REC's initial comments and questions

- *The application submitted to REC included an approval letter from CNEPS. The approval refers to the ethical and scientific evaluation of the protocol and also cites an annex entitled "Ethical opinion No. Ref. 06/CNES/INASA/2026 of 14 July 2026". It would assist REC's discussion of the project to see what specific ethical considerations were discussed by CNEPS. Please share with the REC any knowledge you may have regarding the specifics of these considerations and any discussions that may have taken place between you and CNEPS concerning the ethical evaluation of this project in a local context. In addition, please submit a copy of the above-mentioned annex to the REC, if possible.*

Response:

The application submitted to REC included the approval letter from CNEPS, the National Guinea-Bissau Ethics Committee dated July 14, 2026 and the letter from CNEPS to the Ministry of Health (dated July 27, 2026). These were attached as PDF files in Portuguese, with English translations of each document also provided to the REC.

The requested annex "Ethical opinion No. Ref. 06/CNES/INASA/2026 of 14 July 2026" refers to the approval letter from July 14 which was included in the submission to SDU REC. We have not received other letters nor did we have any formal or informal communication or deliberations with CNEPS, which is an institution that is independent from the Bandim Health Project.

- *A significant part of the research ethics considerations relating to the study is connected to the fact that it is being conducted in Guinea-Bissau. REC requests your comments on the possibility of investigating the study's hypotheses regarding the non-specific effects of the HBV0 vaccine in a alternative research design, for instance a comparison with historical data.*

Response:

HBV0 has not previously formed part of the national vaccination schedule in Guinea-Bissau, and we are not aware of systematic historical data on newborns receiving hepatitis B vaccine at birth.

A historical comparison would therefore have to compare infants born before program introduction with infants born after introduction. Such a before-and-after comparison could not provide a sufficiently valid estimate of the causal effect of HBV0 on overall health. Generally speaking, observational studies are prone to biases as receipt and timing of neonatal vaccination are related to circumstances and place of birth, neonatal health, vaccine availability, access to health services and socioeconomic factors. A historical comparison would additionally be affected by factors such as secular changes in neonatal mortality and infectious morbidity; healthcare access and hospital admission practices; infection pressure and seasonality; and implementation of other maternal and neonatal interventions. Historical data thus cannot replace the randomised comparison for estimating the overall health effect of adding HBV0 to BCG and OPV0.

Importantly, there has never been a randomised trial of HBV0 with overall health outcomes anywhere in the world, so currently the effect is unknown. This is particularly important in the light that earlier observational studies from Guinea-Bissau (Garly et al, 2004) and The Gambia (Aaby et al, 2006) found increased female-to-male mortality following hepatitis B-containing vaccination, indicative of potential harmful non-specific effects.

In addition, REC requests your comments on the possibility of conducting the study, or another study with the same scientific objectives, in Denmark.

Response:

Denmark has almost universal antenatal hepatitis B screening and provides a targeted neonatal and infant hepatitis B vaccine series and immunoglobulin to infants born to mothers with hepatitis B. Danish newborns do not routinely receive BCG and OPV0 at birth, whereas the intervention to be evaluated in Guinea-Bissau is the overall health effects of the specific addition of HBV0 to that neonatal vaccine combination. The underlying risks of neonatal death and infectious hospital admission are also substantially different. Consequently, a Danish trial would differ in the vaccines co-administered with HBV0, the background infectious exposures, the incidence and causes of the primary outcomes, the organisation of hepatitis B prevention, the potential for detecting effects on mortality and serious infection, and the policy question to which the results would apply.

The Declaration of Helsinki states that research involving a population in a situation of particular vulnerability should be responsive to that population's health needs and should only be conducted in that population when the research cannot validly be carried out in a less vulnerable group. In this case, the vaccination context, disease burden, outcomes and policy question are specific to the population in which the study is proposed.

A trial conducted in Denmark would answer a fundamentally different scientific question and could not address the principal clinical and policy objectives of the present protocol; the results of such a trial would thus provide no relevant information for the policy decision on introducing HBV0 in Guinea-Bissau or other African countries where the vaccine is now being rolled out. Only a randomised evaluation in the relevant population and co-administration context can produce the knowledge needed to inform policy decisions before the planned introduction of a universal HBV0 birth dose in Guinea-Bissau.

- *REC requests that you address and comment on the possible situation in which one or more infants who, at the time of the study, were included in the study's control group and therefore did not receive the early HBV0 vaccine, subsequently, in the short or longer term, develop hepatitis or another health problem that could have been avoided had the individual been included in the study's intervention arm.*

Response:

We acknowledge directly that this possibility cannot be completely excluded. An infant allocated to the placebo group could, in principle, acquire hepatitis B before the routine hepatitis B-containing vaccination series begins at 6 weeks, and HBV0 might have prevented that infection. Although the probability is expected to be very small in the screened population, the potential consequence is serious because hepatitis B infection acquired in early infancy may become chronic and may ultimately lead to cirrhosis or hepatocellular carcinoma.

In the trial, only infants whose mothers have a negative peripartum HBsAg result are eligible for randomisation; infants of HBsAg-positive mothers are excluded from randomisation and offered HBV0 immediately. Infants whose maternal HBsAg status cannot be established are also not randomised and are offered HBV0. Thus, only infants of women who test negative are offered participation. All randomised infants remain scheduled to receive the routine hepatitis B-containing vaccinations at 6, 10 and 14 weeks.

These safeguards substantially reduce but do not eliminate the risk. Residual routes include a false-negative HBsAg result, occult maternal HBV infection, testing or laboratory error, and early-life horizontal exposure to another infected person before six weeks of age.

The best available evidence suggests that the absolute incremental risk of infection in children of HBsAg-negative mothers is small. A systematic review and meta-analysis included 27 studies and 10,003 children aged 0–5 years in sub-Saharan Africa (Ansari et al., The Lancet Global Health 2023, PMID: 37061310). The study assessed the risk of early horizontal transmission of HBV infection in children of HBsAg-negative mothers, stratified by vaccination schedule.

The pooled risks of HBV infection were 0.2% (10/3,425) among children whose first vaccine dose was given at 6–8 weeks and 0.05% (3/2,902) among children vaccinated at birth. After adjustment for study period, region and maternal HIV status, the difference was not statistically significant. The authors concluded there is no **clear additional benefit of the birth dose** for newborns born to HBsAg-negative mothers.

Critically, our trial itself substantially lowers the overall risk of vertical transmission at the study sites by introducing systematic maternal HBsAg screening and immediate targeted HBV0 for all infants born to HBsAg-positive or untested mothers - measures that are not currently standard of care.

With regard to *another health problem that could have been avoided*, it is not currently established that HBV0 would have prevented a particular non-HBV outcome. For these outcomes, an infant in either group might retrospectively have had a different outcome under the alternative allocation. This counterfactual possibility applies in both directions.

The purpose of randomisation is to determine the balance of these outcomes at population level. This does not reduce our obligation to monitor outcomes continuously. If accumulating data indicate that the risks outweigh the potential benefits, or provide conclusive evidence of harm or benefit, the investigators and the Data Safety Monitoring Board will review whether the study should be modified or stopped.

- *In the ethics self-assessment part of the REC application, you briefly note that "genuine equipoise exists concerning the broader health effects of HBV0 in this population". The question of this equipoise is, in REC's assessment, central to the research ethics evaluation. REC therefore requests that you elaborate on and justify the statement that there is a genuine and relevant scientific disagreement and/or knowledge gap regarding the research questions that justifies the study and the risks it entails. This is particularly important in light of the fact that, as REC understands it, there is robust scientific evidence that early administration of HBV0 provides infants with meaningful protection against early hepatitis infection, which is not obtained if the vaccine is not given or is administered only at a later stage.*

Response:

We agree that the term "genuine equipoise" requires precise definition.

There is no equipoise regarding the established pathogen-specific efficacy of HBV0 for infants born to HBsAg-positive mothers. Such infants will not be randomised, but offered HBV0 immediately, together with BCG and OPV0.

The relevant scientific uncertainty concerns clinically stable newborns of mothers with a documented negative peripartum HBsAg result who will receive the routine hepatitis B-containing vaccination series from 6 weeks of age.

For these infants, the pathogen-specific benefit of a birth dose is minimal: vertical transmission risk is already very low once the mother has tested HBsAg-negative, and protection against horizontal transmission is provided by the routine series that begins at 6 weeks of age. According to the literature, providing HBV0 to this group is not associated with a clear additional benefit in regard to prevention of hepatitis B infection. At the same time, the overall health effects of adding HBV0 in this group is unknown – it has never been evaluated in a randomised trial whether co-administering HBV0 with BCG and OPV0 has beneficial, neutral, or adverse non-specific effects on all-cause mortality and infectious hospital admissions during the first 42 days of life (and on longer-term outcomes such as atopic dermatitis and neurodevelopment).

It is relevant to note that BCG has already been shown to have marked beneficial non-specific effects on neonatal mortality in randomised trials conducted in Guinea-Bissau and in India. Adding another vaccine (HBV0) to this combination therefore requires careful evaluation of possible vaccine interactions and overall health effects.

The trial does not withhold established beneficial care. It compares the current national neonatal schedule (BCG + OPV0) with the WHO-recommended schedule (BCG + OPV0 + HBV0) under conditions in which infants at recognised risk of vertical transmission are excluded from randomisation and actively protected. All participants receive care that meets or exceeds the prevailing standard of care in Guinea-Bissau. In addition, the trial platform introduces systematic maternal screening, at-birth-vaccination of all children with BCG and OPV also beyond the current health service provision, and free access to consultations and essential medicines - benefits that extend to non-participants as well.

The policy context further underscores the importance of resolving this uncertainty. Guinea-Bissau's Ministry of Health is considering to move from the current schedule to universal HBV0. If HBV0 has no negative non-specific effects (or has positive non-specific effects), universal vaccination is the most efficient approach.

If, however, HBV0 has adverse non-specific effects when added to BCG + OPV0, a targeted strategy limited to infants of HBsAg-positive mothers would be preferable. Only a randomised evaluation conducted in the relevant population and co-administration context can provide the evidence needed to help guide this policy decision before universal introduction.

Despite WHO's recommendation of universal HBV0, there is substantial global variation in how the birth dose is implemented. The majority of European countries (including Denmark) provide only targeted HBV0 to neonates born to HBsAg-positive mothers, whereas most countries in the WHO Western Pacific and South-East Asia regions provide universal HBV0. Most African countries have not yet introduced HBV0. The proposed trial will therefore generate critical evidence to guide how the vaccine is best implemented in high-burden settings across Sub Saharan Africa.

Conclusion

In summary:

- the residual possibility that a placebo-group infant could acquire preventable hepatitis B is not zero and it will also not be zero in the intervention arm;
- the protocol substantially reduces the risk of hepatitis B infection in the cohort through maternal screening and immediate vaccination of infants at recognised increased risk;
- the available evidence indicates that the remaining absolute incremental risk in infants of HBsAg-negative mothers is small;

- the broader health effects of adding HBV0 to BCG and OPV0 have not been adequately assessed in a randomised trial; and
- neither a historical comparison nor a Danish trial could provide a valid answer to this important clinical and policy research question;
- CNEPS has recently completed a documented local ethical and scientific review and issued a favourable opinion, and also previously issued a favourable opinion for a trial that does not include maternal screening and the use of a placebo.