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Racial Disparities in Liver Disease in the US: Addressing the High Prevalence of Hepatitis B Infection in the APIA Community

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**Racial Disparities in Liver Disease in the US:
Addressing the High Prevalence of Hepatitis B Infection in the APIA Community**

A Thesis Presented
By

Lindsey Trinh

To the Keck Science Department
Of Claremont Mckenna, Pitzer, and Scripps Colleges

In partial fulfillment of
The Degree of Bachelor of Arts

Senior Thesis in Biology

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ABSTRACT

Chronic liver disease and hepatocellular carcinoma are some of the leading causes of death in the United States, resulting in a number of annual deaths that has only increased over the past several decades. A vast proportion of these liver-related deaths is due to chronic hepatitis B infection, which currently affects approximately 1.2 million people in the US. However, the hepatitis B virus does not affect every racial group in the United States equally: Asian Americans experience a disproportionately high prevalence of HBV infection. In fact, even though the APIA community comprises only 4% of the US population, they account for approximately 60% of the 1.2-2 million individuals affected with chronic hepatitis B in the US. This striking racial demographic of HBV-infected individuals is due to a myriad of biological and cultural factors such as emigration from regions with high HBsAg prevalence, a high rate of HBV vertical transmission from mother to child, and suboptimal HBV screening and management among immigrants and non-native English speakers. This paper proposes a two-part study, which utilizes surveys distributed to patients and health providers to create a free clinic event that will model optimal HBV screening and treatment strategies for Asian immigrants. From this study, we hope to implement changes in healthcare for Asian immigrants that will remedy cultural barriers and the disproportionate prevalence of HBV in APIA communities, in order to ultimately lower the overall rate of liver-related death in the US.

INTRODUCTION

The Epidemiology of Liver Disease: liver cirrhosis, HCC, Hepatitis B and C

Chronic liver disease and liver cirrhosis are two of the leading causes of death in the United States, contributing to approximately 45,000 annual deaths in the country (Center for Disease Control & Prevention, 2020), and 2 million deaths annually worldwide (Asrani et al., 2019). These deaths are a result from both complications due to decompensated liver cirrhosis and viral hepatitis-related hepatocellular carcinoma (HCC). Liver disease can be caused by viral infection, immune system abnormalities, vertical transmission and other genetic factors, excessive alcohol consumption, and metabolic disease. In the United States, the most common causes of viral hepatitis are hepatitis B and C viruses, which are known to lead to the formation of liver cirrhosis and HCC. While information on virally transmitted liver diseases needs to be more widespread across the country, hepatitis B and C viruses do not affect all racial groups across the US equally -- immigrants from countries in Asia and sub-Saharan Africa are significantly more likely to be infected with hepatitis B than other racial groups in the US (Figure 1), with HBV prevalence in Asian subgroups ranging from 9% to 25% (Li et al., 2018).

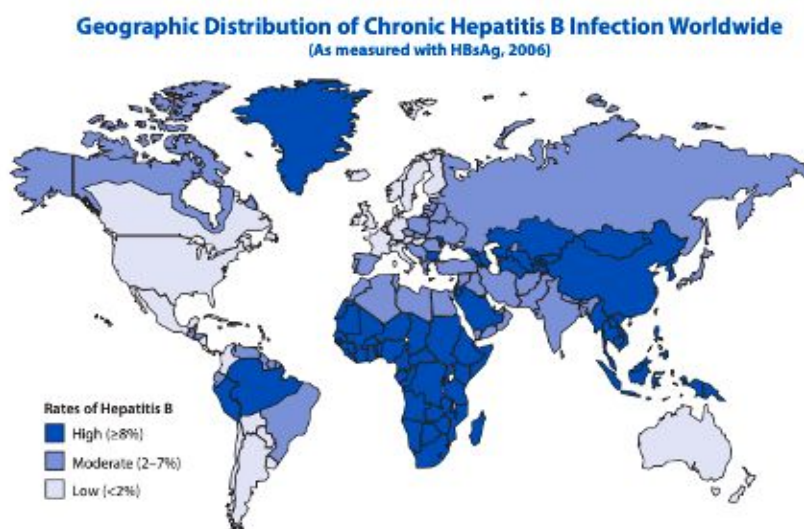


Figure 1. World map of countries with high rates of positive HBsAg, a serologic indicator for acute or chronic HBV infection (CDC, 2013).

The Epidemiology of Hepatitis C and Disease Progression

Hepatitis C infection is the second most likely viral infection to cause liver cirrhosis and hepatocellular carcinoma. Of the world's population, approximately 3% are infected with hepatitis C virus (Vescovo et al., 2016). The most common forms of hepatitis C transmission is through intravenous drug use in developed countries, while in developing countries, the most common forms of viral transmission are via contaminated instruments during invasive procedures or injection-based therapies (Morozov and Lagaye 2018). When acute hepatitis C infection goes untreated, this often develops into chronic hepatitis C (CHC), which can then result in inflammatory lesions in the liver known as hepatic steatosis, progressive fibrosis, compensated and decompensated cirrhosis, and hepatocellular carcinoma. Of the patients that develop hepatic steatosis and liver fibrosis, 10-20% of these patients' liver disease develops into liver cirrhosis (Figure 2). Of these individuals, 1-5% eventually develop HCC, which requires treatments such as transarterial chemoembolization, chemotherapy, liver ablation, and, in most serious cases, liver transplantation. Progression of the virus is made more severe by other cofactors such as excessive alcohol consumption and metabolic liver disease.

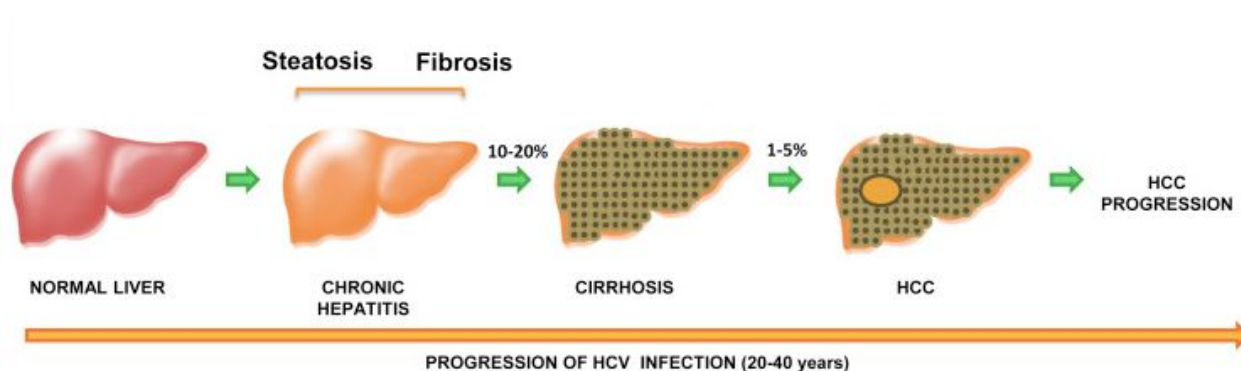


Figure 2. The progression of HCV infection, outlining the progression from a healthy liver to liver cirrhosis and liver cancer (Vescovo et al., 2016).

Epidemiology of Hepatitis B

Although HCV infection continues to be a problem globally, compared to hepatitis C virus, hepatitis B is more transmissible and more deadly. At least 240 million people are affected by chronic hepatitis B infection (Dandri and Peterson, 2016), 60% of liver cancer diagnoses are due to cases of chronic hepatitis B, and 15-25% of those with inadequately screened and suboptimally treated hepatitis B will die prematurely from liver cirrhosis, liver failure, or hepatocellular carcinoma (Hepatitis B Foundation, 2019).

Furthermore, the molecular biology of the hepatitis B virus is less understood than that of the hepatitis C virus (HCV). As a result, complete eradication of HCV in 12-24 weeks is possible through antiviral medication, while HBV treatment requires life-long antiviral treatment that does not cure the infection or eradicate the virus, but greatly minimizes the risk of developing potentially fatal liver cirrhosis or HCC. In contrast to HCV, chronic hepatitis B infection can develop into hepatocellular carcinoma in the absence of liver cirrhosis, potentially making the virus more lethal due to fewer cirrhosis-related symptoms such as ascites, hepatic encephalopathy, and variceal bleeding, which can typically serve as a warning to start immediate treatment before the formation of HCC (Shim et al., 2017). In addition to these key differences between hepatitis B and C, HBV is more transmissible and causes more annual cases of cancer and death than hepatitis C. In total, the higher transmissibility of HBV and its ability to result in the formation of HCC in the absence of cirrhosis overall make the virus more deadly in comparison to HCV. Given the APIA population's higher risk for HBV infection, it is essential to address HBV infection and liver disease as an endemic within the Asian community in order to decrease rates of liver-related mortality.

Molecular Biology and Infection Mechanism of Hepatitis B Virus

The hepatitis B virus is also unique in its molecular biology and structure: its virion contains a nucleocapsid of the HBcAg core protein, and the genome within the nucleocapsid forms a relaxed circular partially double-stranded DNA, linked to the viral polymerase (Dandri and Petersen, 2016). When the virus reaches the host, it sheds high rates of subviral particles that bear both small and large HBV surface antigens (HBsAg). Serum levels in individuals infected with chronic hepatitis B can have HBsAg levels of up to 400 µg/mL (Mohebbi et al., 2018). Although only approximately 1 of 10,000 subviral particles are infectious, those infected with chronic hepatitis B who also carry HBsAg have at 25-37% higher risk for later developing HCC (Kondo et al., 2013). The biological function of the many non-infectious subviral particles is still unknown, although studies have suggested that they may have a role in suppressing the host immune response, and in neutralizing antibodies produced by the host in response to high levels of HBsAg (Dandri and Petersen, 2016). In addition to vertical transmission from mother to child, the hepatitis B virus is transmitted through percutaneous exposure to other infected body fluids. The virus travels via the bloodstream to the liver, where it enters the hepatocyte nucleus via endocytosis. Upon entry and interaction with the nuclear pore complexes, the mature capsids of the virus disintegrate, allowing partially double-stranded DNA to enter the nucleus and to be converted to cccDNA (Dandri and Petersen, 2016). The cccDNA serves as the template for the transcription of viral mRNA, which is then sent out of the nucleus into the cytoplasm for protein synthesis (Figure 3). This translation of viral mRNA in the cytoplasm is followed by protein packaging and synthesis of plus and minus-strand DNA. Finally, the new nucleocapsids are enveloped and packed, and secreted from the cell as virions (Tong et al., 2013).

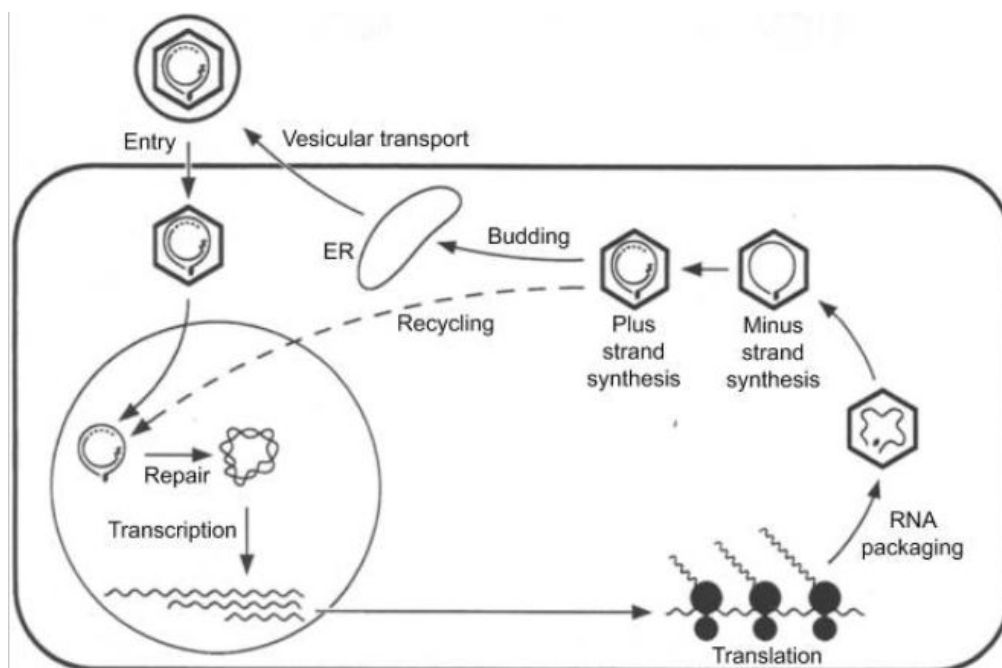


Figure 3. Portrayal of the HBV life cycle and interaction with host cell (Tong et al., 2013).

Common Methods for Prevention and Treatment of Chronic Hepatitis B

HBV treatments can be divided into the categories of either prevention or catch-up.

Global pre-infection vaccination has proven to be the most effective and cost-efficient method for reducing the threat of HBV infection. Since 1991, the World Health Organization (WHO) has recommended that all countries incorporate the HBV vaccine into their national immunization programs (Das et al., 2019). Infant immunization is the most effective and now most common form of prevention, and the vaccination is delivered on day 0, month 1, and month 6 of infancy. Pre-infection vaccinations are intended to boost the immune system of the host, which eradicates any HBV surface antigen in the individual and keeps the replication of introduced HBV under control.

Catch-up strategies for HBV treatment are of equal importance especially for individuals born outside the United States and those born after the HBV vaccination was widely used.

Extensive research for HBV cures is still underway. Two treatments for chronic hepatitis B have

been approved for public use: interferon treatment (IFN) and nucleos(t)ide analogs (NAs). These treatments unfortunately do not eliminate the virus in those diagnosed with CHB, but are successful in suppressing continued HBV replication and decreasing risk for fatal CHB symptoms such as liver cirrhosis, liver failure, and hepatocellular carcinoma development (Lok, 2019). Commonly used treatments for chronic hepatitis B include interferons such as interferon alpha-2b and PEGylated interferon, and the more common antiviral nucleos(t)ide analog medications entecavir and tenofovir.

The diagnosis criteria for acute or chronic HBV infection include liver enzyme tests, lab tests for the presence of the alpha-fetoprotein tumor marker, lab tests for the presence of HBV serological markers (Figure 4, 5), and screening via CT or MRI.

Interpretation of Serologic Tests		
Tests	Results	Interpretation
HBsAg	Positive	Currently infected with the hepatitis B virus. Follow up with IgM anti-HBc to determine if chronically infected
HBsAg anti-HBc IgM anti-HBc anti-HBs	Positive Positive Positive Negative	Acute infection with the hepatitis B virus
HBsAg anti-HBc IgM anti-HBc anti-HBs	Positive Positive Negative Negative	Chronic infection with the hepatitis B virus
HBsAg anti-HBc anti-HBs	Negative Negative Negative	Susceptible (consider for vaccination)
HBsAg anti-HBc anti-HBs	Negative Positive Positive	Immune by natural infection
HBsAg anti-HBc anti-HBs	Negative Negative Positive	Immune by hepatitis B vaccination
HBsAg Anti-HBc Anti-HBs	Negative Positive Negative	Interpretation unclear; four possibilities: 1. Resolved infection (most common) 2. False-positive anti-HBc, thus susceptible 3. "Low level" chronic infection 4. Resolving acute infection

Figure 4. An outline of the interpretations of various serologic test results: how HBsAg, anti-HBc, IgM anti-HBc, anti-HBs results indicate acute or chronic HBV infection along with HBV vaccination history (CDC, 2013).

<p>HBsAg: Hepatitis B surface antigen. Positive HBsAg indicates that the individual is infectious with acute or chronic HBV.</p> <p>anti-HBs: Hepatitis B surface antibody. Generally indicates recovery and/or immunity from HBV infection, and develops in those successfully vaccinated against hepatitis B.</p> <p>anti-HBc: Total hepatitis B core antibody. Typically appears at the onset of symptoms and persists for life, including in treated individuals. Indicates previous or ongoing HBV infection.</p>

Figure 5. Definitions and implications for the presence of HBV serological markers HbsAg, anti-HBs, anti-HBc. Derived from the CDC article "Testing Asian Americans and Pacific Islanders for Hepatitis B."

Genetic Factors for Chronic Hepatitis B

While modes of chronic hepatitis B transmission such as via bodily fluids of infected individuals and vertical transmission from mother to child is well known, other genetic factors that contribute to hepatitis B susceptibility are still being widely researched. Currently, there are ten known genotypes of the hepatitis B virus, with 4-12 subgenotypes within each. HBV genotypes and subgenotypes are known to have different clinical outcomes, and genotype prevalence and distribution are dependent on ethno-geographical location (Gao et al., 2019). Several studies highlighting the differences between HBV genotypes found that the effects of HBV genotype B are less severe than those of genotype C, with overall slower liver damage and disease progression via earlier HBeAg seroconversion, higher HBsAg seroclearance rates, and lower HBV DNA levels, implying that HBV genotype C may have stronger pathogenicity (Tian and Jia, 2016). While the ethno-geographical distributions of HBV genotypes are not as distinguished within the United States, there are clearer distributions based on international geographic locations. HBV genotype F is most prevalent in various South American countries, while genotypes A and E have high prevalence in West Africa, and genotypes A and D have highest prevalence in northeast African countries and Asia (Figure 6).

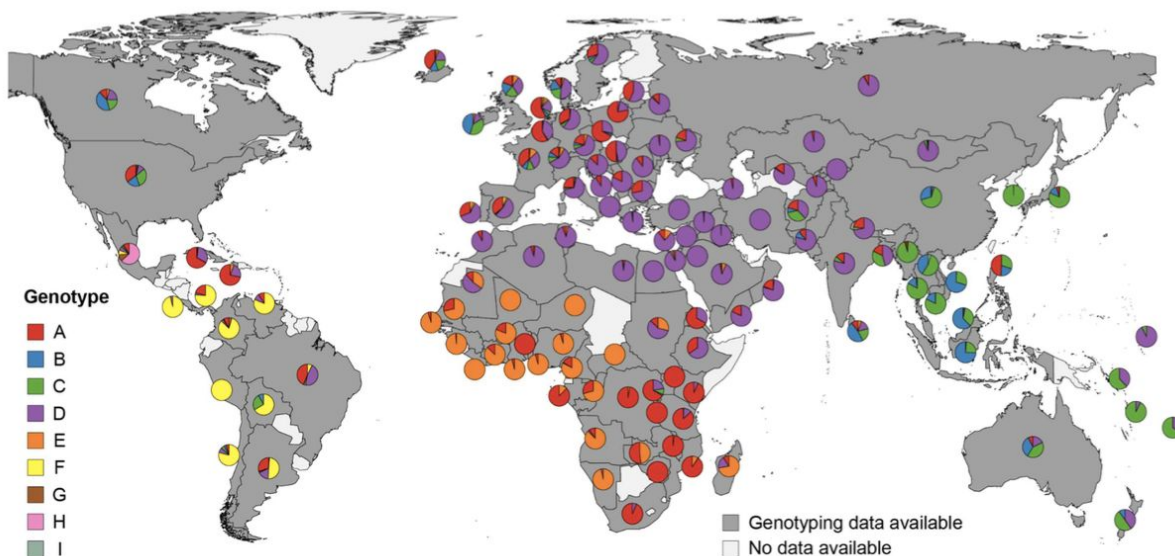


Figure 6. Geographic distributions of HBV genotypes by country. The figure excludes inter-genotype recombinant viruses and co-infections with greater than one HBV genotype (Velkov et al., 2018).

Studies have found that treatment and prevention effectiveness can vary across different HBV genotypes, suggesting that detailed knowledge of HBV genotype can increase the effectiveness of HBV replication suppression. In total, regarding treatment, studies suggest that optimizing CHB treatment depends on geographic region, accessibility to care, timing of intervention before progression of liver-related symptoms, and HBV genotype. With these factors in mind, physicians can treat and prevent CHB with highest efficacy and ultimately decrease the number of global deaths resulting from CHB. As indicated by Figure 6, the HBV genotype distribution across the US is less understood than in other countries, emphasizing the need to record the genotype and subgenotype in HBV patients more consistently, ultimately offering a better understanding of the effects of racial and ethnic background on HBV infection rates.

Epidemiology of HBV in Asian Immigrants in the US

Asian Americans in the United States are especially at risk for having chronic hepatitis B. Although Asian Americans make up only 4% of the US population, they comprise approximately 60% of the 1.2-2 million individuals infected with CHB in the US. Additionally, only 1 in 1,000 non-Hispanic Whites are chronically infected with hepatitis B compared to 1 in 12 Asian Americans, indicating one of the greatest racial health disparities in the United States (Stanford Medicine Asian Liver Center, 2020). There are several proposed reasons for this striking disparity: high CHB prevalence has been an issue in East Asian countries due to a history of improper sterilization or disposal of needles and other medical supplies over previous decades. Since treatment that drives successful eradication of the virus does not yet exist, and because the rate of vertical transmission of HBV from mother to child is particularly high (1-28%) compared to other chronic diseases including HCV, the HBV endemic persists in East Asian countries, resulting in a high prevalence of HBV infection in both Asian immigrants and the children of Asian immigrants (Mavilia and Wu, 2017). While the prevalence of CHB infection is relatively low in the United States as a whole, increasing rates of immigration from East Asia, a region with a higher prevalence of positive hepatitis B surface antigen, have resulted in health disparities among Asian American populations (Chen Jr and Dang, 2015).

Liver-Related Death in Asian Americans

While the hepatitis B virus itself does not cause death in infected individuals, untreated HBV infection can lead to fatal liver impairment, via development of liver cirrhosis or hepatocellular carcinoma. As already stated, HBV infection can lead to the formation of HCC even in the absence of liver cirrhosis. Because of the disparately high prevalence of chronic hepatitis B among Asian Americans, they also have the highest incidence of hepatocellular

carcinoma compared to other racial or ethnic groups across the United States (Table 1). In fact, Asian Americans are the only racial or ethnic group in the US whose leading cause of cancer-related death is liver cancer (Sarpel et al., 2018). Because Asian Americans make up a quickly growing demographic within the US, and because many Asian immigrants have not been routinely vaccinated for HBV, the prevalence of HCC development as a result of chronic hepatitis B infection remains a growing problem in the US. Studies have shown that Asians have received more liver transplantations due to hepatocellular carcinoma development than other racial groups in the US (Kemmer, 2011).

	White	Hispanic	Black	Asian
HCV	29%	36%	33%	18%
HBV	3%	4%	4%	26%
PSC/PBC	13%	7%	12%	4%
Alcohol	15%	13%	6%	3%
HCC	8%	12%	9%	22%
FHF	5%	5%	12%	7%
Other etiologies	27%	23%	24%	20%

FHF=fulminant hepatic failure; HBV=hepatitis B virus;
HCC=hepatocellular carcinoma; HCV=hepatitis C virus;
PBC=primary biliary cirrhosis; PSC=primary sclerosing cholangitis.

Reproduced from the United Network for Organ Sharing database.

Table 1. Etiology of Liver Disease in Liver Transplantation Recipients (Kemmer, 2011). Asians received significantly more liver transplantation procedures due to liver complications from HCC. Additionally, Asians received significantly more liver transplantations due to HBV infection than White, Hispanic, or Black populations.

What Are the Known Disparities in HBV Treatment in Asian Americans?

There are several factors that contribute to the growing racial health disparity between Asians and non-Asians in the United States. Studies have shown that Asian immigrants and children of Asian immigrants are less likely to have health insurance coverage than non-Hispanic white individuals. In addition, even those that do have health insurance are less likely to receive high-quality healthcare compared to non-Hispanic Whites (Clough et al., 2013). The disparities in health insurance coverage and quality in healthcare are primarily due to language barriers between health providers and their patients, cultural differences regarding approaches to health, lack of access to health services, and racial discrimination within the healthcare system.

Throughout history, US immigrants and children of immigrants have had a high likelihood of being uninsured, and in 2012, it was estimated that up to 6 million immigrants could benefit from universal health coverage. Provisions to the 2010 Patient Protection and Affordable Care Act were made in 2013, and subsequent changes in rates in insurance coverage followed in 2016. While these changes somewhat ameliorated the low coverage for Asian immigrants by reducing the waiting period required for US residence prior to qualifying for health insurance, there still remains a significant disparity in medical care that Asian Americans receive compared to non-Hispanic White Americans.

The racial disparities in healthcare quality are only further driven by differences in socioeconomic status within the Asian American community. Millions of more individuals have received health insurance coverage under the Affordable Care Act, which allows low-income individuals, which equated to those receiving an annual income of \$17,236 or less in 2019, to be eligible for Medicaid (Garfield and Orgera, 2020). Fourteen states in the US failed to participate in this expansion of Medicaid eligibility, making the income cutoff point that qualifies for

eligibility of Medicaid much lower in these states. Although the Medicaid eligibility expansion has resulted in significantly more health insurance coverage in communities of color across the country, there is still a significant coverage gap which represents those who are not eligible for Medicaid under the Affordable Care Act, yet are still unable to afford coverage through private health insurance companies (Figure 6).

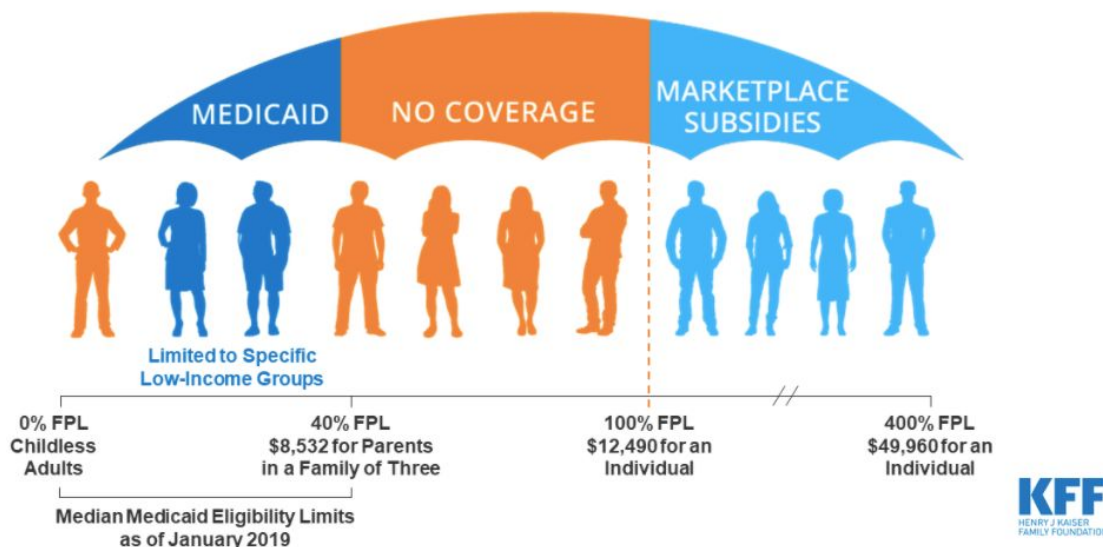


Figure 7. Highlights populations of people that make up the “Coverage Gap,” or those whose income is above the upper limit of Medicaid eligibility, but below the lower limit for other private means of health insurance (Garfield and Orgera 2020).

The national health insurance coverage gap in addition to lower quality healthcare faced by US immigrants is especially alarming for Asian immigrants in the US who suffer from HBV infection. Despite the fact that the CDC recommends that anyone born or with one parent born in any Asian country, any Pacific Island, and any other countries with moderate to high rates of hepatitis B (Figure 1) should be tested for Hepatitis B with an HBsAg test (CDC, 2013), many primary care physicians are either unaware of or do not practice this recommendation.

Studies have shown that physician adherence to the American Association for the Study of Liver Disease (AASLD) guidelines for management of HBV infection has been suboptimal across the country, ultimately affecting communities of Asian immigrants whose undiagnosed

HBV infections progress past the stage at which treatment is most effective. There were several factors significantly associated with more effective HBV screening, such as provider ability to speak an Asian language and having more than 25% of Asian patients in practice (Mukhtar and Kathpalia et al., 2017). These findings suggest that there is significant room for improvement in HBV management among health providers, especially among those that serve a minimal Asian demographic.

In addition to the evident disparity in HBV management knowledge among health providers, racial discrimination and cultural differences within the healthcare system are critical barriers for Asian immigrants seeking healthcare. Non-native English speakers and people of color have a pattern of choosing non-white physicians due to implicit racial bias among healthcare professionals and resulting increased comfort during their appointments (Hall et al., 2015). Though, many patients, especially those in rural areas, are not given the privilege of choosing health providers that share parts of their cultural background. Implicit racial bias and cultural differences between provider and patient lead to gaps in communication and health education, ultimately contributing to the already existing racial disparity in HBV infection in the US.

There are several primary factors that contribute to the racial disparity in hepatitis B prevalence among Asian and non-Asian communities in the US: these factors include differences in health education due to a lack of English fluency, differences in health provider management of HBV infection, genotypic differences in HBV depending on country of birth, and variance in patient compliance with prescribed treatment. The objective of this study is to highlight the significant change in patient outcome that could result from alterations in general screening protocols in addition to increased efforts to prioritize cultural competence among health

providers. This paper proposes a study consisting of a patient survey, provider survey, and long-term longitudinal study which utilizes genetic testing for HBV genotype to target treatment. The first survey, directed toward older individuals in the APIA community in the Orange County area, is intended to indicate a disparity in knowledge regarding the dangers of HBV infection and liver disease within the Asian American community. The second survey, which will be distributed to various health providers in both rural and urban regions of the United States, will assess the proposed phenomenon that providers who do not speak an Asian language or serve a significant proportion Asian patients are less likely to provide proper management of HBV infection. The results of these surveys will be consolidated to create a health fair event which will attempt to address both the cultural and clinical disparities found in the surveys, by recruiting multilingual health providers of Asian descent, offering free liver screenings and hepatologist referrals, and providing free educational seminars regarding the importance of HBV management in the APIA community. These particular components of the health fair are intended to increase cultural competence between provider and patient, maximize patient compliance with their HBV treatment, and improve health education among Asian immigrants. The results of this study could lead to the development of more specific treatment plans for Asian immigrants in the US at high risk for CHB, ultimately decreasing the rate of liver-related mortality in APIA communities. With the results of the surveys and longitudinal study, we hope to determine whether or not the current racial disparity in HBV prevalence can be improved with increased health education targeted toward immigrants, improved cultural competence and racial bias training among health providers, and more clinical opportunities for free healthcare for immigrant communities.

METHODS

HBV Awareness Survey

In order to assess the rates of potentially untreated HBV infections and the disparity in knowledge regarding HBV risk in the Asian American community, a survey will be conducted online and in person in areas frequented by individuals of Asian descent. Guidance for the survey questions will be provided by healthcare and governmental organizations that have done previous work on health disparities within the Asian American community, such as the Asian Liver Center, the San Francisco Hep B Free Campaign, and the AsianWeek Foundation. The surveys will be conducted primarily through SurveyMonkey.com, though our results will also include questionnaire answers from telephone surveys and street intercept surveys. Parts of the survey will include ideas from a study performed by the San Francisco Hep B Free Campaign (Shiau et al., 2011). Those surveyed will be individuals of Asian descent that are 40 years old or older, including participants born both in the US and in countries outside the US. This age group was chosen because it comprises a higher percentage of Asian individuals born outside the US: this demographic has a higher risk of hepatitis B infection, and is potentially less likely to have received the HBV vaccine. The identity-based demographics collected through the survey will include age, ethnicity, place of birth, annual income, and health insurance membership. The responses of any individuals with a unique interest and therefore thorough knowledge of hepatitis risks and treatment will be excluded from the study. The survey will offer translations from English to Vietnamese, Chinese, and Korean if needed.

Identity information:
 Age, sex, place of birth, languages spoken (and native language)
 Annual income and health insurance coverage

Have you ever heard of a medical condition called hepatitis B?
How can someone prevent getting hepatitis B, and how can they prevent giving it to others?
Have you ever been tested for hepatitis B?
 What made you get tested for hepatitis B?
 How long ago did you get tested?
 If you have not been tested, why not?
Do you know someone infected with hepatitis B?
Have you heard about hepatitis B risk within your community?

Do you feel like you can easily access medical care if needed?
What race/ethnicity is your medical provider?
Have you ever faced a language barrier with your medical provider?
 Do you think you would benefit from a translator during your medical appointments?

***Some questions derived from study by Shiau et al., 2011.*

Figure 8. List of survey questions addressing the medical needs of hepatitis B awareness among individuals of Asian descent

Identity information:
 Racial identity of physician, languages spoken

What is the racial demographic of your patients?
What percentage of your patients do you screen for hepatitis B?
Is hepatitis B screening part of your routine screening protocol?

Figure 9. List of survey questions for primary care providers, assessing the prevalence of hepatitis B screening for at risk populations

The Health Fair -- A Longitudinal Study

To assess whether adequate screening and early intervention makes a significant difference in Asian patient outcomes, a longitudinal study over sixteen years will be conducted that compares the outcomes of optimally screened individuals at risk for HBV infection with the current national statistic of HBV infections in Asian Americans. A free clinic event or “health fair”, modeled after that of the San Francisco Hep B Free Campaign, will be held in Orange County, CA for individuals at high risk for HBV infection. The health fair will be advertised to Asian patients at risk for HBV via posts on Facebook pages, TV advertisements on Vietnamese and Chinese TV channels, and radio stations with high rates of Asian listeners. The event will also be advertised with flyers (translated into Vietnamese, Mandarin, Cantonese, Cambodian, and Korean) that will be posted in areas frequented by older Asian individuals, and the waiting rooms of doctor’s offices.

The health fair will offer several free services to patients in attendance with or without health insurance coverage. Services will include liver function blood tests, hepatitis B vaccinations for those not yet vaccinated or infected, and referrals to hepatology specialists for individuals with HBV infection or abnormal liver function results. Along with typical liver function lab tests, consenting attendees will undergo HBV serologic tests for HBsAg, anti-HBc, and anti-HBs* (Figure 5). For individuals infected with hepatitis B, their genotype and subgenotype will also be recorded, to optimize the form of treatment and to add to the existing database of hepatitis B genotype by geographic location (or country of birth). Multilingual providers or translators will also be available for any patient questions.

A total of 5-6 physicians and other healthcare providers will comprise the health fair team. Their responsibilities will include running liver function labs, administering hepatitis B

vaccines, writing referrals to specializing hepatologists for infected individuals, and annual follow-ups with the primary care physicians and liver specialists of the health fair participants. In exchange for these free services, participating patients will be asked to consent to a non-invasive longitudinal study, in which their medical records will be checked every 4 years for 16 years by the health fair physician team (Figure 10).

In addition to health services and screening, the fair will also include an educational aspect to spread awareness about the increased risk for hepatitis B in individuals of Asian descent. Several seminars will be offered to the patients in attendance: topics covered will include modes of hepatitis B prevention and the importance of the hepatitis B vaccine, common symptoms and forms of treatment for chronic HBV infection, and tools to navigate healthcare for non-English speakers. Although the health fair will be open to all individuals interested in learning more about hepatitis B and receiving free screening, the demographic is expected to consist of mostly older Asian immigrants with limited English proficiency, a population that often receives inadequate healthcare due to language barriers, social practice, cultural beliefs, and racial prejudice in the health industry.

A follow up every four years will be led by the health care physician team with the primary care physicians and liver function specialists of the participating health fair patients. The following patient information will be collected:

How many patients have received regular screening for liver function abnormalities?

How many patients have positive HBsAg (if any)?

How many patients with HBV infection are not receiving treatment?

What are the reasons for not receiving treatment (insurance denial, patient refusal, etc.)

How many patients are on HBV treatment?

What form of treatment (interferon, nucleos(t)ide analogs -- tenofovir, entecavir, adefovir)?

How many patients (if any) have developed hepatocellular carcinoma?

Has their HCC been effectively treated?

Have there been any reported liver-related deaths?

Figure 10. Data to be collected every four years in patients being treated for HBV infection following the health fair.

EXPECTED RESULTS

HBV Awareness Among Asian Individuals

Results from Part 1 of the patient survey are intended to indicate what aspects of hepatitis B are typically well-known among Asian individuals along with testing and screening adequacy among this population. Based on the results in other community-based studies such as those by Shiau et al and Chen Jr & Dang, it is expected that older Asian individuals will have a relative misunderstanding about the ways to successfully prevent hepatitis B infection. In addition, while we expect that most individuals will have heard about hepatitis B that many have either not been tested, or were tested at an older age (above 50 years old). Lastly, we also expect that the reasons for never having gotten tested for hepatitis B were due partly to cultural preferences, but mostly because their health provider did not mention hepatitis B, and the patient therefore never asked for a test.

Differences in HBV Management Among Health Providers

The second portion of the patient survey is intended to point more directly toward the disparities in healthcare between Asians and non-Asians in the US, and significant results would offer insight as to how differences in healthcare accessibility has tangible effects in disease prevalence across different races. It is expected that older Asian immigrants will feel less access to their healthcare providers, due to language barriers or technical difficulties in the increasingly used Telehealth system. Additionally, we expect that many Asian immigrants whose native languages are not English are likely to have Asian doctors with similar ethnic backgrounds. While we expect that a significant proportion of older Asian patients will have bilingual doctors and/or doctors with translators, we also foresee that those with physicians that are purely English-speaking have faced language barriers with their providers, and feel that they would benefit from a translator or interpreter during their appointments.

Health Fair -- Changes in Disease Progression and Patient Outcome

The overall objective of the health fair study is to alter the typical pathway of Asian immigrants untreated for HBV infection (Figure 11) into one which intervenes HBV progression early and reduces the overall rate of liver-related death (Figure 12). Due to the evidence pointing to a disparity in medical service provided to older Asian immigrants (especially those without English fluency), we expect the health fair to have several hundred attendees. Of these attendees, our goal is to be able to track the results of 200 patients following the health fair for the longitudinal study. With this goal in mind, we expect 1-2 health fairs will be necessary to gather sufficient data. From the results of other studies that have outlined the importance of early screening for HBV such as those by Post et al., 2014 and Lok, 2019, we expect to see significant differences in health outcomes when comparing the patients who attended the health fair, and the

current HBV statistics among Asian American populations. Specifically, we expect to encounter a higher prevalence of positive HBsAg in the patients attending the health fair than the national statistic. We also believe that we will encounter a significant number of patients that have been living unknowingly with chronic HBV infection. We hope that during the four year check-ins we will find that more Asian patients than the national average are receiving adequate treatment for their chronic hepatitis B infection, and therefore fewer diagnoses for hepatocellular carcinoma.

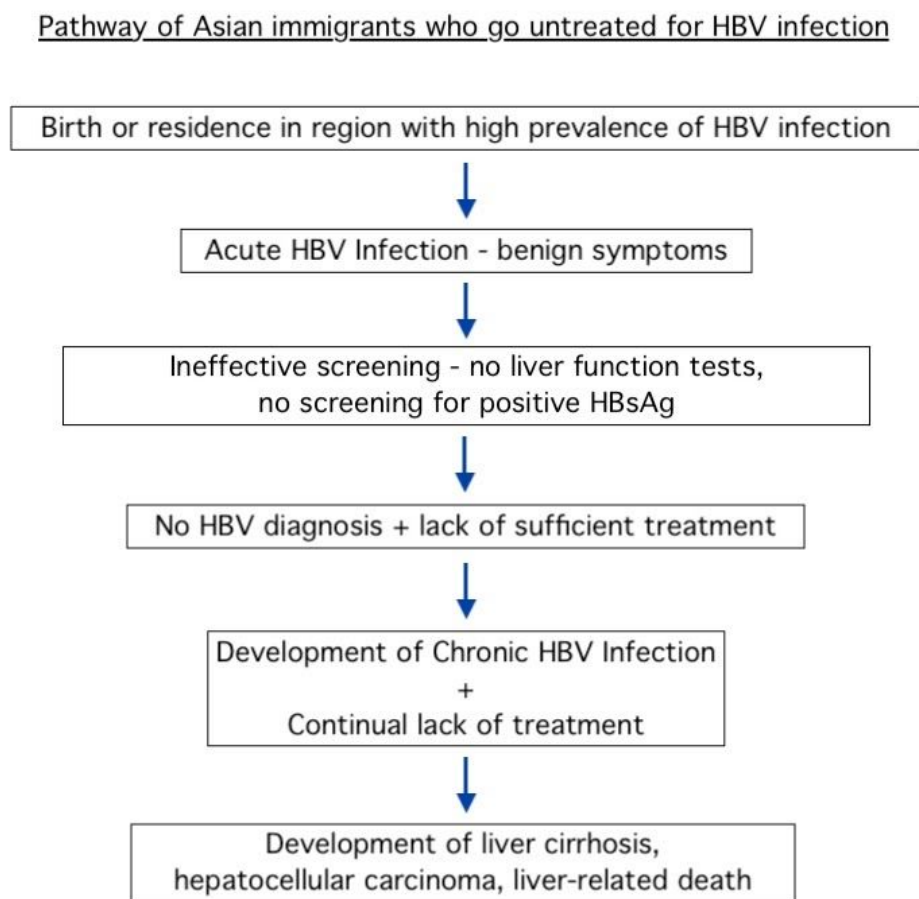


Figure 11. The pathway of Asian immigrants who go untreated for HBV infection, indicating that lack of adequate treatment can lead to the development of liver cirrhosis, HCC, and death.

Pathway of Asian Immigrants who undergo adequate treatment for HBV Infection

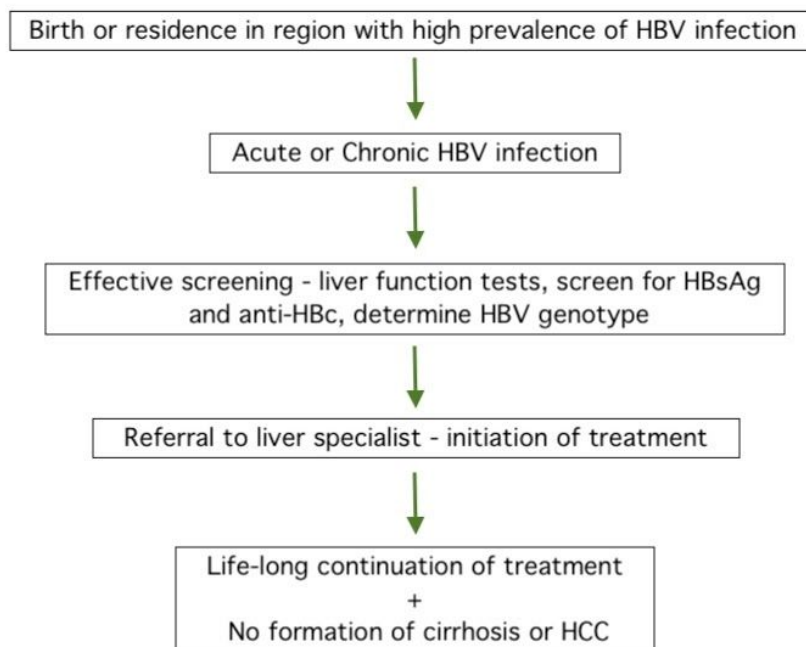


Figure 12. Pathway of Asian immigrants that are adequately screened and treated for HBV infection.

DISCUSSION

We expect to find a high prevalence of HBV misinformation in older individuals of Asian descent. Immigrant populations not only face more difficulty accessing health-related information through informative posters and advertisements, but also are unable to advocate for themselves during appointments with their physicians as effectively as non-Hispanic white patients, leading to an apparent health disparity that has compounded over decades. Because of this, Asian patients continue to be informed of high health risks not necessarily by medical professionals but by friends and family, resulting in overall inadequate screening for diseases that have high prevalence in Asian immigrants and their descendants, such as hepatitis B.

The intention of the survey for the general public is to gather the extent to which older Asian individuals are aware of their higher risk for hepatitis B, and whether they have received

the adequate information from health providers to protect themselves from infection or disease progression. From the survey answers we will consolidate the common misinformation and gaps in HBV knowledge in the APIA community to create an informational pamphlet to be distributed to older Asian individuals throughout Orange County. Although some organizations such as the San Francisco Hep B Free Campaign and the Asian Liver Center have been fairly successful in providing education on HBV prevention among higher risk individuals in the APIA community, we expect there to still be a need for further hepatitis awareness not only on the patient side, but on the health provider side as well. While of course the majority of health providers are well-educated in the dangers and means of prevention for HBV infection, studies have shown that health providers who do not typically serve communities at high risk for infection, such as individuals from certain countries in Asia and sub-Saharan Africa, do not screen for liver disease as much as necessary. In fact, factors such as the ability to speak an Asian language and having more than 25% of Asian patients in practice were significantly associated with differences in rates of HBV screening (Mukhtar and Kathpalia, 2017). Based on the results of these studies, we expect the results of the provider survey to reflect that Caucasian doctors, and other doctors who lack cultural connection to patients with ties to Asian and sub-Saharan African countries, screen for HBV significantly less than health providers who have exposure to high-risk communities. Additionally, we expect that providers that serve predominantly Caucasian patients to be less familiar with the AASLD guidelines for HBV management and liver cancer screening. Because of this disparity in knowledge, there may be a risk that Asian patients who see doctors with limited experience serving the APIA community may not be receiving adequate care for their HBV infection. Given the importance of early treatment intervention in liver disease progression,

these shortcomings in provider management may have widespread fatal consequences for APIA populations.

While effective therapies are available for HCV cure and HBV suppression, challenges remain in screening and linkage to care and treatment, particularly for vulnerable populations both domestically and worldwide. The health fair study is intended to serve as an example for a population of APIA patients adequately screened and treated for HBV infection. The results of the longitudinal study will provide essential information to determine whether the liver health of the APIA community can be significantly improved with early HBV intervention. At the health fair we expect to find a higher prevalence of patients with positive HBsAg than the national average for APIA communities, which will add to the existing evidence that cases of chronic HBV infections in Asian communities are being under-diagnosed. Finding positive HBsAg in patients not yet diagnosed for chronic hepatitis B is essential, given that early treatment in individuals with HBsAg greatly decreases the risk of developing liver cirrhosis or hepatocellular carcinoma. In addition to screening for positive HBsAg, we will record the genotype and subgenotype for every patient infected with HBV, streamlining the process of determining the most effective treatment for each patient. Following the health fair event, we hope to provide care and hepatologist referrals to HBV patients who would otherwise go undiagnosed. We believe that the health fair will provide an unorthodox form of healthcare that is both financially and culturally accessible to the APIA community, and will result in more HBV patients receiving necessary treatment for their infection. In addition, we predict that those who attended education seminars at the health fair will advocate for themselves more effectively during their visits with their physicians. Because of the expected increase in HBV surveillance from patients who attended the health fair, our aim is to decrease the number of APIA patients with liver cirrhosis

or HCC as a result of untreated HBV infection. By following the patients over 16 years, we will be able to compare the long-term outcome of adequately screened patients with the current average outcome of Asian HBV patients.

Unfortunately, even if a significant number of patients are successfully made aware of their HBV infection at the health fair, there are several reasons why these individuals may not receive treatment. The first is explained by unaccommodating health insurance plans: companies continue to discriminate against patients who are too “high-cost,” or in other words, patients with pre-existing conditions such as diabetes, asthma, and cancer. Although the policies in the Affordable Care Act prevent discrimination against pre-existing conditions including chronic hepatitis B, some health plans continue to discourage individuals affected by CHB from starting treatment by dramatically increasing copays for the two most common HBV antiviral drugs, Viread and Entecavir (Hepatitis B Foundation, 2016). Because of these obstacles, many CHB patients that need treatment are unable to receive it, due to health plans making their health deliberately unaffordable. Because early treatment of hepatitis B is essential in lowering the risk of liver cirrhosis and hepatocellular carcinoma formation, this prevention of patient care can ultimately have fatal consequences.

The second, perhaps less common reason for HBV patients not receiving needed treatment is due to differences in cultural beliefs. Cultural practices that prevent necessary treatment are inherently associated with other barriers such as the inability to communicate in English, negative perceptions of Western medicine, and underrepresentation of APIA individuals among health care providers. A combination of these factors can lead to patient refusal for HBV medication, failure to follow up with their health provider, and miscommunication regarding the seriousness of their chronic disease.

Potential Pathways Toward Remediating the Racial Disparity in HBV Prevalence

Adjusting CDC and AASLD Protocols

There are several potential solutions to remedy this apparent disparity in suboptimal screening for HBV infection. The first is to improve on existing CDC and AASLD guidelines to highlight the importance of addressing HBV risk in target populations. Studies have shown that a significant proportion of health providers are not only unfamiliar with the AASLD guidelines for HBV management, but are also unaware of the effectiveness of HBV therapy in reducing risk of liver disease progression. In addition, many health providers fail to identify vaccine-eligible patients in high-risk populations, and many are also unaware that HBV infection can lead to the formation of HCC in the absence of liver cirrhosis, highlighting the need for further health education and communication between primary care physicians and liver specialists. The CDC and AASLD guidelines recommend that individuals born in countries with an HBsAg seroprevalence $\geq 2\%$, in addition to U.S.-born individuals not vaccinated as infants with parents born in these high-risk regions be screened for HBsAg and anti-HBs, but these guidelines are often not implemented in practice. As a first step to mend the racial disparity in HBV prevalence, it is essential that physicians and other health providers be trained using the AASLD guidelines for HBV management, and normalize the practice of adjusting the typical screening protocol to address the needs of higher-risk populations.

Cultural Competence and Racial Bias in Healthcare

As important as medical knowledge in the field of healthcare is the practice of cultural competence. It is a common trend for patients to pursue care from doctors with similar cultural backgrounds -- for example, APIA patients prefer to seek care from doctors that share their native language and cultural values. As studies have shown, doctors that speak an Asian

language and those who serve a significant proportion of APIA patients are more likely to optimally screen for HBV infection. The results from these studies point to the importance of increased cultural competence and sensitivity training among health providers, especially those in rural areas that have a shortage of non-Caucasian physicians. In addition to training sessions focusing on cultural competence, hiring translators and interpreters at every practice that provides health services to non-native English speakers is likely to establish more trust between patient and provider, and ultimately give the patient more autonomy in their own care.

Additional Opportunities for Free Healthcare

To continue to provide care to underserved communities in Southern California, it is essential to find funding for additional free clinic events for the public. We expect there to be a significant turnout of participants at our health fair event, because it will be specifically advertised to non-English speaking individuals whose needs are often dismissed by healthcare professionals. Free clinic events that are successfully targeted toward immigrant populations often are well-attended, implying the need for more attentive and accessible healthcare for individuals born outside the US. Overall, more opportunities for free healthcare are essential to remedy the racial and economic disparities in health in the US. In addition to the need for increased opportunities to free healthcare is the need for increased health education to communities that do not have the same access to medical information and treatment. The need for more accessible health education reaches far beyond hepatitis B and liver disease, given the multitude of other chronic diseases that also require constant screening early intervention for treatment to be successful. Chronic diseases such as cardiovascular disease, benign neoplasms, diabetes mellitus and others can be treatable if discovered at the right time -- this only highlights

the necessity of serving vulnerable communities of individuals who lack English fluency in the US who ultimately face the most fatal consequences of these chronic diseases.

Shortcomings and Future Studies

We want to acknowledge that while this study may deliver essential implications regarding the racial disparity in healthcare and disease in the US, there are significant shortcomings in its methodology. Due to the high proportion of Asian immigrants in the Southern California area, the study intentionally puts an emphasis on remedying the health disparity in individuals of Asian descent, but there are countless other communities in the country whose health continues to be neglected. For example, rates of hepatitis C infection and colorectal cancer are significantly higher in Black Americans than the national average, with evidence that American individuals of African descent are not only 20% more likely to have colorectal cancer than other racial groups, but also 40% more likely to die from it (Cancer.org, 2020). This alarming disparity is only one of many in the US, yet racial disparities in health are not discussed nearly enough in medical education and provider training. Black Americans not only face a higher genetic risk for particular cancers, but they also face significant discrimination and bias in the healthcare field, in addition to obstacles to optimal healthcare due to factors such as lower paying jobs, minimal health insurance coverage, lack of access to healthy and affordable foods, and low-quality education and housing. While the methodology of this study does not address the significant health disparities faced by Black Americans, we hope that the results of the survey and longitudinal study may serve as a call to action to alter the current healthcare system so that it serves the entire country, and not just those with financial and racial privilege.

CONCLUSION

Great strides have been made in the past decades in the treatment options for hepatitis B infection -- while paths toward the complete eradication of the virus have not yet been found, there are several commonly used treatments that, if used early enough in disease progression, can drastically minimize the risk of developing liver cirrhosis or hepatocellular carcinoma. More research has yet to be conducted to obtain a better understanding of the role of HBV genotypes and subgenotypes in developing more targeted treatment for specific racial groups. Despite our current ability to control disease progression with existing HBV treatments, the continuing research to improve the efficacy of existing HBV treatment is moot unless more efforts are directed toward ensuring that individuals in high-risk communities are accurately diagnosed and given access to affordable treatment. We hope that more health fairs similar to the one proposed become a more common practice, but ultimately, our goal is to find a path toward ensuring that all individuals in the US that are most at risk for having chronic hepatitis B infection are adequately screened and treated before their liver disease progresses to a stage past treatment.

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