts for approximately 20% of HCC cases. Despite broader hepatitis B vaccine recommendations, current data suggest that HCC mortality increased between 1980 and 2001. In this study, we used an age-period-cohort (APC) analysis of HCC hospitalizations between January 1st 1996 and December 31st 2011 to examine trends of hepatitis B infection and determine the impact of hepatitis B vaccines on rates of HCC in the United States.

Methods:

We estimated hospitalization rates for HCC using the Nationwide Inpatient Sample database.
To determine the rate of HCC in individuals with a chronic hepatitis B diagnosis, a combination of ICD-9-CM codes was used. HCC with a risk factor of hepatitis B infection was identified if the individual had a primary or secondary discharge for HCC and the patient had an additional discharge diagnosis listed in positions 3-10 for hepatitis B infection. Age, period and birth cohort effects on risk of hospitalization for HCC with a hepatitis B diagnosis were also estimated for each sex using a logistic regression model.

Results:

Across all age groups and both sexes, the rate of HCC with chronic hepatitis B diagnosis declined between 1996-2011. Logistic modeling showed a large increase in the log likelihood of all reduced models compared to the full APC model demonstrating that age, period, and birth cohort effects should all be taken in to account. For males the likelihood ratio test was smallest for the PC model vs. the APC model (likelihood ratio test statistic= 97.3) followed by the AC vs. APC model (likelihood ratio test statistic = 462.3. Similarly, in females, the likelihood ratio test statistic was lowest for the PC vs. APC model (likelihood ratio test statistic = 93.35), followed by the AC model vs. the APC model (likelihood ratio test statistic = 640.0). These results suggest that birth cohort effects play an important role for risk of HCC with a hepatitis B diagnosis in both males and females.

Logistic regression of birth cohort effects alone showed a dramatic decrease in risk of hospitalization for HCC in males born after the introduction of the hepatitis B vaccine. Males born in the 1948-1957 birth cohort had the highest risk of hospitalization for HCC, 2.72 (95%CI: 2.37-3.21). Risk of hospitalization for HCC decreased for all subsequent birth cohorts in males. Similar trends were seen among females. Females born in the 1948-1957 birth cohort also had the highest risk of hospitalization for HCC, 1.80 (95% CI: 1.21- 2.68).

Conclusion:

Previous research has showed an increase in HCC rates over the past two decades. This study demonstrates that this increase may not be due to chronic hepatitis B infection. Modeling of birth cohort specific effects show that broadening hepatitis B vaccine recommendations may be associated with the reduction seen in hospitalization rates for HCC with a chronic hepatitis B diagnosis. Given this trend, HCV infection and changing immigration trends may be playing an increasing large role in increasing HCC trends over the past decade.

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List of Abbreviations

ALF	Acute Liver Failure
APC	Age-Period-Cohort
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
IDU	Intravenous Drug Use
NIS	Nationwide Inpatient Sample

CHAPTER 1
BACKGROUND

Part 1: Hepatitis B Pathogenesis and Diagnosis:

HBV is one of the seven viruses that comprise the Hepadnaviridae family of virus [1,2]. Viruses in this family are small, enveloped and composed of double-stranded DNA [2]. HBV primarily infects and replicates in hepatocytes [2]. Present research suggests that HBV infection and replication is not specifically cytopathic [2]. Rather, the adaptive immune response produced by hepatocytes due to infection is responsible for both clearance of the virus and injury to infected hepatocytes [2]. During acute infection, cytotoxic T lymphocytes (CTL) aid in HBV elimination by destroying HBV infected hepatocytes and by destroying HBV replicative intermediates therefore limiting viral spread to infected cells [2]. In contrast, persistent infection is characterized by a weak adaptive immune response [2]. During persistent infection hepatocyte injury leads to inflammation and regeneration [3]. This continual regeneration processes increases the risk for cirrhosis and hepatocellular carcinoma (HCC) through DNA damage and direct activation of cellular oncogenes or inactivation of tumor suppressor genes [2,3].

Decreased age at infection is correlated an increase risk of developing chronic hepatitis B infection. Neonates are at a specifically high risk of developing chronic infection if infected at birth. One reason for this may be immune tolerance to viral antigens and poor T-cell response [2]. However, the reasons for this are not well understood [2].

Part 2: Outcomes of Hepatitis B Infection:

Acute Infection

Signs and Symptoms:

Acute hepatitis B infection is characterized by jaundice (yellowing of the skin and eyes), dark urine, extreme fatigue, nausea, vomiting and abdominal pain, although individuals can also be

asymptomatic [1,2]. Clinically it is indistinguishable from other hepatitis infections and therefore a definitive diagnosis requires serologic testing[2]. The incubation period for hepatitis B is approximately 90 days but ranges from 60 to 150 days from infection to the onset of jaundice [2]. Clinical signs and symptoms usually resolve within 1 to 3 months and the infection is cleared form the blood within 6 months [2]. Acute liver failure (ALF) occurs in 0.5% to 1.0% of adult acute hepatitis B infections but rarely occurs in infections of infants and children [2]. AFL is characterized by hepatic encephalopathy that results in disturbed sleep patterns, asterixis, confusion, disorientation, and possibly coma [2].

Treatment:

Antiviral medications are not generally prescribed for individuals with acute hepatitis B infection[2]. The goal of treatment is to prevent or delay the progression of liver damage[2]. Furthermore, permanent elimination of HBV infection from the body cannot be achieved due to viral integration into the host genome[2]. Currently available antiviral medications are costly, have toxicity related side effects and can lead to drug resistant[2]. Therefore, treatment for acute HBV infection is focused on symptomatic relief until the body's own immune response clears the virus[2].

Prognosis:

The risk of developing chronic HBV infection ranges from 90% in newborns of HBV-Positive mothers to 25%-30% in children under 5, to less than 5% in adults[1,2]. More than 90% of individuals infected with HBV during adulthood have acute infections and clear the virus within 6 weeks[4]. Immunosuppressed individuals are more likely to develop chronic HBV infection. [2]

Chronic HBV Infection

Hepatitis B Virus Transmission

The main routes of hepatitis B infection include percutaneous blood exposure, sexual intercourse, and from mother to infant during birth. In the United States the risk of HBV from

blood transfusion decreased substantially after the introduction of HBsAg screening of blood donors in 1973. The risk decreased farther in 2010 due to the exclusion of high-risk populations for HBV, HCV and HIV from blood donation.

HBV is 50-100 times more infectious than human immunodeficiency virus (HIV) and certain groups of individuals are at a particularly high risk of infection. These high- risk groups include IDUs, heterosexuals with multiple sex partners, and men who have sex with men (MSM) [16, 22]. The hepatitis B virus can survive outside the human body for more than 7 days, during which time the virus can still cause infection if it enters the body of a person who is not immune to the virus [16].

In highly endemic areas such as sub-Saharan Africa and east Asia, HBV is most commonly spread from mother to child at birth or from person to person in early child hood[16]. In low endemicity areas, such as the United States, sexual transmission and the use of contaminated needles, especially among IDUs are the mains routes of transmission [16]. Although the prevalence of chronic infections are much lower in the United States perinatal and early childhood transmission may still account for more than one third of chronic infections [23].

Signs and Symptoms:

Chronic HBV is characterized by infection by a necroinflammatory infection with the hepatitis B virus lasting greater than 6 weeks [2]. Many people with chronic infection may not experience any signs or symptoms of infection [2,5,6]. Others may have mild non-specific symptoms, which are often overlooked [5]. The most common of these symptoms is fatigue [2,5]. It is usually intermittent and rarely disabling [2,5]. Few individuals also experience nausea, abdominal pain, and muscle or joint aches [2,5]. Common symptoms of acute symptoms such as jaundice, dark urine, poor appetite, and weight loss are rare with chronic infection [5]. Overtime people may develop cirrhosis or HCC even without having previous symptoms [5].

Treatment:

Anti-viral agents can be given to chronically infected individuals. In the United States the most commonly prescribed anti-virals are tenofovir and entecavir [2]. Although treatment cannot cure chronic hepatitis B infection, it can slow the progression of the disease and reduce the risk of cirrhosis and HCC, thus increasing long term survival [2].

Prognosis:

Worldwide less than 10% of healthy adults who are infected during adulthood with hepatitis B virus will develop chronic infection. Of those who do become chronically infected, 15-25% will die from hepatitis B related liver cancer or cirrhosis [6]. Primary infections are more likely to become chronic in immunocomprimised individuals I (i.e. hemodialysis patients and individuals with HIV infection), and individuals with diabetes [6].

Cirrhosis

Signs and Symptoms:

Like other outcomes of HBV infection, cirrhosis may have no signs or symptoms. When an individual does experience symptoms it often signals extensive liver damage [7]. The most common symptoms include jaundice, fatigue, weakness, loss of appetite, itching, ascites, swelling in legs and easy bruising and bleeding [7]. Confusion, drowsiness and slurred speech may also occur in cases of severe liver damage [7]. Individuals without symptoms related to their cirrhosis have compensated cirrhosis [7]. In contrast those with symptomatic complications including jaundice, ascites, variceal hemorrhage and hepatic encephalopathy have decompensated cirrhosis[7].

Treatment:

Individuals with cirrhosis sometimes receive liver transplants with varying success[7]. This however, depends on organ availability and the individual's candidacy for a new liver. Treatment of symptoms such as esophageal varicies and peritonitis has contributed to a reduction in cirrhosis related mortality [8].

Prognosis:

Prognosis and survival is better for individuals with compensated cirrhosis than it is for individuals with decompensated cirrhosis [8,9]. The transition from compensated to decompensated cirrhosis in about 5% to 7% individuals with cirrhosis every year [9]. The median survival time for individuals with compensated cirrhosis is 9 to 12 years [9]. In contrast individuals with decompensated cirrhosis have on average a markedly shorter survival time. After developing ascites, an individual's 1-year survival time is only 50% [9]. Mortality rate from each episode of variceal hemorrhage is about 15% to 20% [9].

Hepatocellular Carcinoma

HCC accounts for approximately 6% of all human cancers [8]. It is estimated to be the fifth most common malignancy in men and the ninth most common malignancy in women. Development of HCC is often preceded by cirrhosis, HBV infection, and/or Hepatitis C virus (HCV) infection[8]. Of HCC cases, approximately 53% are due to chronic HBV infection [10].

Risk Factors for Hepatocellular Carcinoma:

HBV infection and Cirrhosis:

HBV infection is one of the most common underlying cause of HCC worldwide [2]. Research has shown a strong positive correlation between the prevalence of HBV antigens in the population and HCC incidence, particularly in countries with high endemicity (China, Taiwan, and sub-Saharan Africa) [8]. Hepatitis B virus can be found in the host genome of both infected cells and malignant hepatic cells; however, the precise mechanism by which HBV infection may cause HCC is unknown [8]. Cirrhosis is also a major determinant for HCC. Studies have shown that hepatic lesions caused by cirrhosis predispose individuals to HCC formation. Additionally, between 70% and 90% of HBV-related HCC occurs in patients who develop cirrhosis[8].

Hepatitis C

Hepatitis C virus (HCV) is a RNA virus that can be found in the blood, liver and tumor tissues of individuals with HCC [8]. Unlike HBV, HCV does not integrate into the genome[8]. HCV antigens are found in between 25% to 55% for HCC cases in the United States [8]. Although the exact mechanism is unknown, HCV infection increases the risk of HCC by inducing fibrosis and eventually liver cirrhosis [8]. Thus, the risk of HCC in individuals with HCV depends on the degree of fibrosis [8].

Age

HCC is very rare in individuals under the age of 40, except in areas where HBV infection is hyperendemic [8,11]. Worldwide, HCC incidence progressively increases with age and reaches a peak between the ages of 50 and 70 [8].

Sex

Worldwide men are two to four times more likely to develop HCC compared to women [8,11]. This trend may be explained in part by higher incidence of viral hepatitis and alcoholic cirrhosis in men. However, reasons for much of this difference between men and women remain unknown [8].

Signs and Symptoms:

Individuals with HCC develop signs and symptoms related to declining liver function such as hepatic encephalopathy, jaundice, and ascites [2]. Hepatomegaly is often seen on physical examination with hard and irregular palpable borders [2,12]. Often complications resulting from tumor growth are the initial findings that lead to diagnosis [12]. This is particularly common in non-cirrhotic patients [12]. Non-cirrhotic individuals are more likely to present with symptoms consistent with a long-term malignancy such as weight loss, anorexia, malaise, and abdominal distention [12,13]. HCC can metastasize to various organs via the lymphatic and hematologic routes [12]. Most commonly, HCC metastasizes to the lungs, bone and adjacent abdominal viscera [12, 14].

Treatment:

In high-income countries treatment for HCC includes surgery and chemotherapy [15]. These measures can prolong life for up to a few years [15,16]. In low-income countries, no treatment currently exists for HCC and most people die within a few months of diagnosis [15,16].

Prognosis:

The five-year survival rate for patients with HCC remains low at around 6% [8]. There is no ethnic, gender, or age-related differences in the survival rate of individuals with HCC [8]. One reason for the poor prognosis of HCC is that it is usually diagnosed at a late stage in individuals with advanced cirrhosis [8]. This makes curative treatment such as complete surgical removal or transplantation highly unlikely [8].

Part 3: Epidemiology of HBV infection and HCC

Worldwide

In 2002, the WHO estimated that cirrhosis causes about 783,000 deaths yearly and primary liver cancer caused another 619,000 deaths yearly [10, 17]. Together, these deaths represent one in forty deaths worldwide (2.5%) [10]. Of the various types of primary liver cancer, HCC is the most common histological type. It accounts for approximately 70% to 85% of cases [8,10].

United States

In the United States, mortality due to primary liver cancer declined from the early 1900s through the 1950s then remained stable until the early 1980s [8,18,19]. This initial decline was in part due to improved diagnostics [8]. Since the early 1980s, however, hospitalizations for HCC increased. [8] Between 1992 and 2005 HCC incidence increased from 3.1 to 5.1 per 100,000 person and liver cancer mortality rose from 3.3 to 4.0 per 100,000 persons [20]. Although HCC related mortality increased between the 1980s and early 2000s, incidence of hepatitis B infection decreased more than 80% from 8.5 to 1.9 per 100,000 population during this time period [6].

Among adolescents under 19 years of age incidence decreased 96%. It is estimated that about 40,000 new hepatitis B infections occur yearly in the United States [6].

Currently, the highest incidence of acute hepatitis B occurred among adults between the ages of 25 and 45 [21]. Among the various causes of adult infection of HBV in the United States 39% of new HBV infections occur among heterosexual individuals with multiple sexual partners and 24% of new infections occur among MSM [6]. Injective Drug Users (IDUs) contribute to about 16% of new HBV infections in the United States [16]. Among unvaccinated IDUs incidence if HBV infections is particularly high, about 10-31 cases per 100 person-years [16]. In the United States, occupation exposure to HBV occurs among persons who are exposed to blood while caring for patients or working in laboratories [16].

As off 2010, approximately 1.2 million people in the United States had chronic hepatitis B. Every year, approximately 3,000 people in the United States die from hepatitis B related liver disease [6].

Incidence of HCC varies drastically across ethnic groups in the United States. In general Caucasians are two to three times less affected by HCC compared to African Americans who in turn are two to three times less affected than Asians, Hispanics and Native Americans [8]. These ethnic differences may be due to ethnic differences in the age of acquisition as well as the prevalence of major HCC risk factors including HBV, HCV and alcoholic cirrhosis [8].

Part 4: HBV Prevention

Safe and effective Hepatitis B vaccines have been commercially available since 1982. Currently five Hepatitis B vaccines are used in the United States.

1.Pediarix:

Pediarix, made by Glaxo Smith and Kline (GSK), is a pentavalent vaccine including Diphtheria, Tetanus Toxoid, Acellular Pertussis, Recombinant Hepatitis B and Inactivated Poliovirus Vaccine

(IPV) [24]. It was approved for use in 2002 for infants born to HBsAg- negative mothers. Pediarix may be given as early 6 weeks of age; however, the series should be completed before the child's 7th birthday [21]. Typically, Pediarix is administered as three, 0.5mL intramuscular injections at 2,4, and 6 months of age [21,24]. Contraindications of this vaccine include severe allergic reaction to a previous does of Pediarix, encephalopathy within 7 days of administration of a previous pertussis-containing vaccine, or progressive neurological disorders [25].

2. Engerix-B:

Engerix-B, made by GSK, is a Hepatitis B recombinant vaccine licensed for use in the United States in 1989. It protects against infection caused by all known subtypes of Hepatitis B virus [21,26-27]. Engerix-B is administered as an intramuscular injection in a 3 dose series of 0.5mL at 0-, 1- and 6-months of age [26,27]. This vaccine is recommended for infants born to mothers who are either HBsAg positive or negative. This vaccine can also be used in adults and for persons 20 years of age or older; a three dose (1mL) series is given at 0-, 1- and 6- months [21]. Engerix-B is also approved for adults on hemodialysis as a 4 dose series of 2mL given at 0-, 1- and 6-months [21,26-27]. Engerix-B is contraindicated in individuals who have had an allergic reaction to any previous dose of a Hepatitis B vaccine or to any component of Engerix-B including yeast [26-27].

3. Recombivax HB:

Recombivax-HB, made my Merck Co.,is a recombinant Hepatitis B vaccine approved for use in the United States in 1983. It prevents against infection of all subtypes of Hepatitis B virus and is approved for use in all ages [28]. For individuals under 19 years of age, Recomivax is given in a 3 dose series of 0.5mL at 0-, 1- and 6- months [21,28]. This vaccine is recommended for infants born to mothers who are either HBsAg positive or negative. Adults over the age of 20 and

predialysis or dialysis patients should receive the vaccine in a 3 dose, 0.5mL series at 0-, 1- and 6-months[28]. Recombivax is contraindicated in individuals who are allergic to yeast [28].

4. Twinrix:

Twinrix, created by GSK, is composed of a Hepatitis A and Hepatitis B recombinant vaccine [21,29]. Twinrix was licensed in 2001 for individuals 18 years of age or older [29]. It is administered as a (1mL) intramuscular injection in a three dose series at 0-, 1- and 6-months[21,29]. Twinrix can also be given in an accelerated dosing schedule of 4, 1mL doses at days 0, 7, 21 to 30 and a booster at month 12 [21]. Contraindications include sever allergic reaction to any previous dose of Twinrx or any Hepatitis A or Hepatitis B vaccine [29]. Additionally, Twinrix should not be used in individuals who are allergic to yeast or neomycin [29].

5. Comvax**:**

Comvax, manufactured by Merck Co. protects against Hepatitis B as wells as *Haemophilus influenza* type B in infants 6 weeks to 15 months of age [30]. It contains a Haemohphilus b Conjugate (Meningococcal Protein Conjugate) and a Hepatitis B recombinant component [21,30]. Comvax is recommended for children born to HBsAg-negative mothers in a 2, 4 and 12 to 15 months series [21,30]. Comvax is not recommended in infants younger than 6 weeks of age because vaccination will lead to a reduced anti-PRP (Antibodies to Hib antigen) response and may lead to a decreased ability to respond to subsequence PRP antigen exposure [21]. Comvax is contraindicated in infants with hypersensitivity to yeast or any other component of the vaccine [30].

Immunogenicity and Vaccine Efficacy:

Although hepatitis B vaccines are available in various multi-vaccine combinations, there are only two main formulations of the hepatitis B vaccine with differ in antigen content but are

interchangeable in terms of schedule and efficacy [21]. After 3 doses of hepatitis B vaccine, 98-100% of infants and 90-95% of teens and adults develop protective levels of antibody titers [21]. Larger doses of vaccine (2-4 times the normal adult dose) may be required to produce protective antibody titers in hemodialysis patients and other immunocompromised individuals [21].

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CHAPTER 2
MANUSCRIPT

Abstract

Background:

The hepatitis B vaccine was licensed in 1986 and between 1986 and 1991 was only recommended for use in high-risk individuals. The hepatitis B vaccine recommendation was revised in 1991 to include children under the age of 18, and was revised again in 1994 when it became part of the childhood immunization schedule. Due to the high incidence of perinatal infections the vaccine recommendation was most recently revised in 2005 to include a birth dose.

In the United States, chronic hepatitis B infection accounts for approximately 20% of HCC cases. Despite broader hepatitis B vaccine recommendations, current data suggest that HCC mortality increased between 1980 and 2001. In this study, we used an age-period-cohort (APC) analysis of HCC hospitalizations between January 1st 1996 and December 31st 2011 to examine trends of hepatitis B infection and determine the impact of hepatitis B vaccines on rates of HCC in the United States.

Methods:

We estimated hospitalization rates for HCC using the Nationwide Inpatient Sample database. To determine the rate of HCC in individuals with a chronic hepatitis B diagnosis, a combination of ICD-9-CM codes was used. HCC with a risk factor of hepatitis B infection was identified if the individual had a primary or secondary discharge for HCC and the patient had an additional discharge diagnosis listed in positions 3-10 for hepatitis B infection. Age, period and birth cohort effects on risk of hospitalization for HCC with a hepatitis B diagnosis were also estimated for each sex using a logistic regression model.

Results:

Across all age groups and both sexes, the rate of HCC with chronic hepatitis B diagnosis declined between 1996-2011. Logistic modeling showed a large increase in the log likelihood of all reduced models compared to the full APC model demonstrating that age, period, and birth cohort effects should all be taken in to account. For males the likelihood ratio test was smallest for the PC model vs. the APC model (likelihood ratio test statistic= 97.3) followed by the AC vs. APC model (likelihood ratio test statistic = 462.3. Similarly, in females, the likelihood ratio test statistic was lowest for the PC vs. APC model (likelihood ratio test statistic = 93.35), followed by the AC model vs. the APC model (likelihood ratio test statistic = 640.0). These results suggest that birth cohort effects play an important role for risk of HCC with a hepatitis B diagnosis in both males and females.

Logistic regression of birth cohort effects alone showed a dramatic decrease in risk of hospitalization for HCC in males born after the introduction of the hepatitis B vaccine. Males born in the 1948-1957 birth cohort had the highest risk of hospitalization for HCC, 2.72 (95%CI: 2.37-3.21). Risk of hospitalization for HCC decreased for all subsequent birth cohorts in males. Similar trends were seen among females. Females born in the 1948-1957 birth cohort also had the highest risk of hospitalization for HCC, 1.80 (95% CI: 1.21- 2.68).

Conclusion:

Previous research has showed an increase in HCC rates over the past two decades. This study demonstrates that this increase may not be due to chronic hepatitis B infection. Modeling of birth cohort specific effects show that broadening hepatitis B vaccine recommendations may be associated with the reduction seen in hospitalization rates for HCC with a chronic hepatitis B

diagnosis. Given this trend, HCV infection and changing immigration trends may be playing an increasing large role in increasing HCC trends over the past decade.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer globally, yet the five-year survival rate for patients with HCC is only about 6% [1]. Chronic infection with the hepatitis B virus (HBV) is the one of the most frequent cause of hepatocellular carcinoma (HCC) worldwide and is responsible for approximately 20% of HCC cases in the United States [2-4].

The development of chronic HBV infection is inversely correlated to age at HBV infection [2]. Perinatal and early childhood infections cause more than a third of chronic HBV infections in low endemicity areas such as the United States [2]. In 1994 hepatitis B vaccines were introduced into the childhood immunization schedule to reduce rates of chronic hepatitis B infection. Hepatitis B vaccine recommendations were further expanded in 2005 to include a birth dose.

Despite broader hepatitis B vaccine recommendations, current data suggest that HCC mortality increased between 1980 and 2001[5,6]. Increasing incidence of hepatitis C virus (HCV) infection and increasing immigration trends from high endemicity areas, such as Southeast Asia, may explain this increase in HCC mortality; however, these explanations have not been recently evaluated. Additionally, little is known about the specific effect of changing hepatitis B epidemiology on rates of HCC in the United States, especially after introduction of the hepatitis B vaccine birth dose in 2005. Secular age-specific trends of hepatitis B infection may help determine the impact of hepatitis B vaccines on rates of HCC, yet to date no such study has been done in the United States.

In this study, we used an age-period-cohort (APC) analysis of HCC hospitalizations between January 1st 1996 and December 31st 2011 to examine trends of hepatitis B infection and determine the impact of hepatitis B vaccines on rates of HCC in the United States.

Methods

Data Sources

We used hospitalization data from the Agency for Healthcare Research and Quality's National Inpatient Sample (NIS). NIS is the largest publically available all-payer inpatient care database in the United States[9]. Between 1996 and 2011 NIS data came from hospitals in 19 to 44 states and contained data from about 8 million hospitalizations per year [9]. Data from NIS were used to assess trends in hospitalization frequency and rates for hepatocellular carcinoma as the primary or secondary listed discharge diagnosis. United States population estimates were based on the U.S census bureau's decennial census, intercensal data, or the yearly American Community Survey.

This study did not require IRB review, as assessed by the Emory University institutional review board.

Definition of Hospitalization for Outcomes

Hospitalization for HCC and chronic hepatitis B were defined using the International Statistical Classification of Diseases, 9th revision (ICD-9-CM). Outcomes included in this study had a primary or secondary discharge diagnosis of HCC or a primary diagnosis of chronic hepatitis B infection. Hospitalization for HCC was identified by the ICD-9 code 155.0 and chronic hepatitis B infection was identified by the ICD-9 codes 70.22, 70.23, 70.32, and 70.33.

To determine the rate of HCC in individuals with a chronic hepatitis B, a combination of IDC-9-CM codes was used. HCC with a risk factor of hepatitis B infection was identified if the individual had a primary or secondary discharge for HCC (ICD-9 code: 155.0) and the patient had an additional discharge diagnosis listed in positions 3-10 for hepatitis B infection (ICD-9 codes: 70.20, 70.21, 70.22, 70.23, 70.30, 70.31, 70.32, 70.33 or V02.61).

Statistical Analysis

NIS data from 1996 through 2011 were used to calculate the annual number of hospitalizations for HCC with a chronic hepatitis B diagnosis among all age groups. Data were stratified in to multiple groupings to assess trends in hospitalization rates of HCC with a chronic hepatitis B diagnosis due to changing hepatitis B vaccine recommendations. The first hepatitis B vaccine was licensed in 1986 and between 1986 and 1991 was only recommended for use in high-risk individuals including injecting drug users (IDUs), heterosexuals with multiple sex partners, men who have sex with men, individuals who frequently require blood or blood products, incarcerated individuals, healthcare workers and travelers to or from hepatitis B endemic areas [10,11]. The hepatitis B vaccine recommendation was revised in 1991 to include children under the age of 18, and was revised again in 1994 when it became part of the childhood immunization schedule [10]. Due to the high incidence of perinatal infections the vaccine recommendation was most recently revised in 2005 to include a birth dose [10].

An age-period-cohort (APC) analysis was used in order to determine the individual impacts of age, period, and cohort on changes in hospitalization rate for HCC with a chronic hepatitis B diagnosis. Ten age groups (0-4, 5-9, 10-19, 20-29, 30-39,40-49,50-59, 60-69, 70-79 and 80+) with increased stratification under the age of 10 were created to determine the impact of age on rate of hospitalization for HCC with a chronic hepatitis B diagnosis. Age effects allowed us to determine the impact of increasing age on rate of hospitalization for HCC with a chronic hepatitis B diagnosis.

Hospitalization periods provided information about individuals of all age groups hospitalized during a given period. Our data were stratified in to 3 time periods (1996-2000, 2001-2005 and 2006-2011) and were used to assess trends in HCC rates due to changes in pediatric vaccine recommendations. This categorization allowed us to compare the rate of hospitalization in pre-hepatitis B birth dose periods (1996-2000 and 2001-2005) to the post-hepatitis B vaccine period (2006-2011).

Since hepatitis B vaccines recommendations have been expanded multiple times over the past three decades, a birth cohort analysis of the data allowed us to determine the specific impact of broader hepatitis B vaccine recommendations on hospitalization rates for HCC with a chronic hepatitis B diagnosis. Additionally, previous research has suggested that birth cohort trends play a significant role in determining HCC mortality, hypothesizing that events early in life may predispose individuals to HCC which manifest decades later in life [8]. Thus, data were stratified in to ten birth cohorts (1898-1927, 1928-1937, 1938-1947, 1948-1957, 1958-1967, 1968-1977, 1978-1987, 1988-1997, 1998-2007, and 2008-2011). To determine the birth cohort effect by specific changes in vaccine recommendation we treated the 1989-1927, 1928-1937, 1938-1947, 1948-1957, 1958-1967, 1968-1977 and 1978-1987 cohorts as the pre-vaccine cohorts, 1988-1997 and the 1998-2007 as the childhood vaccination cohorts and the 2008-2011 as the birth dose cohort.

HCC disproportionally affects men two to four times more than women [5,6]. Thus, variations between sex were estimated by further stratifying the data in to male and female. Annual hospitalization rates for each age group, period and cohort were calculated by dividing the annual number of hospitalizations by the appropriate populations estimates from the U.S Census Bureau. Rates were expressed as hospitalizations per 100,000 persons.

Age, period and birth cohort effects on risk of hospitalization for HCC with a chronic hepatitis B diagnosis were also estimated for each sex using a logistic regression model. Age, period and birth cohort were each included in the model alone, in two-factor groups Age+ Period (AP model), Age+Cohort (AC model) and Period +Cohort (PC model), and as a full Age+Period+Cohort (APC) model.

Model:

$$\text{Log } P(x) = \alpha + \beta_{1i} + \beta_{2j} + \beta_{3k} + \varepsilon \qquad i = 1,2,\ldots I \quad j = 1,2,\ldots J \quad \gamma = 1,2,\ldots K$$

Where α is the intercept term, and β_1, β_2, and β_3 represent age, period, and birth cohort, respectively. Likelihood ratio test statistics were calculated for each model, using the difference in log likelihood between each model and the full APC model. This test was used to compare the goodness-of-fit of the reduced models to the full APC model. The likelihood ratio (LR) test statistic was based on a χ^2 distribution with degrees of freedom derived from the difference in number of parameters between the APC model and the reduced models. The LR tests statistics were assessed for significance at an α of 0.05. The Statistical package SAS 9.1 was used to perform the statistical analysis.

Results

Between 1996 and 2011 there were a total of 123,363,230 hospitalizations of which 50,565,044 were males and 71,798,188 were females. Across sex and age there were 14,454 hospitalizations for HCC in individuals with a chronic hepatitis B diagnosis. The average age (standard deviation) of individuals discharged with HCC with a chronic hepatitis B diagnosis was 55.3 (13.2). Among individuals with HCC with a chronic hepatitis B diagnosis, Asian/ Pacific Islander's accounted for the majority of cases (50.6%). Across all age groups and both sexes, the rate of HCC with chronic hepatitis B diagnosis remained relatively constant between 1996-2008, the declined between 2008-2011 (Fig. 1a). When stratified by sex HCC with a chronic hepatitis B diagnosis increased in men between 1998-2011 but remained relatively constant for female during this same time period (Fig. 1b).

A logistic regression model was fit to the data for each sex to determine the impact of age category, period and birth cohort on risk of hospitalization for HCC with a hepatitis B diagnosis. All reduced models showed a large increase in the log likelihood compared to the full APC model demonstrating that age, period, and birth cohort effects should all be taken in to account. Additionally, for both males and females, at an α of 0.05, the LR test statistic was significant for all models for when compared to the full APC model (Table 2). For males the likelihood ratio test was smallest for the PC model vs. the APC model (likelihood ratio test statistic= 97.3) followed by the AC vs. APC model (likelihood ratio test statistic = 462.3. Similarly for females, the likelihood ratio test statistic was smallest for the PC vs. APC model (likelihood ratio test statistic = 93.35), followed by the AC model vs. the APC model (likelihood ratio test statistic = 640.0) (Table 2). These results suggest that birth cohort effects play an important role for risk of HCC with a hepatitis B diagnosis in both males and females.

Birth cohort effect

Logistic regression of birth cohort effects accounting for age and period effects showed a dramatic decrease in HCC with a chronic hepatitis b diagnosis between the pre vaccine birth cohorts and both post-vaccination birth cohorts. Specifically, a dramatic decrease in risk of hospitalization for HCC was seen in males born after 1958. Males born in the 1948-1957 birth cohort had the highest risk of hospitalization for HCC, 2.72 (95%CI: 2.37-3.21). Risk of hospitalization for HCC decreased for all subsequent birth cohorts in males. The decrease in risk of hospitalization for HCC with a chronic hepatitis B diagnosis was less pronounced in the post-vaccination birth cohorts (after the 1978-1987 birth cohort), possibly due to the reduced years of follow-up data available for individuals born in those birth cohorts. Similar trends were seen among females. Females born in the 1948-1957 birth cohort had the highest risk of hospitalization for HCC, 1.80 (95% CI: 1.21-2.68). However, unlike the trend seen in males, risk of hospitalization for HCC increased between the pre-vaccination birth cohorts and childhood vaccination birth cohorts, specifically between the 1978-1987 and 1988-1997 birth cohorts. The risk of hospitalization for HCC then decreased in all subsequent birth cohorts. This trend may be due to the lag time between vaccine introduction and vaccine effects (Fig. 2).

Age effect

Logistic regression of HCC with a chronic hepatitis b diagnosis by age category showed that risk of hospitalization increased with increasing age. Those above the age of 50 had a notable increase in risk of hospitalization for HCC compared to individuals in younger age groups. However, the risk of hospitalization for HCC did not change dramatically for individuals above the age of 50. The risk of HCC hospitalization for the highest risk group (60-69 years old) was 1.2 (95% CI: 1.93- 0.84) for males and 0.76 (95% CI: 0.54-1.03) for females (Fig. 3).

Period effect

All periods showed a similar trend of HCC hospitalization increasing exponentially between the ages of 40-60, peaking in the 60-69 year old age group then dropping sharply in the 70-79 and 80+ age groups. Logistic regression of period effect on risk of HCC hospitalization showed a very slight increase in risk for each period for both males and females. For males, the risk of hospitalization for HCC with a chronic hepatitis B diagnosis increased from 0.47 (95% CI: 0.21-0.76) in the 1996-2000 period to 0.93 (95% CI: 0.87-1.02) the 2006-2011 period. For females, the risk of hospitalization for HCC increased from 0.23 (95%CI: -0.92-0.53) to 0.49 (95% CI: 0.45-0.56) in the 2006-2011 period (Fig. 4).

Discussion

Goodness of fit testing for age, period, and birth cohort effects on the risk of hospitalization for HCC with a chronic hepatitis B diagnosis indicate that age category, period, and birth cohort are important variables to consider when determining risk of hospitalization for HCC with a chronic hepatitis B diagnosis (Table 2). Specifically, the APC analysis of hospitalizations showed that birth cohort effects play the most important role for risk of HCC with a chronic hepatitis B diagnosis in both males and females. Analysis of birth cohort effects, accounting for age and period effects, demonstrate a reduction in the risk of hospitalization for HCC with a chronic hepatitis B diagnosis after the introduction of the hepatitis B vaccine. The reductions in the risk of hospitalization for HCC seen in birth cohorts born after the introduction of the hepatitis B vaccine may be associated with the expansion of hepatitis B vaccine recommendations. Furthermore, these results support hypotheses that events in early life such as hepatitis B infection are critical determinates HCC risk.

Existing research has showed that the rate of hospitalization for HCC is increasing in the United States; however, results from this study suggest that these increases in HCC hospitalization rates are not due to chronic hepatitis B infection. An analysis of hospitalization rates for HCC with a chronic hepatitis B diagnosis showed a decrease in hospitalization rate over the past decade. Furthermore, the rate of chronic hepatitis B alone decreased between 2008-2011 suggesting that chronic hepatitis B infection may no longer be the major cause of HCC in the United States. Instead factors such as hepatitis C infection and immigration trends, specifically from high endemicty areas such as Southeast Asia, may be playing an increasingly larger impact on the rate of HCC.

Previous research has suggested that in developed countries with low incidence of HCC, HCV rather than HBV infection may be the leading predisposing factor of HCC [13,16]. In the United States, approximately 2.7 million individuals are chronically infected with HCV and are therefore at risk for long-term sequelae [17]. Additionally, research has shown that in the United

States, hepatitis C antigens are found in between 25% to 55% for HCC cases [13]. Although the exact mechanism is unknown, HCV infection increases the risk of HCC by inducing fibrosis and eventually liver cirrhosis [13].

An analysis of hospitalization trends provides difficulty attributing HCC cases to a specific pre-existing condition. Additionally, the average age of hospitalization for HCC with a chronic hepatitis B diagnosis is 55 years. Therefore, a long duration of follow up may be necessary to ascertain the specific effect of the birth does of hepatitis B.

Conclusion

An APC analysis of HCC with a chronic hepatitis b showed that the risk of hospitalization for HCC with a chronic hepatitis B diagnosis decreased after introduction of the hepatitis B vaccine. These results suggest the that this reduced risk in HCC with a chronic hepatitis b diagnosis may be associated with expansions in hepatitis B vaccine policy. Furthermore, these results demonstrate that increases in HCC rates over the past three decades may not be due to chronic hepatitis B infection and though chronic hepatitis B used to account for about 20% of HCC cases in the United States, HCV infection and changing immigration trends may be playing an increasing large role in increasing HCC trends.

Reference

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Figures and Tables

Figure 1.

Hospitalization rates for hepatocellular Carcinoma in the United States, 1996-2011

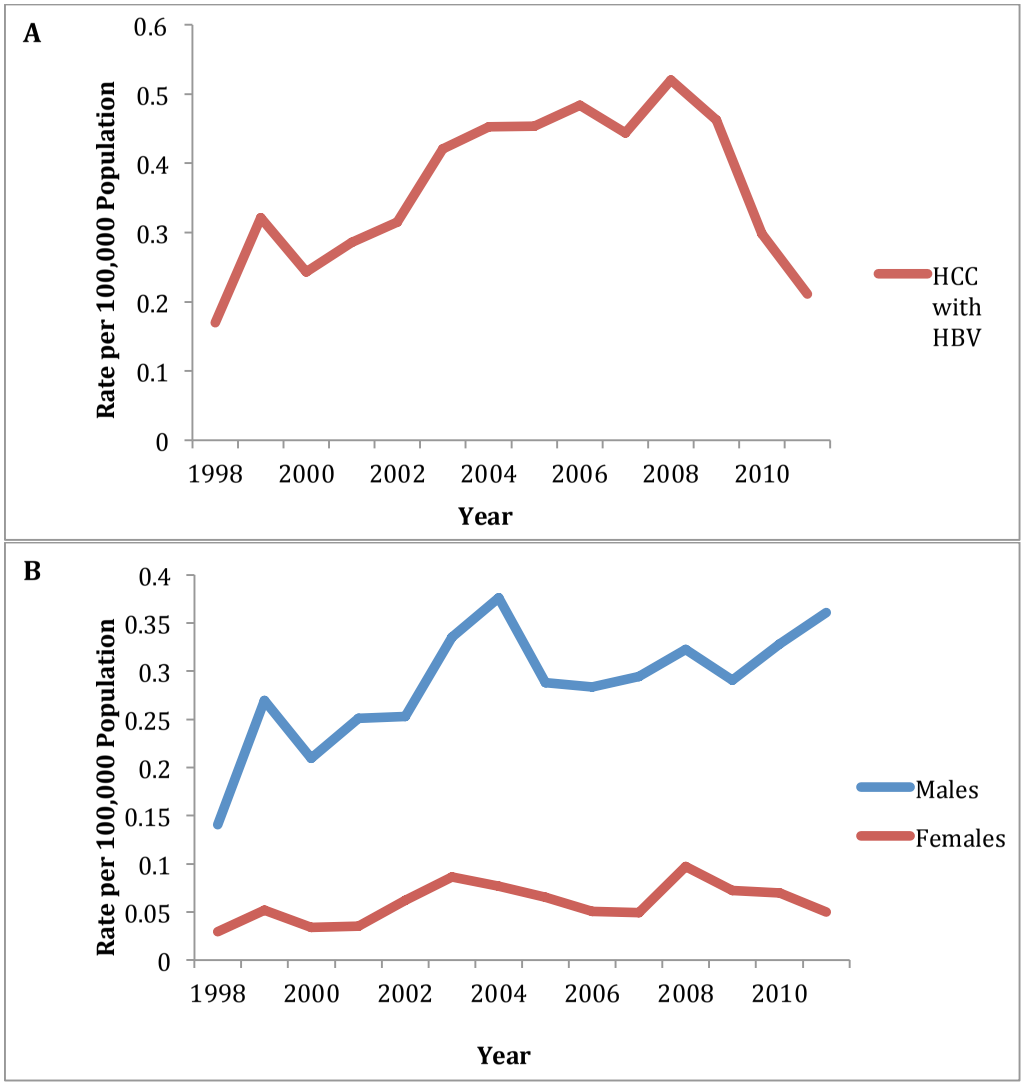

Figure 2. Birth cohort effect
Birth cohort effect of hospitalization for HCC with a Chronic Hepatitis B diagnosis in males and females

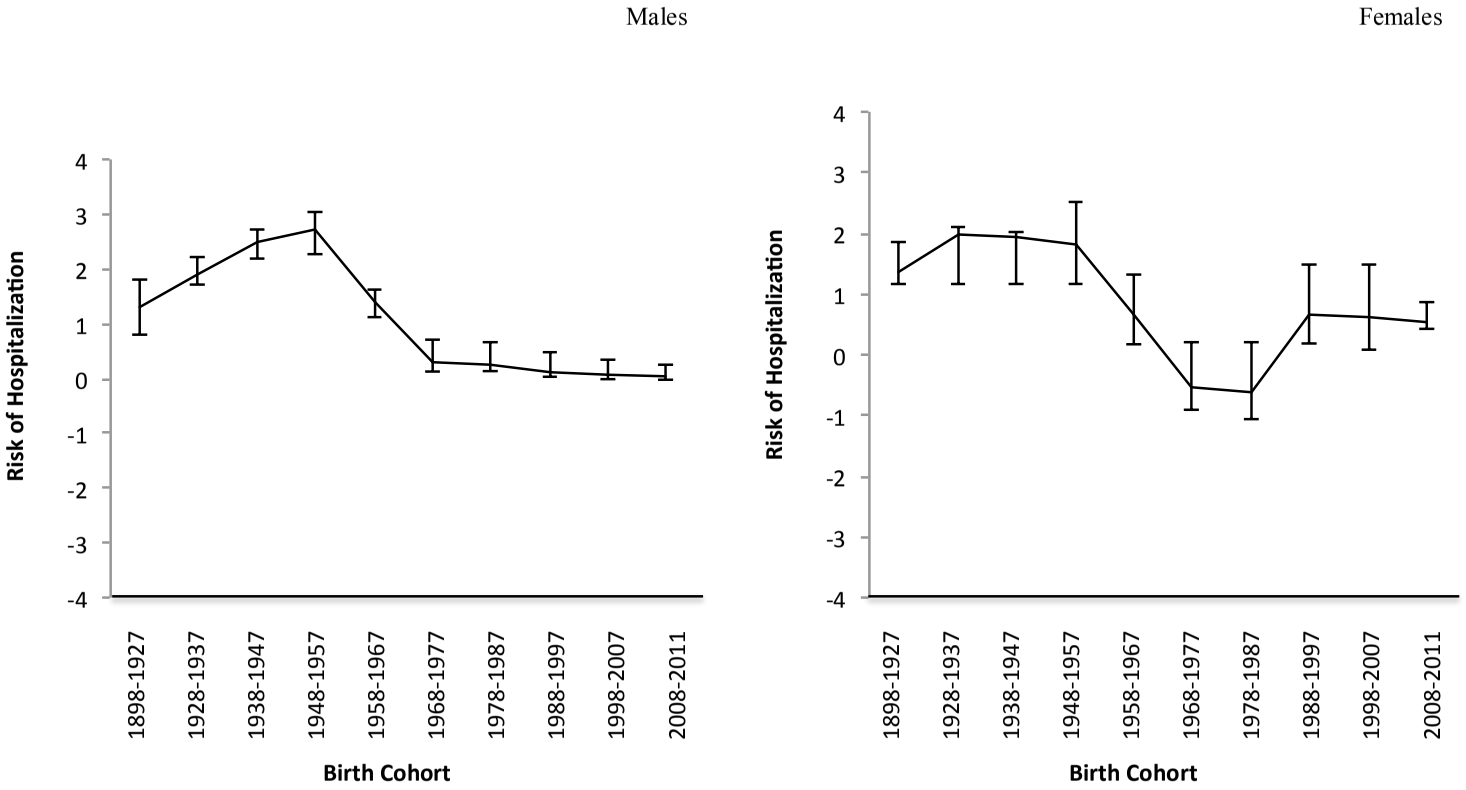

Figure 3. Age effect
Age effect of hospitalization for HCC with a Chronic Hepatitis B diagnosis in males and females

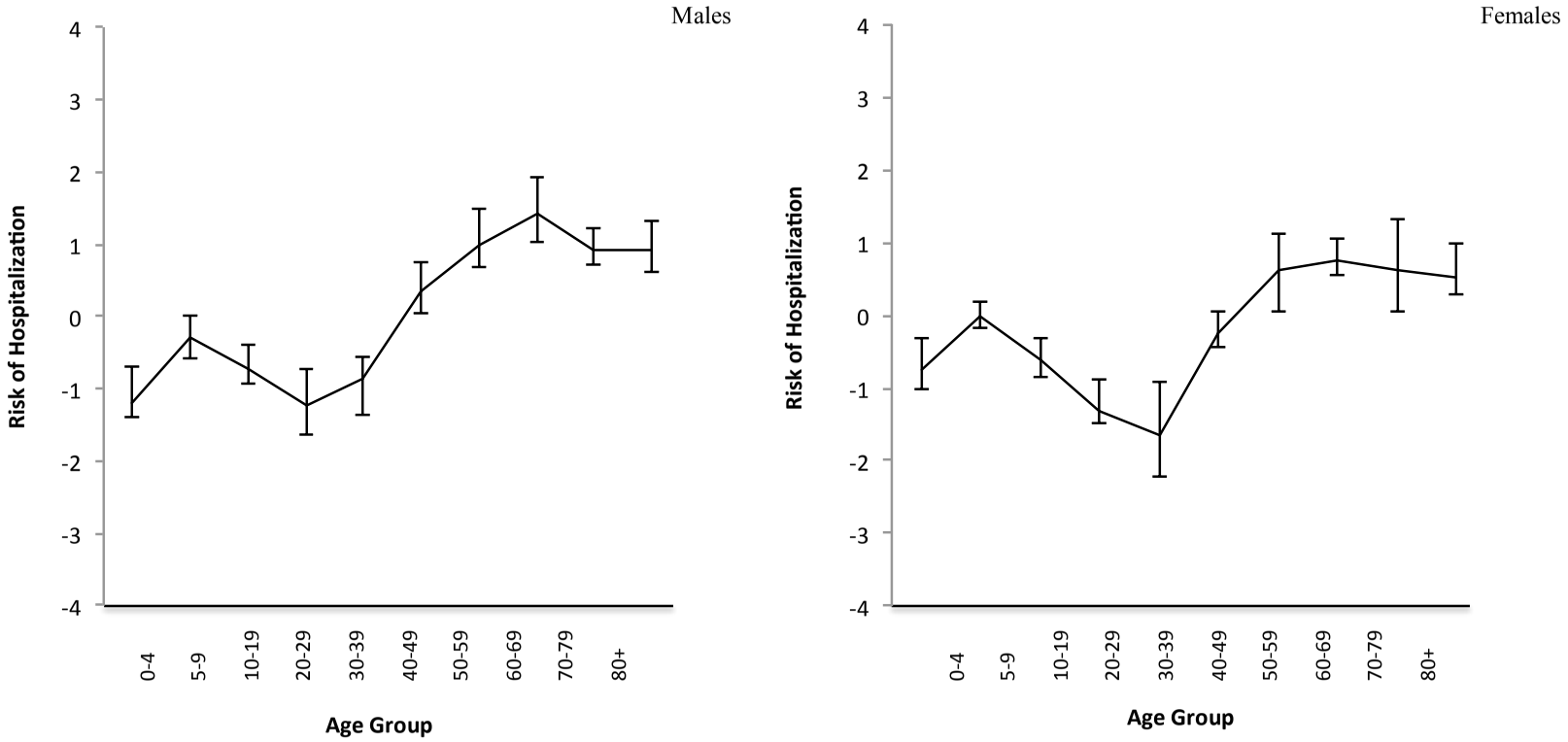

Figure 4. Period Effect
Period effect of hospitalization for HCC with a Chronic Hepatitis B diagnosis in males and females

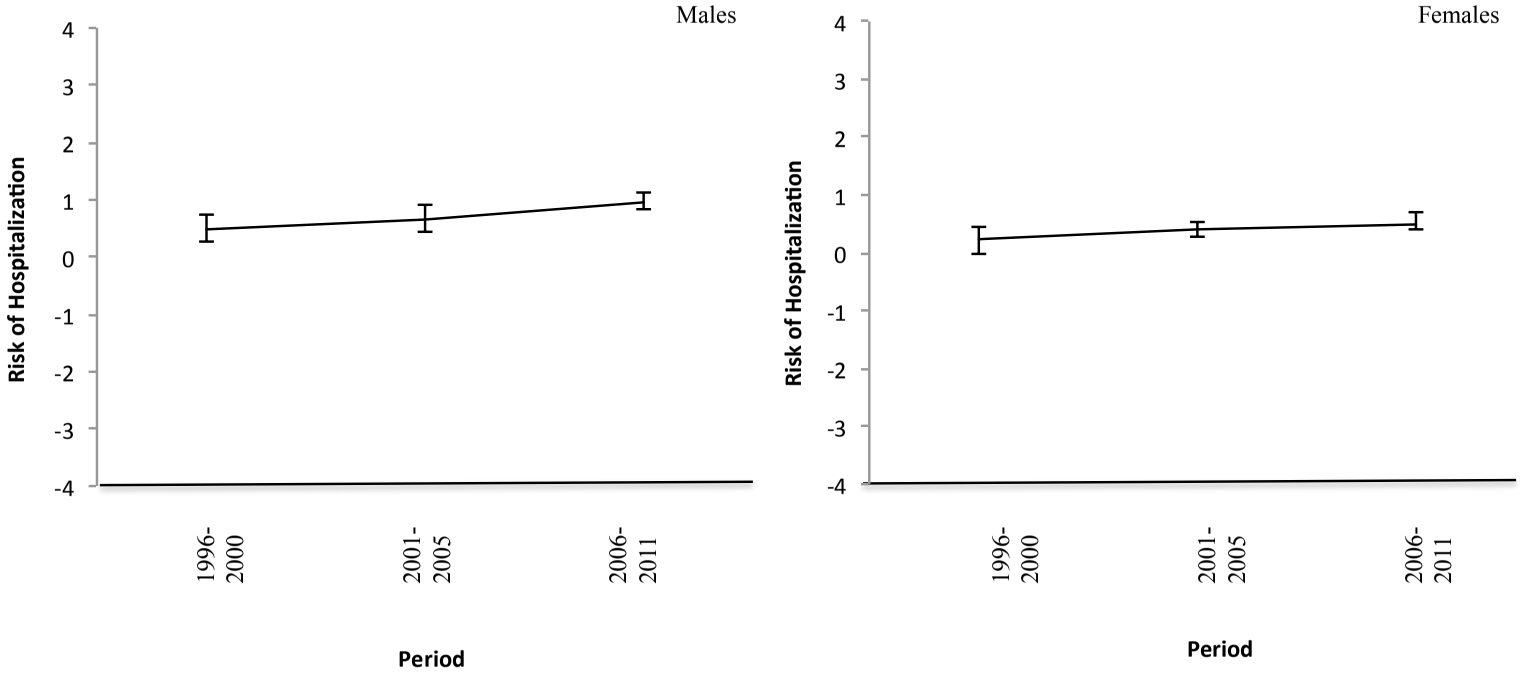

Table 1. Age, Race, and Hospitalization Rate of HCC with a Chronic Hepatitis B Diagnosis in the United States, 1996-2011

	HCC with Chronic Hepatitis B
Age Distribution	
Mean (SD)	55.3(13.2)
Median (IQR)	55(17)
Race Distribution # (%)	
White, non-Hispanic	255 (21.6)
African American	172 (14.6)
Hispanic	82 (7.0)
Asian/Pacific Islander	597 (50.6)
Native American	4 (0.3)
Average Annual Hospitalizations no./100,000 (95% CI)	0.35 (0.33, 0.37)
1996-2000	0.24 (0.21, 0.28)
2001-2005	0.37 (0.33, 0.40)
2006-2011	0.39 (0.35, 0.43)

Table 2 Age-Period-Cohort logistic regression models for risk of hospitalization for HCC with a hepatitis B diagnosis, in the United States, 1996-2011

Model	df	-2Log Likelihood	LR Statistic (df)	P-value
Males				
Age	8	705167.5	9109.0 (52)	<0.0001
Period	1	704162.0	8103.4 (59)	<0.0001
Birth cohort	8	736365.2	40306.6 (52)	<0.0001
AC	31	696520.9	462.3 (29)	<0.0001
AP	26	725334.2	29275.6 (34)	<0.0001
PC	24	696155.8	97.3 (36)	<0.0001
APC	60	696058.6	*Reference*	*Reference*
Females				
Age	8	333240.4	2136.7 (52)	<0.0001
Period	1	338384.1	5280.2 (59)	<0.0001
Birth cohort	8	354333.3	21229.4(52)	<0.0001
AC	31	333740.8	640.0 (29)	<0.0001
PC	26	353586.7	20.482.9 (34)	<0.0001
PC	24	333197.1	93.35 (36)	<0.0001
APC	60	333103.7	*Reference*	*Reference*

CHAPTER 3
PUBLIC HEALTH IMPLICATIONS

Although hepatitis B vaccines are safe and have shown to provide effective levels of protection, there is little knowledge about how this protection has translated in to protection from hepatitis B disease outcomes. Specifically, there remains a gap in our knowledge about the impact of hepatitis B vaccines on rates of HCC in the United States. This study aimed to use an APC analysis to determine the impact of hepatitis B vaccines on hospitalization rates for HCC. Such an analysis allowed us to determine the possible effects of changing hepatitis B epidemiology on rates of HCC in the United States. Logistic regression of birth cohort specific effects, accounting for age and period effects, allowed us to isolate the specific effect of broadening hepatitis B vaccine recommendation on risk of hospitalization for HCC. This analysis demonstrated that risk of hospitalization for HCC with a chronic hepatitis B diagnosis decreased as hepatitis B vaccine recommendations were expanded, thus suggesting an association between hepatitis B vaccines and risk of hospitalization for HCC with a chronic hepatitis B diagnosis. Although HCC rates continue to increase in the United States, both rates and risk of hospitalization of HCC with a chronic hepatitis B diagnosis have decreased notably since 2008, suggesting that chronic hepatitis B infection may not be the reason for increasing HCC trends.

Though this study allowed us to determine HCC hospitalization rates in individuals with specific risk factors for HCC (chronic HBV infection and cirrhosis) there remains a need for additional prospective birth cohort studies to determine the extent to which hepatitis B vaccines impact rates of HCC between vaccinated and unvaccinated individuals. However, ethical barriers to the use of placebo vaccines greatly reduce the possibility for such studies.

Additionally there is a need for more research regarding the effect of chronic HCV infection on rates of HCC in the United States. There currently exist effective HCV treatments that can prevent progression to chronic HCV infection [1]. However, cost-effectiveness of such

treatments vary widely across different patient subgroups [1]. Greater information about the role of chronic HCV infection may help guide policy about the inclusion of HCV treatments in insurance plans.

These finding can be used by policymakers to justify continued investment in current hepatitis B vaccine recommendations, primarily including the hepatitis B vaccine as a birth dose and in the childhood immunization schedule in the United States. The analysis methods used in this study have also been used to analyze trends in HCC internationally. An APC analysis approach using country specific HCC data allows for country specific analysis of varying hepatitis B epidemiology and changing hepatitis B vaccine recommendations on rates of HCC. Thus such an approach can also be used to justify the expansion of hepatitis B vaccine recommendations globally.

Policy makers can use information from this study to justify efforts to increase in vaccination rates among immigrants, specifically Asian/Pacific Islander race. Additionally, results from this study can be used as a starting point to justify increased investment in HCV screening and treatment to prevent development of chronic HCV infection.

Results from this study were made based on United States hospitalization discharge data and are not necessarily generalizable to other settings. Rates of hepatitis B infection and disease epidemiology vary widely through the world. Countries can be classified in to “high risk” and “low risk” based on prevalence and modes of HBV transfer [2]. The United States is considered a “low risk” area and results from this study may be generalizable to other low-risk areas including Western Europe but not to high risk areas.

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