



January 2, 2019

To the U.S. Preventive Services Task Force:

Re: Comments on Draft Research Plan for Hepatitis B Virus Infection: Screening in Nonpregnant Adolescents and Adults

On behalf of the Hep B United coalition, we appreciate the opportunity to comment on the *Draft Research Plan for Hepatitis B Virus Infection: Screening in Nonpregnant Adolescents and Adults*. It is currently estimated that about 2.2 million people are living with hepatitis B (HBV) infection in the United States, yet between 65-75% of those are undiagnosed. While we support the standing grade of “B” for HBV screening, especially for its critical role in removing barriers and increasing access to screening and treatment, we believe in order to achieve HBV elimination goals, we must move beyond targeted to universal screening in order to close the major gaps in identifying all undiagnosed cases.

We offer the following comments and recommended evidence for review related to the Proposed Analytic Framework, the Proposed Key Questions to Be Systematically Reviewed, the Proposed Contextual Questions, and the Proposed Research Approach.

Proposed Analytic Framework

In order to achieve the 2030 viral hepatitis elimination goals established by the World Health Organization and supported by the National Academies of Sciences, Engineering, and Medicine recommendations, we believe the proposed analytic framework should take into consideration universal screening of all asymptomatic non-pregnant adolescents and adults (see comments on KQ3).

Additionally, regarding the framework, we believe that a specific outcome of HBV testing is currently omitted. As it stands, the framework includes “Chronic HBV Infection,” “Evidence of HBV Immunity,” and “No Evidence of HBV Immunity.” We believe this framework should also include two other important outcomes – for those who have evidence of past HBV infection and those who have possible occult HBV infection. When screening for HBV as per current CDC guidelines, the recommended tests are HBsAg, Anti-HBs, and Anti-HBc. Those who have recovered from a past HBV infection will test positive for both Anti-HBs and Anti-HBc – and it is important that these individuals are counselled to be aware of their risk for reactivation with immune suppression (and associated with initiation of Direct Acting Antiviral treatment for hepatitis C). Additionally, a subset of the population will test positive for Anti-HBc alone (isolated Anti-HBc). These individuals need further testing to assess their current HBV infection status, as they could be chronically infected. The role of Anti-HBc in HBV screening is critical – an overall important key question to include in the review is what is the value of screening for hepatitis B core antibody? Current anti-HBc tests have a false positive rate in low risk individuals of 2/1000. We believe this is a critical gap in the analytic framework. Individuals whose serologic test is positive for HBV

core antibody do not require vaccination, are at risk for reactivation and thus, require appropriate education and counseling.

In the intervention portion of the analytic framework, an important intervention is not included: medical management (regular monitoring without antiviral treatment) of people with chronic HBV infection. A proportion of chronically HBV infected individuals do not have active liver disease when they are diagnosed, therefore, they do not need antiviral medication unless there is a positive family history for liver cancer. Instead, it is recommended that they receive regular monitoring, which includes semi-annual visits with a knowledgeable provider for a physical examination, blood tests to detect HBV replication status, progressive liver disease and/or liver cancer, and ultrasound imaging of the liver, as well as a consideration for elastography. It is important to include this in the analytic framework, as regular monitoring, even in the absence of antiviral treatment, leads to early detection of advancing liver disease, as well as cirrhosis and liver cancer, and can improve patient outcomes. In addition, education and behavior change counseling are important to include for all chronically infected individuals, but the importance of culturally and linguistically appropriate health education cannot be overlooked, as well as testing family members and intimate contacts. Culturally appropriate services, especially for a disease that disproportionately impacts Asian Americans, Pacific Islanders, Eastern European, Central Asian, and those of African origin, can improve a patient's understanding of hepatitis B transmission, prevention and disease progression, which can lead to better health management, reduced transmission to others, reduced stigma about the disease, and better outcomes.

Proposed Key Questions to Be Systematically Reviewed

KQ1: What are the benefits of screening for hepatitis B virus (HBV) infection in asymptomatic, nonpregnant adolescents and adults on morbidity, mortality, and disease transmission?

There are significant benefits to screening for HBV infection in asymptomatic, non-pregnant adolescents and adults on the reduction of morbidity, mortality, and disease transmission. We are at an important juncture in addressing HBV infection in the U.S. and globally, and the World Health Organization (WHO) and the National Academies of Sciences, Engineering and Medicine have officially called for elimination of hepatitis B and hepatitis C by 2030. Screening of asymptomatic, nonpregnant adolescents and adults is critical to elimination, and continues to be a major challenge in reducing HBV-related illness and death, in the U.S. and worldwide. We must significantly improve HBV screening in order to improve the rate of infected individuals who are identified – which in the U.S. remains low, at only 25-30%.

We ask that the Task Force review publications that highlight the current low screening rates, current challenges and failures associated with risk-based HBV screening, the underestimation of chronic hepatitis B in the U.S., as well as the health and outcome-related disparities associated with hepatitis B. A number of studies have focused on the cost effectiveness of HBV screening. These studies indicate that screening is cost effective in populations where HBV prevalence is as low as 0.3%. These studies should be included in the research plan, and cost-effectiveness should be included in the analytic framework.

Global Hepatitis Report 2017. Geneva: World Health Organization; 2017. License: CC BY-NC-SA 3.0 IGO.

National Academies of Sciences, Engineering, and Medicine. 2016. *Eliminating the public health problem of hepatitis B and C in the United States: Phase one report*. Washington, DC: The National Academies Press.

National Academies of Sciences, Engineering, and Medicine. 2016. *Eliminating the public health problem of hepatitis B and C in the United States: Phase two report*. Washington, DC: The National Academies Press.

National Academies of Sciences, Engineering, and Medicine. 2017. *A National Strategy for the Elimination of Hepatitis B and C: Phase Two Report*. Washington, DC: The National Academies Press.

Toy, Hutton, So. (2018). Population Health and Economic Impacts Of Reaching Chronic Hepatitis B Diagnosis And Treatment Targets In The US. *Health Affairs*; 37(7):1033-1040.

Artz, Paul. (2018). Screening for Hepatitis B Virus Infection: Are We Asking the Right Questions? *J Clin Oncol*; 36(10):935-936.

Nayagam, Thursz, Sicuri, Conteh, Wiktor, Low-Ber, Hallett. (2018). Requirements for global elimination of hepatitis B: a modelling study. *Lancet Inf Dis*; 16(12):1399-1408.

Lancet Global Health. (2016). The hidden threat of hepatitis B. 4(8): e502.

Cohen, C., Evans, A. A., London, W. T., Block, J., Conti, M., & Block, T. (2008). Underestimation of chronic hepatitis B virus infection in the United States of America. *J Viral Hepat*, 15(1), 12-13. doi: JVH888 [pii] 10.1111/j.1365-2893.2007.00888.x

Cohen C, H. S., McMahon BJ, Block JM, Brosgart CL, Gish RG, London WT, Block TM. (2011). Is chronic hepatitis B being undertreated in the United States? *Journal of Viral Hepatitis*, 18, 377-383.

Gish, R. G., & Gadano, A. C. (2006). Chronic hepatitis B: current epidemiology in the Americas and implications for management. *J Viral Hepat*, 13(12), 787-798. doi: JVH787 [pii] 10.1111/j.1365-2893.2006.00787.x

Kowdley, K. V., Wang, C. C., Welch, S., Roberts, H., & Brosgart, C. L. (2012). Prevalence of chronic hepatitis B among foreign-born persons living in the United States by country of origin. *Hepatology*, 56(2), 422-433. doi: 10.1002/hep.24804

Hutton DW, Tan D, So SK, Brandeau ML. Cost-effectiveness of screening and vaccinating Asian and Pacific Islander adults for hepatitis B. *Ann Intern Med* 2007; 147(7): 460–469.

Spackman DE, Veenstra DL. A costeffectiveness analysis of currently approved treatments for HBeAgpositive chronic hepatitis B. *Pharmacoeconomics* 2008; 26(11): 937–949.

Kanwal F, Gralnek IM, Martin P, Dulai GS, Farid M, Spiegel BMR. Treatment alternatives for chronic hepatitis B virus infection: a cost effectiveness analysis. *Ann Intern Med* 2005; 142(10): 821–831.

Veldhuijzen IK, Toy M, Hahne SKM et al. Screening and early treatment of migrants for chronic hepatitis B virus infection is cost-effective. *Gastroenterology* 2006; 138: 522–530.

Shepherd J, Jones J, Takeda A, Davidson P, Price A. Adefovir dipivoxil and pegylated interferon alfa-2a for the treatment of chronic hepatitis B: a systematic review and economic evaluation. *Health Technol Assess* 2006;10(28): iii–iv, xi–xiv, 1–183.

Brooks EA, Lacey LF, Payne SL, Miller DW. Economic evaluation of lamivudine compared with interferon-alpha in the treatment of chronic hepatitis B in the United States. *Am J Manag Care* 2001; 7(7):677–682.

Wong JB, Koff RS, Tine F et al. Costeffectiveness of interferon-alpha 2b treatment for hepatitis B e antigenpositive chronic hepatitis B. *Ann Intern Med* 1995; 122: 664–675.

Armbruster B, Brandeau ML. Costeffective control of chronic viral diseases: finding the optimal level of screening and contact tracing. *Math Biosci* 2010; 224: 35–42.

Post SE, Sodhi NK, Peng CH, Wan K, Pollack HJ. A simulation shows that early treatment of chronic hepatitis B infection can cut deaths and be cost-effective. *Health Aff (Millwood)*. 2011 Feb;30(2):340-8.

Toy M, Onder FO, Idilman R, Kabacam G, Richardus JH, Bozdayi M, Akdogan M, Kuloglu Z, Kansu A, Schalm S, Yurdaydin C. The cost-effectiveness of treating chronic hepatitis B patients in a median endemic and middle-income country. *Eur J Health Econ*. 2012 Oct;13(5):663-76. doi: 10.1007/s10198-012-0413-8. Epub 2012 Jul 20.

KQ2: What are the harms of screening for HBV infection (e.g. labeling, anxiety, and harms of confirmatory tests, including biopsy)?

It is risk-based screening strategies themselves that increase potential labeling, anxiety and stigma of individuals and communities. It is important to take into account that a targeted screening strategy of those labeled as high risk for HBV infection, which includes foreign-born individuals who face multiple barriers to health care access, exacerbates stigma and discrimination for already marginalized communities. Moving to universal screening of all asymptomatic nonpregnant adolescents and adults is the best way to reduce labeling associated with infectious diseases, as has been demonstrated by population-based screening for HIV. Thus, this question should include a search of how labeling has been decreased by moving to a population-based screening regimen for HIV. In addition, this question should include research on how to reduce potential negative effects of risk-based screening. Research highlights the vital role of culturally and linguistically appropriate health education in reducing potential harms. This includes reducing stigma and fear of discrimination, as well as minimizing fear of labeling. In terms of potential liver biopsy harms, it is important to remember that only a very small minority of chronically infected individuals will receive a biopsy (<1%). Also, serious adverse effects are seen in less than 1 in 1000 biopsy procedures performed. Finally, it is important to remember to the potentially devastating outcomes of living with undiagnosed HBV.

KQ3: What is the yield (number of new diagnoses per tests performed) and sensitivity of alternative HBV screening strategies (e.g. universal vs. targeted screening, or screening strategies based on alternative risk factors)?

A key question to consider is how likely are we to achieve the 2030 hepatitis B elimination goals with a targeted screening strategy compared to a universal screening strategy? Targeted HBV screening strategies are being implemented primarily through community-based settings by smaller and often under-resourced organizations and clinics. While this approach reaches high-risk individuals, it has been challenging to reach a majority of high-risk populations. Targeted screening is difficult to implement in hospitals and health care systems where there is little provider awareness and incentive. Additionally, electronic clinical decision support technology which can assist providers in identifying high-risk patients is extremely challenging to integrate. For example, electronic health records currently do not capture country of birth which is one of the major factors for those at high risk for HBV infection.

We must point out that there has been no indication that HBV screening rates have increased since the CDC risk-based screening guidelines were published in 2008 and the USPSTF risk-based guidelines were published in 2014. Risk-based guidelines that are based on country of birth and stigmatizing risk behaviors are difficult to implement and face so many challenges that they often cannot be implemented within health care systems in the U.S. Risk-based testing for HBV puts great burden on clinicians, who are typically unaware of the risks, are unsure of who to test, and too overburdened in primary care settings to learn the intricacies of who to test. There are not many incentives for providers to change their clinical patterns. And instituting electronic Clinical Decision Support faces its own challenges – current risk-based HBV screening has a complexity of risk determination – institutions have difficulty implementing electronic data collection and flags based on country of birth. Electronic health records used by most health systems do not include a field for country of birth. Nor does it include information about parental infection or parental HBV risk. It is even difficult to identify behavior risks – as patients are often hesitant to share sexual and drug use behaviors with clinicians. All of this makes it complicated for clinicians to figure out who is at risk, making risk-based screening guidelines difficult to implement.

There have been a few studies published on implementing risk-based HBV screening at hospitals and within health systems, and these are important to include in the research strategy. They showed effectiveness to varying degrees, but many implementation challenges. Furthermore, recently reported state HBV prevalence data has revealed significant gaps in the risk-based screening strategy and have missed other high-risk groups. For the first time since 2006, the number of reported acute HBV cases across the country is rising and increased by 20.7% in 2015 alone tied to the current opioid crisis. In Maine, the rate of HBV infection increased by 489% from 2015 to 2016. Between 2009 and 2013, new cases of HBV increased by 114% in Kentucky, Tennessee, and West Virginia. From 2014-2016, new cases of HBV increased by 56% in North Carolina, and Southeastern Massachusetts had a 78% increase in new HBV cases in 2017. There are clearly gaps in targeted screening approaches; with a universal screening strategy, we will ensure all health care and other settings for public health interventions have the incentive and resources to identify infected individuals, and vaccinated those adults who are vulnerable to infection.

Bouton L. Massachusetts Dept. of Public Health, Bureau of Infectious Disease & Laboratory Sciences. Acute Hepatitis B Cluster- Bristol County, MA. Presentation, February 8, 2018.

Chak et al. (2018). Electronic Medical Alerts Increase Screening for Chronic Hepatitis B: A Randomized, Double-Blind, Controlled Trial. *Cancer Epidemiol Biomarkers Prev.*; 27(11):1352-1357.

Waldorf et al. (2014). Assessing adherence to accepted national guidelines for immigrant and refugee screening and vaccines in an urban primary care practice: a retrospective chart review. *J Immigr Minor Health.*; 16(5):839-45.

Chak et al. (2016). Improving Healthcare Systems to Reduce Healthcare Disparities in Viral Hepatitis. *Dig Dis Sci.*; 61(10):2776-2783.

Harris AM, Iqbal K, Schillie S, et al. Increases in Acute Hepatitis B Virus Infections — Kentucky, Tennessee, and West Virginia, 2006–2013. *MMWR Morb Mortal Wkly Rep* 2016;65:47–50. <http://dx.doi.org/10.15585/mmwr.mm6503a2>.

Hepatitis B, C on the Rise in N.C.; Health Officials Encourage Precautions, Testing.
<https://www.ncdhhs.gov/news/press-releases/hepatitis-b-c-rise-nc-health-officials-encourageprecautions-testing>, May 2017.

Maine Center for Disease Control and Prevention. Infectious Disease Epidemiology Report: Hepatitis B in Maine, 2016. http://www.maine.gov/dhhs/mecdc/infectiousdisease/epi/hepatitis/documents/2016-HBV_SurvReport.pdf.

Surveillance for Viral Hepatitis – United States, 2015.
<https://www.cdc.gov/hepatitis/statistics/2015surveillance/commentary.htm>.

Viral Hepatitis and Young Persons Who Inject Drugs.
<https://www.cdc.gov/hepatitis/featuredtopics/youngpwid.htm>.

World Health Organization. Global Hepatitis Report 2017. Geneva: WHO; 2017.
<http://www.who.int/hepatitis/publications/global-hepatitis-report2017/en>.

KQ4: How effective is antiviral treatment at improving intermediate outcomes in nonpregnant adolescents and adults with chronic HBV infection, including virologic or histologic improvement, clearance of hepatitis B eantigen (HBeAg) (as indicated by loss of HBeAg or acquisition of antibody to HBeAg [antiHBe]), or clearance of hepatitis B surface antigen (HBsAg) (as indicated by loss of HBsAg or acquisition of hepatitis B surface antibody [antiHBs])?*

There is good evidence that treatment of moderate fibrosis with antivirals is effective at reducing fibrosis, or even reversing fibrosis and liver cirrhosis, based on randomized trials done to support U.S. FDA approvals of current Direct Acting Antivirals (DAAs) licensure.

However, although the trends are promising, it is less clear, with much more limited information available, how much benefit of long term treatment there is in reducing mortality in those for whom DAAs are currently recommended by current guidelines, and even less information on the benefit in people with chronic HBV who fall outside the guidelines (HBsAg+, low DNA) but are clearly, relative to uninfected individuals at greater risk of liver disease. For these individuals, there is a lack of data on prevention of cirrhosis, reduction in HCC or liver-related death available. This is due to a lack of long-term trials with a large enough sample size and long enough period of follow-up.

In addition, studies have shown that treatment of cirrhosis is justified due to successes seen with antiviral therapies. We recommend including these studies, including presentations at AASLD and EASL, in the research protocol.

Finally, in looking at intermediate outcomes, it is important to look not only at virologic and histologic improvement, but also at other health indicators. This would include assessing quality of life as an intermediate outcome in those who undergo antiviral treatment, and there is a small but very respectable body of work that has looked at this.

Marcellin et al. (2013). Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. *The Lancet*;381(9865): 468-475.

Wong et al. (2013). Entecavir treatment reduces hepatic events and deaths in chronic hepatitis B patients with liver cirrhosis. *Hepatology* 58, no. 5 (2013): 1537-1547.

Chang et al. (2006). A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. *New England Journal of Medicine*; 354(10): 1001-1010.

Chang et al. (2010). Long-term entecavir therapy results in the reversal of fibrosis/cirrhosis and continued histological improvement in patients with chronic hepatitis B. *Hepatology*; 52(3):886-893.

KQ5: How effective is antiviral treatment at improving health outcomes in nonpregnant adolescents and adults with chronic HBV infection?*

Currently FDA-approved antiviral treatments for HBV can reduce the five-to ten-year risk of liver cancer in older patients, who have a lifetime risk of ~25% if untreated (40% in males, lower in females) (Block, 2018). However, although these inhibitors suppress viral replication and slow down disease progression, they do not cure HBV (Gordon et al., 2014; Lok et al., 2016; Papatheodoridis et al 2015), and viremia and disease progression typically rebound once therapy is stopped (Terrault et al., 2016). Researchers are making progress towards the development of curative therapies (Alter et al, 2018; Block et al, 2018) and are optimistic that a more effective, shorter term therapy (or combination of therapies) will be developed – many of these therapies are nearing or currently in clinical trial. We are at a critical time to improve identification of infected individuals so that when these new therapies become available, all infected individuals can be given the opportunity to benefit from them.

Block et al. (2018). Research priorities for the discovery of a cure for chronic hepatitis B: Report of a workshop. *Antiviral Res*; 150:93-100.

Alter et al. (2018). A research agenda for curing chronic hepatitis B virus infection. *Hepatology*; 67(3):1127-1131.

Gordon, S.C., Lamerato, L.E., Rupp, L.B., et al., 2014. Antiviral therapy for chronic hepatitis B virus infection and development of hepatocellular carcinoma in a US population. *Clin. Gastroenterol. Hepatol.* 12, 885–893.

Lok, A.S., McMahon, B.J., Brown Jr., R.S., et al., 2016. Antiviral therapy for chronic hepatitis B viral infection in adults: a systematic review and meta-analysis. *Hepatology* 63 (1), 284–306.

Papatheodoridis, G.V., Chan, H.L.-Y., Hansen, B.E., et al., 2015. Risk of hepatocellular carcinoma in chronic hepatitis B: assessment and modification with current antiviral therapy. *J. Hepatol.* 62, 956–967.

Terrault, N.A., Bzowej, N.H., Chang, K.M., et al., 2016. AASLD guidelines for treatment of chronic hepatitis B. *Hepatology* 63, 261–283.

KQ6: What are the harms associated with antiviral treatment of chronic HBV infection in nonpregnant adolescents and adults?*

We have no comments on KQ6.

KQ7: What is the association between improvements in intermediate outcomes as a result of antiviral treatment of chronic HBV infection and reduction in risk of HBV related adverse health outcomes?

We have no comments on KQ7.

Proposed Contextual Questions

1. What are the effects of different risk- or prevalence-based methods for screening for HBV infection in modeling studies?

There have been a number of modeling studies and studies testing different strategies for risk-based testing, in the U.S. and globally. Below are some published studies, we encourage inclusion of these, and others, in the research plan. Studies in the U.S. have focused mostly on risk-based testing in community settings, and many of these studies have seen successes in improving HBV diagnosis in small community settings. However, it is important to note that these types of community-based testing programs are often not sustainable long-term, and put a burden on under-resourced community-based organizations to lead HBV screening efforts in the U.S. A shift to universal testing would help to remove some of this burden and create a more sustainable system where HBV testing could take place primarily within the health system. Community-based screening can and should play a very important role, but should not be expected to take up the burden of identifying HBV infections in the U.S., especially with current challenges regarding linkage to sustainable care. There are very few studies that model universal HBV testing outside of low- and middle-income countries.

Nayagam, Thursz, Sicuri, Conteh, Wiktor, Low-Beer, Hallett. (2018). Requirements for global elimination of hepatitis B: a modelling study. *Lancet Inf Dis*; 16(12):1399-1408.

Huyn et al. (2016). Chronic hepatitis B in Korean Americans: decreased prevalence and poor linkage to care. [BMC Infect Dis](#);16(1):415.

Ferrer et al. (2018). Hepatitis B Prevalence and Risk Factors in a Foreign-Born Asian and Pacific Islander Population at a Community Health Center in Hawai'i. [Asia Pac J Public Health](#);30(8):727-736.

Tang et al. (2018). Disparities in Hepatitis B Virus Infection and Immunity Among New York City Asian American Patients, 1997 to 2017. [Am J Public Health](#);108(S4):S327-S335.

Chandrasekar et al. (2015). A comparison of effectiveness of hepatitis B screening and linkage to care among foreign-born populations in clinical and nonclinical settings. [J Multidiscip Healthc](#);8:1-9.

Bastani et al. (2015). Cluster-Randomized Trial to Increase Hepatitis B Testing among Koreans in Los Angeles. [Cancer Epidemiol Biomarkers Prev](#);24(9):1341-9.

Tran et al. (2015) Hepatitis B Virus Screening Patterns amongst Physicians in Hawaii: Changes in a Decade. *Open Journal of Gastroenterology*, 5, 139-145. <http://dx.doi.org/10.4236/ojgas.2015.510023>

Nguyen and Lin. (2015). Hepatitis B Screening in Asian and Pacific Islanders: New Guidelines, Old Barriers. [J Immigr Minor Health](#). ;17(5):1585-7.

Robotin and George. (2014). Community-based hepatitis B screening: what works? [Hepatol Int](#). ;8(4):478-92.

Chang et al. (2017). Predictors and Barriers to Hepatitis B Screening in a Midwest Suburban Asian Population. [J Community Health](#);42(3):533-543.

Walters and Sullivan. (2016). Early Identification and Linkage to Care of Foreign-Born People with Chronic Hepatitis B Virus Infection, Multnomah County, Oregon, 2012-2014. *Public Health Rep*.;131 Suppl 2:105-11.

Ramirez et al. (2016). Early Identification and Linkage to Care for People with Chronic HBV and HCV Infection: The HepTLC Initiative. *Public Health Rep.*;131 Suppl 2:5-11.

Beckett et al. (2014). Early identification and linkage to care of persons with chronic hepatitis B virus infection--three U.S. sites, 2012-2014. *MMWR Morb Mortal Wkly Rep.*;63(18):399-401.

Djoufack et al. (2017). Hepatitis B virus outreach to immigrant population in Greater Boston Area: Key to improving hepatitis B knowledge. [World J Gastroenterol.](#);23(42):7626-7634.

Harris et al. (2018). Community-Based Services to Improve Testing and Linkage to Care Among Non-U.S.-Born Persons with Chronic Hepatitis B Virus Infection - Three U.S. Programs, October 2014-September 2017. [MMWR Morb Mortal Wkly Rep.](#);19):541-546.

2. What is the accuracy of tools for identifying persons with chronic HBV infection?

Much data have been published, and the current FDA-approved screening tests for HBV are highly sensitive and specific. We are hopeful that in the future, there will be simpler, accurate, point-of-care screening tests made available in the U.S., which could help to improve HBV screening rates.

3. In persons with serologic evidence of HBV infection (positive for antibody to hepatitis B core antigen or positive for HBsAG), what is the likelihood of reactivation following exposure to immunosuppressant therapy, and what is the effectiveness of interventions to improve clinical outcomes associated with reactivation?

This is an important issue, and another reason why we need to identify chronically infected individuals. There is much published data on this topic, and we are glad that this is included in the research strategy. One new article to mention for inclusion in this research area: Artz, Paul. (2018). Screening for Hepatitis B Virus Infection: Are We Asking the Right Questions? *J Clin Oncol*; 36(10):935-936.

Proposed Research Approach

- For KQ2, inclusion of strategies and successes of interventions targeted at reducing potential harms of HBV screening is important.
- For KQ3, there is a lack of published data on the successes and challenges associated with implementing risk-based HBV screening at the health system level. And there are no published studies, to the best of our knowledge, on cost-effectiveness of universal HBV screening in the U.S. It is important to search for such data, but also to include a search on implementation of other risk-based screening strategies, to see if we can learn from other similar attempts to implement risk-based screening based primarily on country of birth (and behavioral risks). It is also important to research implementation of universal testing for other diseases where risk-based testing was not working (for example, HIV). It is also important to include studies that assessed provider knowledge of HBV and screening behaviors, and to collect qualitative data from providers, hospitals, and health systems on their experiences, successes and challenges implementing risk-based screening for HBV.
- For KQ5, inclusion of quality of life as an intermediate outcome is important.

Thank you for this opportunity to comment on the Draft Research Plan. Hep B United is a national coalition of over 40 organizations and local coalitions dedicated to reducing the health disparities associated with hepatitis B by increasing awareness, screening, vaccination, and linkage to care for high-risk communities across the United States.

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