August 9, 2017

Re: Comments on Draft Research Plan for Hepatitis B Virus Infection in Pregnant Women: Screening

To the U.S. Preventive Services Task Force:

On behalf of the *Hep B United* national coalition, we appreciate the opportunity to provide input on *the Draft Research Plan for Hepatitis B Virus Infection in Pregnant Women: Screening*. In the United States, there has been significant progress made towards the reduction of mother-to-child transmission of hepatitis B virus (HBV) infection due to effective screening and vaccination guidelines and established national prevention programs. As the Task Force begins its process to review the evidence and update its recommendation statement, we strongly believe the current evidence will reaffirm the standing "A" grade, recommending screening for HBV infection in pregnant women at their first prenatal visit.

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

We support the draft proposed analytic framework depicting the four key questions to be addressed in the systematic review and the process illustrating that universal screening during pregnancy will result in improved health outcomes as they relate to vertical transmission of HBV infection.

We recommend the analysis and review of evidence include review of case management and follow-up care of hepatitis B surface antigen positive (HBsAg+) women in order to effectively reduce vertical transmission of HBV infection and consider evidence outlined below in our comments.

Proposed Key Questions to Be Systematically Reviewed

1. **What are the population benefits of universal screening programs for hepatitis B virus infection in pregnant women?**

In the United States, we have made good progress towards reducing vertical transmission of HBV infection due to effective and successful implementation of guidelines and recommendations from the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) and the American Congress of Obstetricians and

Gynecologists (ACOG) that all pregnant women in the U.S. be screened for HBV infection in order to prevent mother-to-child transmission (1, 2). We know that through universal screening programs for HBV in pregnant women, vertical transmission can be prevented 85 to 95 percent of the time, protecting babies from lifelong infection and premature death from HBV-related complications (3). In fact, the 2017 National Academies of Sciences, Engineering, and Medicine (NASEM) Phase Two report found that the goal of eliminating perinatal transmission of HBV in the U.S. is highly feasible, but we must close certain critical gaps in the management of HBV-infected pregnant women and provide consistent birth dose of the HBV vaccine (4). Through continued and consistent implementation of universal screening programs for pregnant women and HBV vaccination programs for children (and adults), it is possible to end transmission of HBV in the United States.

(1) CDC (Centers for Disease Control and Prevention). 1988. Recommendations of the Immunization Practices Advisory Committee prevention of perinatal transmission of hepatitis B virus: Prenatal screening of all pregnant women for hepatitis B surface antigen. *Morbidity and Mortality Weekly Report* 37(22):341-346, 351.

(2) CDC. (1991). Hepatitis B virus: a comprehensive strategy for eliminating transmission in the United States through universal childhood vaccination. Recommendations of the Immunization Practices Advisory Committee (ACIP). *MMWR Recomm Rep, 40*(RR-13), 1-25.

(3) Nelson, N. P., T. V. Murphy, and D. J. Jamieson. 2014. Prevention of perinatal hepatitis B virus transmission. Journal of the Pediatric Infectious Diseases Society 3(Suppl 1):S7-S12.

(4) 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.

2. What are the harms of universal screening programs for hepatitis B virus infection in pregnant women?

We do not find any harms in universal screening programs for HBV infection in pregnant women.

3. What is the effectiveness of case management programs to prevent vertical transmission among pregnant women who have hepatitis B virus infection?

Despite progress made in reducing vertical transmission of HBV infection, there are still an estimated 800 to 1,200 babies infected at birth each year in the United States (1). This can be prevented through effective case management programs, including universal screening of pregnant women for HBV infection, a timely HBV birth dose, and post-exposure prophylaxis. ACIP recommends infants born to infected mothers receive their first dose of the HBV vaccine (the “birth dose”) within 24 hours of birth and post-exposure prophylaxis or hepatitis B immune globulin (HBIG) within 12 hours of birth (2). Studies find that in the U.S., about 4 percent of

babies born to HBsAg+ pregnant women are infected each year (3). Addressing critical gaps in the prevention of vertical transmission require effective case management programs for pregnant women who have HBV infection.

Since 1990, the U.S. has prioritized and demonstrated progress in preventing vertical transmission through a national case management program --the *Perinatal Hepatitis B Prevention Program* (PHBPP), which aims to identify HBsAg+ pregnant women through universal screening programs, enroll them in a case management program, and connect with providers and hospitals to ensure their infants receive appropriate post-exposure prophylaxis and HBV vaccine at birth. The PHBPP program demonstrated success in preventing vertical transmission with 50 percent of over 20,000 births to HBsAg+ mothers enrolled in 2000, and new cases of chronic HBV infection declining from 6,000 cases in 1990 to about 1,000 cases in 2000 (4). Studies also show the PHBPP is both cost effective and cost saving (5).

Additionally, other community and clinic-based model case management programs have emerged to prevent vertical transmission and close critical gaps, including in federally qualified health centers. The *Hep B Moms* program at Charles B. Wang Community Health Center in New York City is a patient-centered medical home model that aims to prevent perinatal transmission of HBV. The program tracks mothers and infants through a disease registry and electronic medical records, emphasizing individual care and delivery coordination, patient-empowerment and self-management tools, and improving access through linguistic and cultural competency. Data analyzed since the establishment of the program showed zero cases of infected infants born to mothers in the program (6).

Case management programs such as those mentioned that take a team-centered approach integrated within the health care system to closely follow HBsAg+ pregnant women and their infants are effective in preventing vertical transmission. Other factors to take into account in reviewing of the evidence is lack of provider knowledge and resources. Studies show that providers need education and resources to appropriately screen, manage pregnant women with HBV infection, and report cases to health agencies (7, 8).

(1) Ko, S. C., L. Fan, E. A. Smith, N. Fenlon, A. K. Koneru, and T. V. Murphy. 2014. Perinatal hepatitis B virus infections in the United States, 2000-2009. Journal of the Pediatric Infectious Diseases Society 5(2):114-121.

(2) CDC. (1991). Hepatitis B virus: a comprehensive strategy for eliminating transmission in the United States through universal childhood vaccination. Recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR Recomm Rep, 40(RR-13), 1-25.

(3) Ko SC, Schillie SF, Walker T, Veselsky SL, Nelson NP, Lazaroff J, Crowley S, Dusek C, Loggins K, Onye K, Fenlon N, Murphy TV. Hepatitis B vaccine response among infants born to hepatitis B surface antigen-positive women. Vaccine. 2014 Apr 11;32(18):2127-33.

(4) Smith, E. A., L. Jacques-Carroll, T. Y. Walker, B. Sirotkin, and T. V. Murphy. 2012b. The national perinatal hepatitis B prevention program, 1994-2008. Pediatrics 129(4):609-616.

(5) Barbosa C1, Smith EA, Hoerger TJ, Fenlon N, Schillie SF, Bradley C, Murphy TV. Cost-effectiveness analysis of the national Perinatal Hepatitis B Prevention Program. Pediatrics. 2014 Feb;133(2):243-53.
(6) Weerasinghe I, Bannister N, Huang V, Cohen C, Caballero J, Wang S. 2014. The role of the patient-centered medical home in addressing perinatal hepatitis B transmission: the Charles B. Wang Community Health Center's Hep B Moms program. AAPI Nexus. 12(1-2): 140-160.
(7) Elizabeth J Yang, Chrissy M Cheung*, Samuel K S So, Ellen T Chang, Stephanie D Chao. Education and Counseling of Pregnant Patients with Chronic Hepatitis B: Perspectives from Obstetricians and Perinatal Nurses in Santa Clara County, California. Asian Pacific J Cancer Prev, 14 (3), 1707-1713.
(8) Lai, C. J., Nguyen, T. T., Hwang, J., Stewart, S. L., Kwan, A., & McPhee, S. J. (2007). Provider knowledge and practice regarding hepatitis B screening in Chinese-speaking patients. J Cancer Educ, 22(1), 37-41. doi: 10.1080/08858190701348083.

4. What are the harms of case management programs to prevent vertical transmission among pregnant women who have hepatitis B virus infection?

We do not find harms in case management programs to prevent vertical transmission among pregnant women who have HBV infection.

Proposed Contextual Questions

1. Do any subgroups of pregnant women benefit from repeat screening in the third trimester based on the presence of specific risk factors?

Certain subgroups of pregnant women who have a higher risk of acquiring HBV infection benefit from repeat screening in the third trimester. According to ACIP recommendations and the 2015 CDC and ACOG-endorsed screening and referral algorithm for HBV infection among pregnant women, additional screening in the third trimester is recommended for pregnant women who are at high risk including household or sexual contacts of HBsAg+ persons, injecting drug use, chronic liver disease, and international travel to regions with hepatitis B prevalence of 2 percent or greater, among other risk factors (1, 2).

(1) CDC (Centers for Disease Control and Prevention). 1988. Recommendations of the Immunization Practices Advisory Committee prevention of perinatal transmission of hepatitis B virus: Prenatal screening of all pregnant women for hepatitis B surface antigen. Morbidity and Mortality Weekly Report 37(22):341-346, 351.

(2) https://www.cdc.gov/hepatitis/hbv/pdfs/PrenatalHBsAgTesting.pdf Adapted from the Hepatitis B Foundation. Original publication: Apuzzio J, Block J, Cullison S, et al. Chronic

Hepatitis B in pregnancy: A workshop consensus statement on screening, evaluation, and management, part 2. The Female Patient. 2012; 37(5):30-34

2. What is the effectiveness of vaccination for the hepatitis B virus, immunoglobulin therapy, and antiviral treatment for preventing vertical transmission among pregnant women?

In addition to the effectiveness of the birth dose and completion of the HBV vaccination series and immunoglobulin therapy in preventing vertical transmission described above, antiviral treatment has also been shown to be effective for preventing transmission among pregnant women. In the 2017 NASEM report on a national strategy for the elimination of hepatitis B and C phase two report, the committee found evidence that prophylactic antiviral therapy in the third trimester can further reduce vertical transmission of HBV infection among highly viremic women; the committee recommended that HBsAg+ pregnant women have early prenatal HBV DNA and liver enzyme tests to evaluate whether antiviral therapy is appropriate to prevent transmission and for follow-up treatment of chronic HBV infection (1, 2).

(1) 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.

(2) Pan, C.Q., Z. Duan, E Dai, S. Zhang, G. Han, Y. Wang, H. Zhang, H. Zou, B. Zhu, W. Zhao, and H. Jiang. 2016. Tenofovir to prevent hepatitis B transmission in mothers with high viral load. New England Journal of Medicine 374(24): 2324-2334.

Proposed Research Approach

While we support the study characteristics and criteria that are proposed to be included in the review of evidence, we recommend the following additional criteria be included in order to comprehensively address effective prevention of vertical transmission of HBV infection.

- Viral load follow-up testing among screen-positive women with evaluation for treatment as appropriate (1, 2, 3, 4, 5, 6, 7)
- Settings where universal vaccination of newborns for hepatitis B virus infection is not recommended or practiced

(1) Song YM1, Sung J, Yang S, Choe YH, Chang YS, Park WS. Factors associated with immunoprophylaxis failure against vertical transmission of hepatitis B virus. Eur J Pediatr. 2007 Aug;166(8):813-8.

(2) Wan-Hsin Wen, Mei-Hwei Chang, Lu-Lu Zhao, Yen-Hsuan Ni, Hong-Yuan Hsu, Jia-Feng Wu, Pei-Jer Chen, Ding-Shinn Chen, Huey-Ling Chen. Mother-to-infant transmission of hepatitis B virus infection: Significance of maternal viral load and strategies for intervention. J Hepatol. 2013 Jul;59(1):24-30.

(3) Yin Y1, Wu L, Zhang J, Zhou J, Zhang P, Hou H. Identification of risk factors associated with

immunoprophylaxis failure to prevent the vertical transmission of hepatitis B virus. J Infect. 2013 May;66(5):447-52.

(4) Kubo A, Shlager L, Marks AR, Lakritz D, Beaumont C, Gabellini K, Corley DA. Prevention of vertical
transmission of hepatitis B: an observational study. Ann Intern Med. 2014 Jun 17;160(12):828-35.

(5) Schillie S1, Walker T2, Veselsky S3, Crowley S4, Dusek C5, Lazaroff J6, Morris SA7, Onye K8, Ko S3, Fenlon N9, Nelson NP3, Murphy TV3. Outcomes of infants born to women infected with hepatitis B. Pediatrics. 2015 May;135(5):e1141-7.

(6) Wiseman, E., M. A. Fraser, S. Holden, A. Glass, B. L. Kidson, L. G. Heron, M. W. Maley, A. Ayres, S. A. Locarnini, and M. T. Levy. 2009. Perinatal transmission of hepatitis B virus: An Australian experience. Medical Journal of Australia 190(9):489-492.

(7) http://freepdfhosting.com/19ef8e4f4e.pdf Terrault, N., Zhou, K., 2017. Management of hepatitis B in special populations. Best Practice and Research Clinical Gastroenterology.

Draft Research Plan

We recommend the research plan include criteria and study characteristics on follow-up care or case management of the HBsAg+ pregnant women postpartum in order to achieve the goal to prevent and eliminate perinatal transmission of hepatitis B in the U.S.

Studies show that only 19 percent of HBV-infected mothers met care guidelines one year after being diagnosed with HBV. Inadequate postpartum HBV care affects women of all races and ethnicities (1). Women who tend to be HBsAg+ during pregnancy tend to be from communities that face multiple barriers to access to health care including cultural and linguistic barriers (2, 3, 4). Furthermore, there is an overall decreased access among those likely to be infected as a pregnant woman (5). We need to find ways to increase access to HBsAg screening among pregnant women with decreased access and increased infection rates in order to close the multiple gaps that may exist towards effectively preventing vertical transmission of HBV infection (6, 7).

(1) Chang MS1, Tuomala R2, Rutherford AE3, Mutinga ML3, Andersson KL4, Burman BE5, Brown RS Jr6, Oken E7, Ukomadu C3. Postpartum care for mothers diagnosed with hepatitis B during pregnancy. Am J Obstet Gynecol. 2015 Mar;212(3):365.e1-7.

(2) CDC. (2006b). Screening for chronic hepatitis B among Asian/Pacific Islander populations--New York City, 2005. MMWR Morb Mortal Wkly Rep, 55(18), 505-509.

(3) Chao, S. D., Lee, P. V., Prapong, W., Su, J., & So, S. K. (2004). High prevalence of chronic hepatitis B (HBV) infection in adult Chinese Americans living in California. . Hepatology, 40(Suppl. 1)(717A).

(4) 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.

(5) Ku, L., & Matani, S. (2001). Left out: immigrants' access to health care and insurance. Health Aff (Millwood), 20(1), 247-256.

(6) IOM. (2010). Hepatitis and Liver Cancer: A National Strategy for the Prevention and Control of Hepatitis B and C. Washington, D.C.: Institute of Medicine.

(7) Erica S. Din, MPH,* Annemarie Wasley, SCD,* Lisa Jacques-Carroll, MSW,† Barry Sirotkin, MS,† and Susan Wang, MD, MPH*. Estimating the Number of Births to Hepatitis B Virus-infected Women in 22 States, 2006. The Pediatric Infectious Disease Journal • Volume 30, Number 7, July 2011.

Thank you for this opportunity to comment on the Draft Research Plan. Hep B United is a national coalition of over 30 national health organizations, community-based hepatitis B coalitions, and federal partners with a mission 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. Hep B United was co-founded and is co-chaired by the Hepatitis B Foundation and the Association of Asian Pacific Community Health Organizations (AAPCHO). The coalition works to reduce the impact of hepatitis B through prevention and education efforts, addressing perinatal transmission, improving screening and linkage to care, contributing to national surveillance data, and advocating on a national level.

Please do not hesitate to contact me at kate.moraras@hepb.org with any questions related to our comments.

Sincerely,

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