JHEP|Reports

Reply to: "Does currently recommended maternal antiviral prophylaxis against mother-to-child transmission of hepatitis B virus require enhancement?"

Enhancement of HBV PMTCT is required becausethe *status quo* fails to protect those at highest risk

To the Editor:

In response to our article,[1] Zhou and Zhao pose the question of whether interventions for prevention-of-mother-to-child-transmission (PMTCT) need to be enhanced.[2] As MTCT is now the major contributor to new cases of HBV infection, and approaching one million people die of this infection each year, the answer to this question is unequivocally yes – and with urgency.

We tackle specific points raised by Zhou and Zhao in turn.

First, they contend that '*most HBV-infected women at child-bearing age are in a immunotolerant phase and do not require antiviral therapy*'. This broad assertion is misleading. The eligibility of pregnant women either for treatment in their own right, or for prophylaxis to reduce transmission, depends on many factors including duration of infection, maternal age and HBV genotype. In most high prevalence settings, determination of a clinical 'phase' of infection for risk stratification is difficult or impossible because of lack of access to affordable laboratory testing and/or imaging.[3,4] It would be a dereliction of public health strategy simply to assume ineligibility for prophylactic interventions on the grounds that we are unable to deliver adequate assessment.

Secondly, they raise the point that '*MTCT of HBV can be efficiently prevented by combined immunoprophylaxis with hepatitis B immunoglobulin (HBIG) and hepatitis B vaccine in neonates*'. This statement is biologically true in most cases, although these interventions are not infallible (*e.g.*[5]). However, the major current weakness of this post-exposure strategy is that it is not possible to deliver in practice, as interventions are not available or cannot be implemented. The barriers are explored in our original paper,[1] and include high costs, lack of policy support and healthcare resources, inconsistent cold-chain, high frequency of births outside clinical settings, and poor education and awareness. These factors have the greatest impact in vulnerable populations with high prevalence of HBV infection.

Since our article was published, the Global Vaccine Alliance (Gavi) has announced that birth dose (BD) HBV vaccination will be formally incorporated into their strategy, which is an important stride forward. However, a clear action plan and funding is yet to be announced, and the latest data suggest that <15% of babies in the WHO Africa region receive timely BD vaccination.[6] Is it reasonable to accept that these populations cannot currently be reached, or should we use existing interventions that may be more accessible and affordable? We argue that while BD vaccination programmes scale-up, maternal antiviral prophylaxis plays a particularly important role.

Next, we are deeply concerned by the assertion that antiviral exposure during pregnancy is responsible for '*severe congenital malformation … fetal death, stillbirth, infant sudden death … and premature birth*'. There are no robust data to support these statements, and indeed the references Zhou and Zhao cite universally conclude that there is no significant signal for adverse maternal or foetal outcomes associated with antenatal antiviral HBV prophylaxis (based on comparison with untreated pregnancies or with background population rates), and no evidence to suggest risks associated with either choice or timing of therapeutic regimen. Indeed, there is evidence that earlier prophylaxis can be beneficial.[7] Case reports are clearly not relevant evidence of drug toxicity, as there is no possible way to determine cause and effect. In addition to being reassured by the findings of individual studies, we should also turn to several rigorous reviews and meta-analyses that assimilate international data for many hundreds of pregnancies, none of which find evidence of safety concerns (*e.g.*[7–11]). There are indeed challenges associated with more permissive use of perinatal prophylaxis, but these are primarily associated with implementation (access, infrastructure, monitoring, costs *etc*).

Finally, Zhou and Zhao claim that '*The safety data of maternal ART in HIV-infected pregnant women cannot be directly translated to maternal anti-HBV therapy*.' While these two viruses have different biological consequences, it would be an oversight not to use the wealth of safety data from the HIV field to help inform HBV interventions. Adverse foetal outcomes in the context of HIV infection are multifactorial, but there are no data to suggest a relationship between tenofovir and elevated risks (in fact, the converse is true). Meanwhile, the Antiretroviral Pregnancy Registry (ClinicalTrials.gov ID NCT00404989) has now collated prospective reports of >5,000 pregnancies exposed to TDF (of whom >3,500 were treated during the first trimester) and found no difference between this population and the US population overall. Reassuring safety data are also accumulating from studies of HIV pre-exposure prophylaxis in which the confounding factor of maternal HIV infection is removed.[12,13]

To conclude, we stand firmly by our original rationale in advocating wider use of antiviral prophylaxis for PMTCT, aiming to provide a safe and pragmatic approach to risk reduction in vulnerable populations in which there is very limited – or absent – access to risk-stratification and to other preventive interventions. Revised WHO guidelines are anticipated, but at present, different strategies may be needed for different settings, recognising that maternal risk stratification, BD-vaccine and HBIG are not widely available. There is an onus of responsibility on clinical and academic communities to promote evidence-based messaging and education, while guidelines and clinical practice must now seek to reduce gross health inequities by making HBV prophylaxis and treatment accessible, acceptable and affordable.

Received 14 July 2023; accepted 18 July 2023; ; available online 7 August 2023

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Financial support
PCM is funded by the Wellcome Trust (Grant ref 110110/Z/15/Z), UCLH NIHR Biomedical Research Centre, and receives core funding from the Francis Crick Institute, London.

Conflict of interest
CWS has received speaker fees from GILEAD Sciences and Abbott. CP received research funding and is a speaker for Gilead. PCM supervises a doctoral student with funding support from GSK. SH has received funding from Gilead for HCV Micro-elimination programs. HR has received research funding and speaker's honoraria from Gilead Sciences, AbbVie and Pfizer and is a board member of the CDA foundation. SW has received research funding from Gilead Sciences, and honoraria from Prime Inc, and is on the Board of Directors for the Hepatitis B Foundation, World Hepatitis Alliance, and serves in the patient advisory group and HBV special interest group for the AASLD. FR has received consulting fees from Sanofi Pasteur. GD has received consulting fees and speaker fees from Gilead Sciences, has participated on Data Safety Monitoring Board/Advisory Board for janssen, Glaxo Smith Kline, Arbutus, Aligos, Vir and has roles in the National Medical Research Council Singapore and the World Health Organisation Pediatric Working Group on Viral Hepatitis.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions
PCM drafted the initial response. All authors reviewed, edited and endorsed the final manuscript.

Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2023.100875.

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