Maternal immunisation and neonatal infection of hepatitis A or B virus

I read with interest the review by Angela M Bengtson and colleagues[1] on maternal immunisation to improve the health of HIV-exposed infants. However, I have some concerns regarding maternal immunisation against hepatitis A virus (HAV) and hepatitis B virus (HBV) to prevent neonatal infection.

First, the stated epidemiology of hepatitis A and B in pregnant women is ambiguous. The incidence of hepatitis A in this Review is not the global data, and one cited article[2] clearly stated that less than 0·1% of pregnant women might suffer from hepatitis A. The higher prevalence of HBV infection in pregnant women is the consequence of infection that occurred before pregnancy rather than during pregnancy.

Second, the authors suggested immunisation of pregnant women to prevent primary HAV or HBV infection in women and subsequent mother-to-infant transmission. However, no study has shown that HIV-infected women have increased risk for HAV or HBV infection during pregnancy. As the authors mentioned, mother-to-infant transmission of HAV is rare. Maternal immunisation should have no benefit in preventing hepatitis A in children, who should receive the hepatitis A vaccine aged 1 year. For prevention of hepatitis B, universal vaccination of all infants has been implemented in 186 countries since 2016.[3] Infants of HBV-infected mothers should receive both hepatitis B immunoglobulin and the hepatitis B vaccine within 12 h of birth. Thus, to prevent mother-to-infant transmission of HBV, maternal prenatal screening for HBV, rather than maternal immunisation, is essential.

Third, the statement that "60% of women with acute HBV transmit the virus to their fetus" is misleading in two aspects. One is that 60% is a historical figure from a time when hepatitis B immunoglobulin and the hepatitis B vaccine were unavailable. With the availability of hepatitis B immunoglobulin and hepatitis B vaccine, the overall transmission in infants of HBV-infected mothers is 1–3%.[4,5] The protective efficacy is similar in infants of mothers co-infected with HIV and HBV.[6] The other is that "transmit the virus to their fetus" means in-utero transmission, which is incorrect. Mother-to-infant transmission of HBV dominantly occurs during and after the birth process, and spread in utero is very rare.[5]

In summary, the evidence to improve the health of HIV-exposed infants by maternal immunisation against hepatitis A or B is lacking. No guideline recommends maternal immunisation to prevent neonatal infection of hepatitis A and B in any country.

I declare no competing interests.

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1 Bengtson AM, Sanfilippo AM, Hughes BL, Savitz DA. Maternal immunisation to improve the health of HIV-exposed infants. *Lancet Infect Dis* 2018; published online Dec 7. https://doi.org/10.1016/S1473-3099(18)30545-0

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Authors' reply

We thank Yi-Hua Zhou for their comments on our Review on maternal immunisation to improve the health of HIV-exposed infants.[1] We agree that infant immunisation against hepatitis A and hepatitis B is likely to remain the primary strategy to reduce the global burden of hepatitis. However, pregnant women travelling to endemic areas, those who inject drugs, or (for hepatitis B) those who have multiple sex partners might be at increased risk of contracting hepatitis A or B.[2,3] For these reasons, we support the Advisory Committee on Immunization Practices (ACIP) recommendations that hepatitis A and B vaccination be considered in women at high risk for either infection, if the benefits outweigh potential risks.[2,3]

As noted in our Review and by Zhou, the global prevalence of hepatitis A during pregnancy is low and mother-to-child transmission is rare.[1] However, hepatitis A can lead to substantial morbidity in infected adults and to complications during pregnancy that might increase the risk of preterm birth.[2,4] More data are needed to determine whether hepatitis A vaccination is a safe and effective strategy to prevent morbidity during pregnancy and potentially improve pregnancy outcomes.

Hepatitis B remains an important public health issue, particularly in areas of high HIV burden. Approximately 10% of HIV-infected adults are co-infected with hepatitis B.[3] HIV-infected adults are considered by ACIP to be at high risk for contracting hepatitis B because of the shared routes of transmission for both viruses.[3] A higher prevalence of hepatitis B has been found among pregnant women with HIV than among pregnant women without HIV.[5] As Zhou points out, administering hepatitis B immunoglobulin and hepatitis B vaccine within 12 h after birth is effective at preventing mother-to-child transmission.

However, hepatitis B vaccination during pregnancy remains an important prevention strategy that should be considered for pregnant women with HIV or other risk factors for hepatitis B for both maternal and fetal health.

Available research on maternal hepatitis A and B immunisation is scarce and more data are needed to determine the effectiveness of maternal hepatitis A or B immunisation to prevent neonatal infection. In the meantime, we support ACIP's recommendations that maternal immunisation be considered for high-risk women as part of a comprehensive strategy that includes universal hepatitis B testing during pregnancy, treatment for infected women and prophylaxis for infants when indicated, and universal infant immunisation to reduce the global burden of viral hepatitis.

We declare no competing interests.

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Multiple sites PCR testing for enteroviruses in young febrile infants

Jérémy Lafolie and colleagues[1] reported a prospective multicentre study that evaluated the incidence of enterovirus infection in neonates and young infants with suspected sepsis or fever without a source and children with suspected meningitis. Cerebrospinal fluid (CSF) and blood enterovirus PCRs were done between June 1, 2015, and Oct 31, 2015, and between June 1, 2016, and Oct 31, 2016. They demonstrated the increased diagnostic utility of blood PCR testing in addition to CSF testing, because blood PCR identified 24% of additional enterovirus cases that would have otherwise been missed. In the accompanying Comment, Kevin Messacar and Samuel Dominguez[2] suggested the possibility of also testing samples obtained from non-sterile sites and focusing on periods of higher enterovirus circulation.

At Nationwide Children's Hospital (Columbus, OH, USA), enterovirus PCR testing has been routinely done using blood, CSF, and samples from superficial non-sterile sites (including mucosa, such as throat, eye, and rectum, and skin lesions) in all patients younger than 60 days hospitalised for fever or presumed sepsis, since 2013. We did a retrospective review of infants who had positive enterovirus PCR results from any site between January, 2015, and September, 2016. During this period, 783 patients were tested, and 144 (18%) had a positive enterovirus PCR result. Similar to Lafolie and colleagues' findings,[1] the numbers of enterovirus cases detected were larger between the months of June and September (figure). However, we also identified enterovirus from clinical samples in all but 3 months of our study period. Of the 144 positive enterovirus PCR results, 34 (24%) were identified between the months of October and May. The seasonality also varied between study years (figure). Enterovirus PCR was positive in 75 (52%) infants in CSF samples, 103 (72%) in blood samples, and 119 (83%) in samples from non-sterile sites. 51 (35%) infants had positive results from all three sites, another 51 infants had positive results from two sites, and 42 (29%) infants had enterovirus-positive results in only one of the three sites tested. Among those with only one positive site, the majority were positive in samples from non-sterile sites—27 (19%) of 144—followed by blood samples in 13 (9%), and in CSF samples in two (1%). Infants' median age was 24 days (IQR 15–35); all were full term with normal birthweight, and 50% were

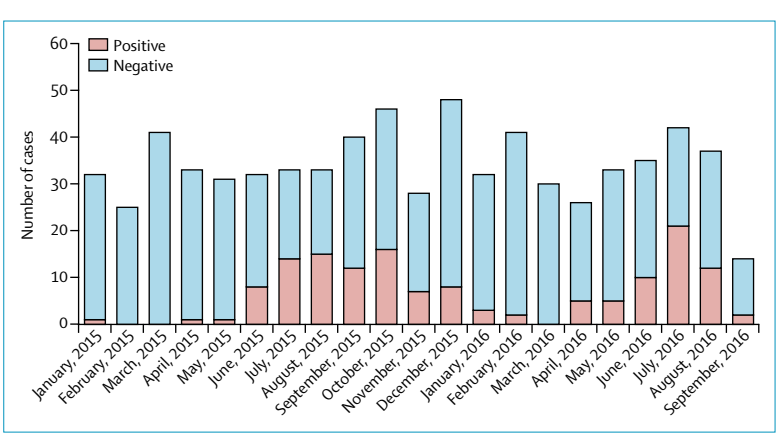

Figure: **Monthly distribution of positive enterovirus PCR from cerebrospinal fluid, blood, and non-sterile sites in infants younger than 60 days**